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Management of Advanced and Castration Resistant Prostate Cancer

Editor
Leonard G. Gomella, MD

Co-Editors
Daniel P. Petrylak, MD
Bobby Shayegan, MD

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Learning Objectives
Upon completion of the activity, participants should be able to:

1. Describe the changing landscape of advanced prostate cancer
2. Evaluate the use of imaging technologies in advanced castrate resistant prostate cancer
3. Assess the emerging role of intermittent hormonal therapy in treating castration resistant advanced prostate cancer
4. Define recent developments in prostate cancer treatment that affect and can impact patient quality-of-life outcomes

Target Audience
The activity is oriented to a targeted audience of physicians and medical care professionals specializing in the diagnosis and treatment of prostate cancer

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CONTRIBUTORS

Editor

Leonard G. Gomella, MD
The Bernard W. Godwin Professor of Prostate Cancer
Chairman, Department of Urology
Clinical Director Jefferson Kimmel Cancer Center Network
Thomas Jefferson University
Philadelphia, PA USA

Co-Editors

Daniel P. Petrylak, MD
Professor, Medical Oncology
Director, Prostate and Genitourinary Cancers
Yale Cancer Center
New Haven, CT USA

Bobby Shayegan, MD
Associate Professor, Urologic Oncology
Deputy Chief of Surgery SJHH
McMaster University
Hamilton, ON Canada

Primary Authors

E. David Crawford, MD
Professor of Surgery and Radiation Oncology
Head of Section on Urologic Oncology
University of Colorado Health Sciences Center
Denver, CO USA

Robert B. Den, MD
Radiation Oncologist
Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, PA USA

Robert Dreicer, MD
Professor, Cleveland Clinic Chairman
Department of Solid Tumor Oncology
Taussig Cancer Institute
Cleveland, OH USA

Christopher Evans, MD,
Professor and Chairman, Department of Urology
Urologic Surgical Oncology
University of California, Davis, Medical Center
Sacramento, CA USA

W. Kevin Kelly, DO
Professor, Medical Oncology and Urology
Director of the Solid Tumor Oncology
Kimmel Cancer Center, Thomas Jefferson University
Philadelphia, PA USA

Daniel W. Lin, MD
Professor, Department of Urology
Chief of Urologic Oncology
University of Washington
Seattle, WA USA

Judd W. Moul, MD
Director, Duke Prostate Center
Division of Urologic Surgery
Duke University Medical Center
Durham, NC USA

Ganesh Raj, MD
Assistant Professor
Oncology Fellowship Director
UT Southwestern Medical Center
Dallas, TX USA

Lawrence Schwartz, MD
Professor and Chairman
Department of Radiology
Columbia University Medical Center
New York, NY USA

Bertrand Tombal, MD
Chairman
Division of Urology
Cliniques Universitaires Saint-Luc
Brussels, Belgium

Eric Winquist, MD
Professor, Department of Oncology
Medical Director, Clinical Cancer Research Program
London Health Sciences Centre
London, ON Canada

CONTRIBUTORS

Co-Authors

Christopher Brian Allard, MD
Division of Urology
McMaster University
Hamilton, ON Canada

Sohaib Al-Asaaed, MD
London Health Sciences Centre
Western University
London, ON Canada

Valentina Butoescu, MD
Department of Urology
Cliniques Universitaires Saint-Luc
Brussels, Belgium

Paul H. Chung, MD
Department of Urology
University of Texas Southwestern Medical Center
Dallas, TX USA

Shawn Dason, MD
Division of Urology
McMaster University
Hamilton, ON Canada

Chaitanya, Divgi, MD
Department of Radiology
Columbia University Medical Center
New York, NY USA

Laura A. Doyle, MS
Department of Radiation Oncology
Thomas Jefferson University
Philadelphia, PA USA

Bishoy A. Gayed, MD
Department of Urology
University of Texas Southwestern Medical Center
Dallas, TX USA

Francisco Gelpi-Hammerschmidt, MD
Department of Urology
Thomas Jefferson University
Philadelphia, PA USA

Jean Hoffman-Censits, MD
Department of Medical Oncology
Kimmel Cancer Center
Philadelphia, PA USA

Jen Hoogenes, MS
Division of Urology
McMaster University
Hamilton, ON Canada

Karen E. Knudsen, MD
Department of Urology
Thomas Jefferson University
Philadelphia, PA USA

Saravanan Krishnamoorthy, MD
Department of Radiology
Columbia University Medical Center
New York, NY USA

Chandan Kundavram, MD
Department of Urology
Thomas Jefferson University
Philadelphia, PA USA

David Leung, MD
Department of Radiology
Columbia University Medical Center
New York, NY USA

Elahe A. Mostaghel, MD
Division of Clinical Research
Fred Hutchinson Cancer Research Center
Seattle, WA USA

Kyle O. Rove, MD
Division of Urology, University of Colorado
Anschutz Medical Campus
Aurora, CO USA

Gregory R. Thoreson, MD
Department of Urology
University of Texas Southwestern Medical Center
Dallas, TX USA

Derya Tilki, MD
Martini-Clinic Prostate Cancer Center
University Hospital Hamburg-Eppendorf
Hamburg, Germany

Jing Gennie Wang, MD(c)
Division of Urology
McMaster University
Hamilton, ON Canada

CONTRIBUTOR DISCLOSURES

Consistent with the current Accreditation Council for Continuing Medical Education policy, the CME Provider must be able to show that everyone who is in a position to control the content of an individual educational activity has disclosed all relevant financial relationships. The CME Provider has a mechanism in place to identify and resolve any conflicts of interest discovered in the disclosure process. The contributors have all made the proper disclosures, and the following relationships are relevant:

Christopher Brian Allard, MD, has no relevant financial relationships to disclose

Sohaib Al-Asaaed, MD, has no relevant financial relationships to disclose.

Valentina Butoescu, MD, has no relevant financial relationships to disclose.

Paul H. Chung, MD, has no relevant financial relationships to disclose.

E. David Crawford, MD, has received honoraria from Bayer and Janssen.

Shawn Dason, MD, has no relevant financial relationships to disclose.

Robert B. Den, MD, has received honoraria from Bayer and Algeta.

Chaitanya, Divgi, MD, has received honoraria from Bayer AG and Wilex AG.

Laura A. Doyle, MS, has no relevant financial relationships to disclose.

Robert Dreicer, MD, has received honoraria from Millenium, Medivation and Bayer.

Christopher Evans, MD, has received honoraria from Janssen, Medivation, Astellas and Oncogenex.

Bishoy A. Gayed, MD, has no relevant financial relationships to disclose.

Francisco Gelpi-Hammerschmidt, MD, has no relevant financial relationships to disclose.

Leonard G. Gomella, MD, has received honoraria from Astellas, Bayer, Dendreon and Janssen.

Jean Hoffman-Censits, MD, has no relevant financial relationships to disclose.

Jen Hoogenes, MS, has no relevant financial relationships to disclose.

W. Kevin Kelly, DO, has no relevant financial relationships to disclose.

Karen E. Knudsen, MD, has no relevant financial relationships to disclose.

Saravanan Krishnamoorthy, MD, has no relevant financial relationships to disclose

Chandan Kundavram, MD, has no relevant financial relationships to disclose.

David Leung, MD, has no relevant financial relationships to disclose.

Daniel W. Lin, MD, has received honoraria from Myriad and Dendreon.

Elahe A. Mostaghel, MD, has received honoraria from Janssen.

Judd W. Moul, MD, has received honoraria from Bayer, Janssen, Medivation, Astellas and Ferring.

Daniel P. Petrylak, MD, has received consulting fees from Bayer, Bellicum, Dendreon, Sanofi Aventis, Johnson and Johnson, Exelixis, Ferring, Millineum, Medivation and Pfizer. He also has received grant support from Oncogenex, Progenics, Johnson and Johnson, Millineum, Celgene and Dendreon.

Ganesh Raj, MD, has received honoraria from Bayer, Medivation, Astellas, Merck and Janssen. He has also received research support from Janssen.

Kyle O. Rove, MD, has received honoraria from JP Morgan and ZS Associates.

Bobby Shayegan, MD, has no relevant financial relationships to disclose.

Lawrence Schwartz, MD, has no relevant financial relationships to disclose.

Gregory R. Thoreson, MD, has no relevant financial relationships to disclose.

Derya Tilki, MD, has no relevant financial relationships to disclose.

Bertrand Tombal, MD, has received honoraria from Amgen and Ferring.

Jing Gennie Wang, MD(c), has no relevant financial relationships to disclose.

Eric Winquist, MD, has no relevant financial relationships to disclose.

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INTRODUCTION

Current management of advanced and castration resistant prostate cancer

Leonard G. Gomella, MD,[1] Daniel P. Petrylak, MD,[2] Bobby Shayegan, MD[3]

[1]Department of Urology Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

[2]Department of Medicine (Medical Oncology) and Urology, Yale Cancer Center, New Haven, Connecticut, USA

[3]Division of Urology, Department of Surgery, McMaster University, Hamilton, Ontario, Canada

GOMELLA LG, PETRYLAK DP, SHAYEGAN B. Current management of advanced and castration resistant prostate cancer. *Can J Urol* 2014;21(Suppl 1): 1-6.

Introduction: *Newer approaches to the management of advanced prostate cancer have rapidly evolved. While basic androgen deprivation remains as the first line in newly diagnosed hormone naïve metastatic prostate cancer, the agents used and strategies followed have undergone significant changes. Numerous new agents such as sipuleucel-T, abiraterone, enzalutamide, cabazitaxel and radium 223 have all been approved since 2010 to treat metastatic castration resistant prostate cancer (CRPC). New imaging techniques to detect advanced disease such as F-18 PET, 11 C-choline PET and other modalities are becoming available. The concepts of "bone health' and the management of side effects related to androgen deprivation therapy are also gaining attention as men are being treated with longer courses of androgen deprivation. Understanding the theory behind these new agents and management approaches while focusing on the practical clinical considerations are essential to improve outcomes in advanced prostate cancer.*

Materials and methods: *A review of the current state of the art in the management of advanced and castration resistant prostate cancer presented in this Canadian Journal of Urology International supplement was performed. Key findings are summarized and presented along with critical updates based on recent publications and meeting presentations.*

Results: *Key concepts identified in the management of advanced prostate cancer included the new understanding of prostate cancer based on translational discoveries, applications of various hormonally based strategies in advanced disease including traditional and recently approved agents. The use of new imaging modalities to identify metastatic disease, immunotherapy approaches and discussions of sequencing and which new agents are likely to be available in the future in the management of CRPC were identified. Bone targeted strategies are also addressed in the setting of androgen deprivation and metastatic disease.*

Conclusions: *The management of men with advanced prostate cancer has become more multidisciplinary as treatment options have expanded. As the use of these agents and new strategies expand, urologists, medical oncologists and radiation oncologists must all become familiar with this rapidly changing field in order to maximize the outcome of patients with advanced and castration resistant prostate cancer.*

Key Words: metastatic prostate cancer, castration resistant prostate cancer, docetaxel, sipuleucel-T, abiraterone, enzalutamide, cabazitaxel, radium 223, bone targeted agents, LHRH agonists and antagonists, prostate cancer imaging

Introduction

The development of new approaches in the management of advanced metastatic prostate cancer has accelerated rapidly over the last few years. Basic androgen deprivation therapy (ADT) has been refined and numerous new agents have been approved since 2010 to treat metastatic castration resistant prostate cancer (mCRPC). Understanding the theory behind these new agents and approaches while focusing on the practical clinical applications are essential to improve outcomes. As the management of these patients with advanced disease becomes more multidisciplinary and the use of these agents expands, urologists, medical oncologists and radiation oncologists must become more familiar with these new treatment strategies. This 2014 CME supplement of *The Canadian Journal of Urology International* will review advanced prostate cancer with a focus on the newer therapeutic agents used for advanced and castration resistant disease.

Address correspondence to Dr. Leonard G. Gomella, Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, 1025 Walnut Street, Room 1102, Philadelphia, PA 19107 USA

Translational research discoveries redefine advanced prostate cancer

Drs. Tilki and Evans have reviewed the latest scientific discoveries that have resulted in critical changes in our understanding of the development and clinical management of advanced prostate cancer.[1] While seemingly minor to the casual observer, the change in terminology from "hormone refractory prostate cancer" to the use of the term "castration resistant prostate cancer" (CRPC) represents an important paradigm shift in how we manage prostate cancer that is progressing in the setting of castrate levels of testosterone. CRPC is defined by disease progression despite androgen deprivation therapy and may present as either a continuous rise in serum PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases. This is deeply rooted in the recent translational discoveries in the field of basic prostate cancer research with these observations having a direct impact on men with advanced disease. Some of the more critical observations concerning biology of androgens and the androgen receptor axis in the development of CRPC have led to the development of many new therapeutic targets and agents. Several new medications such as the androgen biosynthesis inhibitor abiraterone and the androgen receptor pathway blocker enzalutamide have already found their place as Food and Drug Administration (FDA) approved medications in the United States and several other countries around the world.[2]

Androgen deprivation in advanced prostate cancer

Reducing serum testosterone to low levels or so called "castrate" levels has been the mainstay of advanced prostate cancer for decades. The utility of this androgen ablation approach in metastatic disease is clearly established. In addition, the androgen deprivation strategies have been refined and adapted in other clinical settings. These include applications in adjuvant and neoadjuvant settings for radiation therapy and surgery and expanded interest and use of the intermittent hormonal therapy for advanced disease. Critical in the application of androgen deprivation is the importance of periodic measurement of serum testosterone levels to verify effective castration, generally considered to be < 50 ng/dL.[3] Lastly, while the standard androgen ablation relies primarily upon luteinizing hormone releasing hormone (LHRH) analogues, Rove and Crawford provide insights on the use of both LHRH agonists and antagonists for androgen ablation while Moul discusses the practical applications of LHRH antagonists in the spectrum of advanced prostate cancer.[4,5] Dr. Moul also references a recent global pooled trial analysis of the risk of cardiac events within 1 year of initiating androgen deprivation. Cardiac events were noted to be significantly lower among men treated with a GnRH antagonist compared with GnRH agonists, an observation that is likely to continue to fuel the debate over cardiovascular risk and androgen deprivation strategies.[6,7]

Intermittent androgen deprivation therapy (IADT) involves cycles of ADT that are interrupted by injection-free intervals where testosterone levels are permitted to rise above castrate levels. It has proposed that IADT potentially reduces some of the bone and cardiovascular health sequelae of ADT and may improve oncologic outcomes, although this is not without some controversy. Dason and associates review how the approach works and most importantly summarize the major clinical trials that have been performed in this area.[8] The authors also provide useful summaries of the potential long term ADT complications such as the metabolic syndrome and bone health issues.

Secondary hormonal manipulation in advanced prostate cancer

Many new agents have been approved for advanced CRPC over the last few years. Prior to 2010, docetaxel remained the only agent approved when androgen deprivation failed. Secondary hormonal manipulation in CRPC was commonly performed with the concept first widely promoted by Small and Vogelzang.[9] Drs. Al-Asaaed and Winquist review current management guidelines and discuss what the role of secondary hormonal manipulation is in the current CRPC space.[10] Table 1 summarizes some of the more common and traditional secondary hormonal manipulations used before the introduction of newer agents such as abiraterone that some consider as a form of secondary hormonal manipulation.

TABLE 1. **Traditional secondary hormonal manipulations in the setting of castration resistant prostate cancer[9,10]**

Type of therapy	Response rate (rarely durable)
Steroids	10%-20%
Ketoconazole	30%-60%
Estrogens	40%-60%
Antiandrogens	20%
Antiandrogen withdrawal	20%

Role of imaging in CRPC

Determining the transition of CRPC to mCRPC is of vital importance for many reasons. First, the early identification of asymptomatic bony metastatic lesions may allow intervention to minimize the burden in terms of morbidity and cost of skeletal related events.[11] Secondly, medications such as sipuleucel-T are only indicated for asymptomatic or minimally symptomatic mCRPC.[12] This progression to mCRPC with detectable radiographic lesions is a seminal event significantly affecting treatment decisions. There is currently little formal guidance concerning the frequency of imaging in patients without symptoms. Recent recommendations by the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group have been published in attempt to address these limitations.[13] In addition to standard imaging technologies, a series of newer imaging modalities such as F-18 PET, 11 C-choline PET are becoming available to identify more accurately the presence of early metastatic prostate cancer before routine bone scan detection. Prostate cancer imaging advances are reviewed by Dr. Leung and associates.[14]

Immunotherapy in CRPC

While prostate cancer has traditionally been considered a "non-immunogenic tumor" recent discoveries have made prostate cancer a target of immunotherapy.[15] The active cellular immunotherapy, sipuleucel-T, was a first-in-class agent approved for mCRPC in 2010. This was based on the 4.1 months survival in the IMPACT trial demonstrating superiority of this novel approach in mCRPC.[16] The review by Gomella and associates discusses the development of sipuleucel-T and other evolving immunotherapy strategies and addresses the practical applications of administration of the sipuleucel-T.[12]

Androgen biosynthesis inhibition

As noted by Tilki and Evans, the androgen axis remains active in the setting of CRPC.[1] This observation and others including the discovery that metastatic prostate cancer can generate its own androgens has led to the development of agents that can impact androgen production in all sites in the body, including within the tumor itself. Abiraterone is the first approved androgen biosynthesis inhibitor for mCRPC. Abiraterone acetate, a pregnenolone derivative, is an oral inhibitor of the steroidogenic enzyme CYP17. Abiraterone possesses dual 17-α hydroxylase and C17,20-lyase blocking activity that results in decreased gonadal and extra-gonadal androgen synthesis.[17] While initially approved for post-docetaxel administration, it is now available in the pre-chemotherapy setting. The development, mechanisms of action and practical treatment considerations of abiraterone are reviewed by Mostaghel and Lin.[18]

Inhibition of the androgen receptor signaling pathway

In considering the androgen sensitivity of CRPC, inhibition of the androgen receptor signaling pathway is a viable strategy. Enzalutamide, formerly known as MDV3100, was developed and now approved as an orally administered androgen receptor inhibitor indicated for the treatment of patients with mCRPC who have previously received docetaxel. In contrast to the androgen receptor blocker bicalutamide, enzalutamide has no agonist properties. Enzalutamide competitively inhibits androgen receptor binding and androgen receptor nuclear translocation and interaction with DNA.[19] Based on the results of the recently reported PREVAIL trial (enzalutamide in the pre-chemotherapy mCRPC setting) at the American Society of Clinical Oncology (ASCO) 2014 Genitourinary (GU) Cancers Symposium in San Francisco, it is widely anticipated that this agent will be approved in this setting in the future.[20] The PREVAIL trial demonstrated improved overall survival and radiographic progression-free survival in patient with mCRPC who have not received chemotherapy. Drs. Hoffman-Censits and Kelly provide an introduction to the preliminary clinical trials that support the use of enzalutamide and discuss the practical applications of enzalutamide for the clinician.[21]

Bone targeted therapy with radium 223 dichloride

A hallmark of advanced prostate cancer is the frequent involvement of the bone. These metastatic lesions can cause pain or result in skeletal related events such as spinal cord compression or fractures with the extent of osseous metastasis directly correlated with overall survival. Radiopharmaceuticals have been available for many years to palliate painful bony metastasis. Commonly used agents to treat prostate cancer bony metastasis have included the beta particle emitting agents strontium 89 and samarium 153 with marrow suppression being their main limiting toxicity. While effective at short term palliation, neither of these agents has shown any utility in extending survival.[22] Radium

223 dichloride (formerly known as alpharadin) is a first-in-class alpha particle-emitting radiopharmaceutical approved for the treatment of patients with CRPC with symptomatic bone metastases and no known visceral metastasis. Radium 223, a calcium mimetic, targets bone but as an alpha emitter has a shorter range with less bone marrow toxicity when compared to the existing beta emitting agents.

Radium 223 dichloride has been included in the latest 2014 edition of the National Comprehensive Cancer Network (NCCN) prostate cancer treatment guidelines where it has been given a category 1 recommendation as both a first-line and second-line option for the treatment of patients with symptomatic bone metastases and no known visceral disease.[23] The role of all radiopharmaceuticals including the practical considerations in the use of radium 223 is discussed by Dr. Den and associates.[24]

Chemotherapy for mCRPC

Historically, no chemotherapeutic agents had been shown to be effective in the management of advanced prostate cancer. The only agent formally approved for metastatic prostate cancer progressing on hormonal ablation before 2004 was mitoxantrone and that indication was only for palliation when used in combination with prednisone. In 2004 docetaxel was formally approved "with prednisone in androgen independent (hormone refractory) metastatic prostate cancer".[25,26] This taxane served as the mainstay for prostate cancer that escaped hormone suppression until the next medication sipuleucel-T was approved in 2010. Docetaxel has remained as an important agent in this patient population and many of the newer drugs approved including abiraterone and enzalutamide were initially approved only after this chemotherapy had failed. Cabazitaxel, a microtubule inhibitor related to docetaxel, has also recently been approved in the post-docetaxel setting. The official label states cabazitaxel is indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.[27] While much excitement has been generated amongst all of the newer agents recently approved for mCRPC, chemotherapy remains a proven option. Dr. Petrylak, an early pioneer in the use of docetaxel in prostate cancer, provides a review on the recent history of chemotherapy for prostate cancer and explains the effective management strategies to maximize outcome and limit toxicity using docetaxel and cabazitaxel chemotherapy for mCRPC.[26]

Of note it is likely that chemotherapy will become even more critical in the management of metastatic prostate cancer even before the demonstration of castration resistance. The National Cancer Institute (NCI) has just announced the preliminary results of the ECOG 3805 trial (CHAARTED: ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer).[28] Men received either ADT alone or ADT with the chemotherapy drug docetaxel every 3 weeks over a period of 18 weeks. A significant improvement in the overall survival was noted favoring the participants who had received docetaxel chemotherapy in addition to the ADT compared to the ADT alone (3 year survival rates of 69.0%versus 52.5% respectively). Further analysis showed that patients with a high extent of metastatic disease accounted for most of the benefit in the overall survival from docetaxel plus ADT (3 year survival rates of 63.4% versus 43.9% for ADT alone). Median follow up to date is 2 years. Full details are expected at the 2014 ASCO meeting in Chicago but this could represent another major paradigm shift and expanded role for cytotoxic chemotherapy in the initial therapy of hormone naïve metastatic prostate cancer.

Bone health in prostate cancer

Bone health is a major issue in prostate cancer as it can impact quality and duration of life of the patients. The core concepts of "bone health" in prostate cancer as summarized by Dr. Tombal refer to the diagnostic, primary and pharmacological prevention, and treatment of cancer treatment induced bone loss (CTIBL) and metastasis, and their respective complications such as osteoporotic fractures and skeletal related events or SREs.[29] ADT can induce significant changes in bone mineral density and increase the risk of fracture. EAU guidelines recommend treating osteoporotic patients based on DEXA scanning with denosumab or bisphosphonates, but do not provide guidance for patients with osteopenia.[30] NCCN guidelines recommend a variety of agents such as bisphosphonates (zoledronic acid or alendronate), or denosumab 60 mg SQ every 6 months) for men with a high likelihood of fracture on androgen deprivation.[23]

Strategies to prevent bone metastasis are also reviewed here although this still remains a major issue to address. The presence of bony metastatic lesions can further weaken the integrity of the bone. It is estimated that in men with progressive life threatening metastatic prostate cancer over 90% of men will have bone metastasis. EAU and NCCN treatment guidelines recommend that bone metastatic CRPC patients should receive either zoledronic acid or denosumab and both

TABLE 2. **Agents with overall survival benefit in metastatic castration resistant prostate cancer**

Drug	Trial	Comparator	Primary endpoint	FDA approval
Chemotherapy-naïve				
Abiraterone acetate + prednisone	COU-AA-302[33]	Placebo + prednisone	OS benefit 5.2 months*	Dec 2012
Sipuleucel-T	IMPACT[16]	Placebo	OS benefit 4.1 months	Apr 2010
Radium 223 dichloride	ALSYMPCA[34]	Placebo	OS benefit 3.6 months	May 2013
Enzalutamide (interim analysis)	PREVAIL[20]	Placebo	OS benefit 2.2 months	N/A
Post-chemotherapy				
Abiraterone acetate + prednisone	COU-AA-301[35]	Placebo + prednisone	OS benefit 4.6 months	Apr 2011
Enzalutamide	AFFIRM[36]	Placebo	OS benefit 4.8 months	Aug 2012
Cabazitaxel + prednisone	TROPIC[37]	Mitoxantrone + prednisone	OS benefit 2.4 months	June 2010
Docetaxel + prednisone	TAX327[38]	Mitoxantrone + prednisone	OS benefit 2.4 months	May 2004

FDA = Food and Drug Administration; OS = overall survival
*p = 0.0151. Did not meet the prespecified value for statistical significance (Pre-specified significance by O'Brien-Fleming boundary = 0.0008)

note the superiority of the latter in delaying SRE.[23,29] The role of bone targeted therapy such as radium 223 in the setting of mCRPC is also addressed in this supplement by Den and associates.[24]

Sequencing mCRPC: an evolving challenge

The availability of numerous agents in the CRPC space is certainly good news. However, the downside of having multiple choices across the spectrum of advanced disease creates uncertainty concerning the optimum way to combine or sequence the medications to derive maximum benefit. Dr. Dreicer thoughtfully considers where some of these newer agents might be best positioned in a "clinically rational and economically viable manner".[31] He notes that certain sequencing issues will be addressed by formal trials such as an ongoing phase III trial randomizing patients with mCRPC to receive either docetaxel or cabazitaxel (www.clinicaltrials.gov: NCT01308567).

What's next in advanced prostate cancer?

Dozens of clinical trials evaluating new therapeutics in men with metastatic prostate cancer are in progress. Some of these include new first in man agents while others involve the application of existing agents in new settings or in combination with other agents. While many agents under evaluation such as ARN-509, TAK-700 and TOK-001 continue on the theme of interacting within the androgen axis while others interfere with other pathways of prostate cancer progression such as cabozantinib and OGX-011. Based on the proof of principle that of sipuleucel-T immunotherapy is effective, this area continues to be a targeted area of interest in prostate cancer with several other prostate cancer vaccines and immune check point inhibitors in late stage clinical trials. Thoreson and associates have reviewed the emerging therapies in CRPC and focus on some of the trials that will provide near term results.[32]

Conclusions

The rapid advances in our therapeutic options for advanced prostate cancer are impressive and at the same time overwhelming and sometimes difficult to place in proper clinical context. Table 2 summarizes some of the recent agents, trials, and outcomes of the latest medications used in the management of mCRPC. One challenge going forward is to demonstrate that some of these newer agents in development are superior to the previously approved agents. Since patients who fail some of these newer agents can be treated with existing drugs if they progress, the effectiveness of the new drug may not be as pronounced.

Prostate cancer guidelines from many organizations such as the AUA, EAU, CUA and NCCN have incorporated most of these new therapeutic agents and approaches to advanced and CRPC.[23,30,39,40] As clinicians begin to understand the rationale for these newer agents and the practical aspects of their clinical application their use will likely expand to benefit more eligible patients.

Disclosure

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The changing landscape of advanced and castration resistant prostate cancer: latest science and revised definitions

Derya Tilki, MD,[1,2] Christopher P. Evans, MD[1]

[1]Department of Urology, University of California, Davis, Medical Center, Sacramento, California, USA

[2]Martini-Clinic Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany

TILKI D, EVANS CP. The changing landscape of advanced and castration resistant prostate cancer: latest science and revised definitions. *Can J Urol* 2014; 21(Suppl 1):7-13.

Introduction: *One fifth of men with newly diagnosed prostate cancer present with locally advanced or metastatic disease. Androgen deprivation therapy (ADT) is the standard systemic therapy in these patients. Despite initial response, essentially all patients will develop castration resistant prostate cancer (CRPC). In this review, we will discuss the revised definitions of CRPC and the latest understanding of the biology of the androgen/androgen receptor axis in the development of advanced prostate cancer.*

Materials and methods: *A systematic literature review was conducted via electronic database articles based on title, abstract, study format, and content. The majority of selected articles were published between 1992 and 2013. Older studies were included selectively if historically relevant.*

Results: *Prostate cancer becomes castration resistant through numerous pathways, including androgen and androgen receptor (AR) dependent mechanisms as well as ligand and AR independent pathways. Therefore the terms androgen-insensitive and hormone-refractory should be avoided and replaced by the term castration resistant. Recent advances in understanding molecular mechanisms of castration resistance have led to development of novel CRPC therapeutics.*

Conclusions: *CRPC remains an incurable disease. Further understanding of the pathways involved in castration resistance will set the basis for development of therapies to increase survival in these patients.*

Key Words: castration resistant, hormone refractory, prostate cancer, androgen receptor, review

Introduction

Despite early-detection efforts prostate cancer remains the second-leading cause of cancer-related mortality in men in Western societies.[1] One fifth of men with newly diagnosed prostate cancer present with locally advanced or metastatic disease.[2] Androgen deprivation therapy (ADT) is the standard systemic therapy in patients with locally advanced prostate cancer, biochemically recurrent disease after failed curative treatment and metastatic prostate cancer. After initial response to ADT, the vast majority of these patients will go on to castration resistant disease within a median of 2 to 3 years.[3] ADT relies on the dependence of prostate cancer cells on androgen-receptor (AR) signaling.[4] Castration resistant prostate cancer (CRPC) represents a pressing therapeutic challenge. Currently it is believed that AR-mediated pathways remain active in CRPC. Mechanisms of castration resistance have been studied extensively in the last decade and have led to development of new therapeutic options including abiraterone acetate, an androgen biosynthesis inhibitor which blocks cytochrome P450-c17 (CYP17), and enzalutamide, an AR signaling inhibitor which prevents androgen binding, nuclear translocation and chromatin binding.[5-7]

The aim of this review is to summarize the revised definitions of CRPC and the latest understanding of the biology of the androgen/androgen receptor axis in the development of CRPC.

Address correspondence to Dr. Christopher P. Evans, Dept of Urology, University of California, Davis, School of Medicine, 4860 Y St., Suite 3500, Sacramento, CA 95817 USA

Materials and methods

A systematic literature review was conducted via electronic database searches of PubMed/Medline. Searches were conducted with the following combinations and iteration of the following terms: castration resistant prostate cancer, castration resistant, CRPC, prostate cancer, androgen resistance, hormone-refractory, hormone-independent, androgen receptor, androgen receptor axis. Articles were selected based on title, abstract, study format, and content by a consensus of the authors. The majority of selected articles were published between 1992 and 2013. Older studies were included selectively if historically relevant or in case of scanty data in more recent publications.

Results

Changes in the spectrum of advanced prostate cancer clinical presentation

The rate of patients with locally advanced (clinical T3/4NX/+M0) and metastatic prostate cancer at time of presentation has declined since the introduction of prostate-specific antigen (PSA). Nevertheless, these men contribute disproportionately to prostate cancer mortality and morbidity from this disease. PSA screening has also led to a change in clinical presentation of these patients. While patients presented with local symptoms due to locally advanced disease or cachexia, fatigue and bone pain in the pre-PSA era, PSA screening led to diagnosis of locally advanced prostate cancer in asymptomatic patients. It has been recognized that in patients with no evidence of nodal or metastatic disease, reliance on the T stage alone to define locally advanced disease and risk groups within it is not sufficient.[8] Therefore inclusion of pretherapy clinical and pathologic parameters other than clinical T stage such as PSA and Gleason score have led to a broader definition of locally advanced disease and are used to identify men at high risk for prostate cancer progression.[8,9]

Similarly as to patients at time of presentation, PSA has launched a new "clinical state" for CRPC as well, namely patients with or without clinical metastases, who have an increasing level of PSA despite ADT, but no obvious signs of progression based on clinical criteria or available imaging modalities.[10] Metastatic CRPC has a poor prognosis with a mean survival of 16-18 months.[11]

An emerging clinical phenomenon is the finding that up to 25% of men with late stage prostate cancer have a neuroendocrine phenotype.[12] Poorly differentiated neuroendocrine prostate cancer (small cell carcinoma of the prostate) is an aggressive disease and is frequently accompanied by presence of visceral metastases. Neuroendocrine tumors lack AR, do not secrete PSA and show poor response to androgen ablation. While neuroendocrine prostate cancer as a primary diagnosis is rare, neuroendocrine differentiation of prostate cancer increases with disease progression and in response to ADT,[13] which is likely due to selective treatment pressures driving the tumor to become less reliant on signaling through AR. This is therapeutically problematic and mandates finding new mechanisms for tumor growth inhibition.

New definitions of castration resistant and metastatic CRPC

With the demonstration of prostate cancer shrinkage via hormone therapy in 1941, the foundations were laid for a new disease, namely castration resistant prostate cancer.[14] New insights into mechanisms of prostate cancer resistance to ADT over the last two decades have led to revised terminologies of this disease.

Despite initial response to hormone therapy, the majority of patients with advanced prostate cancer will progress within a median of 2 to 3 years from the start of ADT.[15] Prostate cancer cells survive and resume growth despite ADT via adaptation to androgen-depleted conditions and alternative survival and growth pathways.[16,17]

This state of disease was widely referred to as hormone-refractory prostate cancer. The term suggests that further hormonal treatment of the prostate cancer will not be useful.

In 1982, Fowler and Whitmore observed that administration of testosterone led to unfavorable responses especially in those patients who were in symptomatic relapse following endocrine therapy.[18] These results indicated that although the prostate cancer was progressing despite ADT, it was still responding to androgen action and therefore not independent of or refractory to androgens.

Different additional hormonal therapy strategies including maximum androgen blockade, antiandrogen withdrawal, variation of specifc antiandrogens (e.g. bicalutamide, flutamide, nilutamide), estrogen compounds (diethylsilbestrol), adrenal suppressants (ketoconazole) have proven helpful.

Recognizing that the term hormone-refractory was used heterogeneously in a broad spectrum of prostate cancer patients, in 1999 Scher et al proposed a refinement of the classification of patients with relapsing disease despite ADT.[19] The authors reviewed 19 trials of relapsed patients under ADT and found that only one included a definition for hormone-refractory disease based on at least two values of elevated PSA.[19]

Furthermore, in the evaluation of second line hormonal therapies, patients were included who had one to up to six different treatments before enrollment in the same study.[19] Scher et al presented a classification scheme based on hormone sensitivity including the following three categories: 1) Hormone-naive patients who show a decrease in tumor proliferation if androgens are withdrawn or antiandrogens are administered (physiologic levels of androgens in the blood). 2) Androgen-independent and hormone-sensitive patients with decrease in proliferation in response to other hormonal manipulations as mentioned above (castration levels of testosterone). 3) Hormone-independent (androgen-independent and hormone-insensitive) patients who are insensitive to hormonal manipulations (castration levels of testosterone).[19] Extent of prostate cancer has not been included in these definitions, while the later introduced clinical states model of prostate cancer did differ castration resistance based on rising PSA from different states of castration resistance based on clinical metastases.[20,21]

Extensive research in the past decade has uncovered several underlying mechanisms by which prostate tumor cells become resistant to hormone therapy (as discussed below) and led to new definitions for prostate cancer progression despite castration levels of testosterone.

Testosterone levels of < 20 ng/dL after surgical castration have been measured using chemiluminescent technology and suggested as a cut point to define castration.[22,23] Previous to clinical approval of this new technique for testosterone measurement, a castration cut off of 50 ng/dL was used.[23]

Given that the terms androgen-independent and hormone-refractory do not reflect the possibility that a patient may respond to alternative hormone therapies and despite its wide use, the term castration resistant prostate cancer has emerged and established as more accurate.

According to the Canadian Urological Association castration resistant prostate cancer is defined by disease progression despite androgen deprivation therapy and may present as either a continuous rise in serum PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases.[24] Similarly, the American Urological Association guidelines define CRPC as a rising PSA level and/or radiographic evidence of prostate cancer progression despite medical or surgical castration.[25] The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) defines PSA only failure as a rising PSA that is greater than 2 ng/mL higher than the nadir. The rise has to be at least 25% over nadir and confirmed by a second PSA at least 3 weeks later.[25,26]

Summary of the latest understanding of the biology of the androgen and androgen receptor axis in the development of CRPC

Prostate cancer growth and survival depend on androgens which regulate the ratio of cells proliferating to those dying.[15] Testosterone is the main circulating androgen, of which 90% is secreted by the testes. Only a small fraction (3%) of testosterone is unbound and functionally active, while most of it is bound to sex-hormone-binding globulin or albumin. After entry of free testosterone through the cell membrane into the cytoplasm via diffusion, it is converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase.[15] The AR is a member of the nuclear receptor superfamily and acts as a ligand-inducible transcription factor. It consists of a polymorphic N-terminal domain, a central DNA-binding domain, a small hinge region, and a C-terminal ligand-binding domain.[27,28] The AR gene is located on the X chromosome and therefore is single-copy in males, which allows for the phenotypic manifestation of mutations without the influence of a wild-type codominant allele.[28] DHT has a five-fold higher affinity for the AR than testosterone.

The unliganded AR associates with a heat shock protein 90 (HSP90) chaperone complex in the cytoplasm and undergoes proteasome-mediated degradation in the absence of ligand.[29]

Androgen binding to AR results in dissociation of the AR-HSP-complex, homo-dimerization, and nuclear translocation. Subsequently the AR dimer binds to androgen response elements (ARE) in the promoter regions of target genes and recruits cofactors for regulation of the expression of androgen-regulated genes.[15,27,30,31] Other signal transduction pathways which involve TGF, IL-6, and IGF-I, can also enhance AR activity via phosphorylation of AR and/or AR coregulators.[31]

Approaches for ADT, as discussed in detail in the following articles of this supplement, are inhibition of luteinizing hormone (LH) or luteinizing hormone releasing hormone (LHRH), ablation of androgen sources, antiandrogens and inhibition of androgen synthesis. All of these therapeutic approaches have in common that they reduce AR activation through reducing levels of androgen or blocking AR binding. Therefore AR is believed to remain active in CRPC and to be critical in the development of CRPC.[29] Different androgen resistance mechanisms exist, which enable castration resistance. Molecular mechanisms which have been described to play an important role in CRPC are summarized in Table 1.[15,29,31,32] These include androgen and AR dependent

TABLE 1. **Possible molecular mechanisms of castration resistance (not exhaustive)**

Strategy/pathway	Mechanisms/references
Increased androgen sensitivity	• AR gene amplification[36,37] • AR stabilization[33] • Increased local androgen production (e.g. increased conversion of testosterone to DHT)[38] • Androgen transport[34,35]
Aberrant activation of the AR/promiscuity of AR (inappropriate AR activation by non-androgen steroids and androgen antagonists)	• AR mutations[41-44] • Alterations in AR coregulators[39,40]
Ligand independent AR activation/ altered AR transcriptional activity	• Activation of AR by growth factors (IGF-1, KGF, EGF)[48] • Receptor-tyrosine-kinase activated pathway (HER-2/ neu signaling cascade; Src kinase)[46,47,52,57] • AKT pathway[50,51] • E2C (UBE2C)[55] • Upregulation of AR (Rb/E2F/nuclear receptor axis; AR action on enhancer versus suppressor elements)[45,53] • AR splice variants (ligand-binding-domain deficient)[49,54-56] • lncRNA-dependent mechanisms of androgen-receptor-regulated gene activation programs[69]
AR independent pathways (activation of parallel survival pathways)	• Overexpression of oncogenes (BCL2 gene)[58-61]
Stem cells	• Androgen-independence before initiation of androgen deprivation therapy[70,71]
Intratumoral androgens	• Alternative intratumoral steroid biosynthesis pathway[73] • Fatty acids induced androgen synthesis[72]

AR = androgen receptor; DHT = dihydrotestosterone; IGF-1 = insulin-like-growth factor 1; KGF = keratinocyte growth factor; EGF = epidermal growth factor; BCL2 = B-cell lymphoma 2; UBE2C = ubiquitin-conjugating enzyme E2C gene; lncRNA = long non-coding RNA)

mechanisms[33-35] such as AR amplification[36,37] and local androgen production,[38] androgen independent and AR dependent mechanisms[39,40] such as AR mutations[41-44] and ligand independent AR activation,[45-57] as well as androgen and AR independent mechanisms such as alternative survival pathways.[58-61] Ligand-independent AR activation is postulated to eventuate from overexpression, mutation or, most commonly, truncation of the ligand-binding C-terminus of AR.[62-65] Loss of the C-terminus results in splice variants of AR that can be constitutively active. This likely occurs in about 25% of CRPC patients.[54,66] AR differs from other steroid receptors in that the transcriptional activity is mainly through the activation function region 1 in the N-terminal domain rather than in the ligand-binding domain.[67] Therefore treatment of splice variants requiring targeting of the N-terminus to date has lacking pharmacological success. Andersen and colleagues have reported that EPI-001, a marine sponge derivative, can inhibit transactivation of the N-terminal domain and block induction of androgen-regulated genes.[68] Recently it was reported that long non-coding RNAs regulate activation of both truncated and full-length AR, leading to ligand-independent activation of the AR transcriptional program.[69] Targeting the N-terminus is important and new approaches to inhibit AR are being developed.

Tumor-related factors proposed to contribute to castration resistance are stem cells[70,71] and intratumoral androgens,[72,73] Table 1. High levels of androgens in

CRPC samples and increased expression of androgen synthesis enzymes have been shown that tumor cells are involved in androgen synthesis and thus in AR reactivation.[29] Montgomery et al evaluated androgen levels and transcripts encoding steroidogenic enzymes in benign prostate tissue, untreated primary prostate cancer, metastasis from patients with castration resistant prostate cancer, and xenografts derived from castration resistant metastases.[74] They showed evidence that castration resistant metastatic prostate cancers may adapt to low systemic testosterone levels by maintaining intratumoral androgens through modulation of enzymes involved in intracrine steroidogenesis and androgen catabolism.[74] Locke and colleagues used the LNCaP xenograft model and showed that tumor androgens increase during CRPC progression in correlation to PSA up-regulation.[75] Furthermore, the authors demonstrated that all enzymes necessary for androgen synthesis are expressed in prostate cancer with some of them being up-regulated during CRPC progression.

The mechanisms driving the development of castration resistance likely vary among patients. Recently, persistent AR signaling activation has received much attention, leading to the identification of novel therapeutic targets.

Prostate cancer can acquire resistance to ADT through multiple mechanisms. Despite treatment of CRPC with new effective therapeutics such as enzalutamide and abiraterone acetate, all patients will eventually progress.[5,7] Resistance mechanisms evolve against most AR antagonists over time, and thus, it remains a valuable goal to develop other types of therapy targeting the AR or molecules that are specifically required for AR-regulated transcriptional programs. Combined and personalized treatment strategies and different treatment sequences are being evaluated to improve therapy of this disease.

Conclusions

Prostate cancer becomes castration resistant through numerous pathways, including androgen and AR dependent mechanisms as well as androgen/ligand and AR independent pathways. Therefore the terms androgen-insensitive or hormone-refractory should be avoided and replaced by the term castration resistant. Recent advances in understanding molecular mechanisms of castration resistance have led to development of novel CRPC therapeutics. Nevertheless, CRPC remains an incurable disease. Further understanding of the pathways involved in castration resistance will set the basis for development of therapies to increase survival in these patients.

Disclosure

Dr. Derya Tilki has no potential conflict of interest. Dr. Christopher P. Evans received honoraria from Janssen, Medivation, Astellas and has ownership interest in Oncogenex. □

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Traditional androgen ablation approaches to advanced prostate cancer: new insights

Kyle O. Rove, MD, E. David Crawford, MD
Division of Urology, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

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Introduction: *Androgen deprivation therapy (ADT) is a mature therapy for the treatment of advanced prostate cancer, and yet despite many years of use, there is still much about its use, side effects, efficacy, and outcomes for which the urology community does not have answers.*
Materials and methods: *A literature search was performed to review ADT use in the modern era, specifically examining adjuvant ADT after primary therapy, continuous versus intermittent ADT, disadvantages of luteinizing hormone releasing hormone (LHRH) agonists versus newer LHRH antagonists, and controversies of combined androgen blockade.*
Results: *ADT has little role as primary therapy in North American populations. Evidence for the use of neoadjuvant/adjuvant ADT with radical prostatectomy is less compelling than that for radiation therapy. Data supporting combined androgen blockade over LHRH agonist therapy alone are mixed. Newer LHRH antagonists have a faster onset of reduction in serum testosterone and demonstrate other effects on serum follicle stimulating hormone (FSH) that may impact prostate cancer outcomes.*
Conclusions: *ADT remains a mainstay of treatment in prostate cancer, and our knowledge of its effectiveness has improved with time. There are still scenarios where not enough information is available and study is ongoing.*

Key Words: androgen deprivation therapy, prostate cancer, castration resistant prostate cancer, androgen receptor, CRPC

Introduction

Advanced prostate cancer arises in several forms, either recognized because of rising prostate-specific antigen (PSA) after failing primary treatment or, more ominously, bone pain or urinary symptoms signifying locally advanced disease or metastasis. Fortunately, the latter is rare in the modern era. All of these entities, however, are driven by ongoing stimulation and downstream signaling from the androgen receptor (AR). By eliminating ligand (namely serum testosterone), this activity can be markedly downregulated as first discovered by the work of Huggins and Hodges, who were ultimately awarded the Nobel Prize in 1966.[1] Since that time, bilateral orchiectomy has been replaced with medical alternatives, including luteinizing hormone releasing hormone (LHRH) agonists, antagonists, and combined androgen blockade (CAB). The effect of these regimens, however, is limited, as nearly all patients with advanced disease will, if maintained on androgen deprivation therapy (ADT), develop resistance requiring alternative therapies. This review examines traditional strategies to the use of androgen ablation in patients with advanced prostate cancer.

Address correspondence to Dr. E. David Crawford, Section of Urologic Oncology, Mail Stop #F710, P.O. Box 6510, Aurora, CO 80045 USA

LHRH analogues

The decapeptide LHRH was first discovered in 1971 by Dr. Schally, who further demonstrated that synthetic analogues would bind to their receptors in the anterior pituitary to result in agonist activity.[2] Physiologic activity occurs via LHRH release from the hypothalamus in a pulsatile manner.[3] It then acts on the anterior pituitary to induce the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn act on the testes. Ninety to ninety-five percent of circulating androgens are produced by the testes, with the remainder coming from the adrenal glands.[4] With prolonged exposure to LHRH, the anterior pituitary downregulates LH and FSH, which in turn leads to lower testosterone, thus forming the basis for modern medical ADT in the treatment of prostate cancer.[5]

Up to this time, however, bilateral orchiectomy constituted the gold standard of hormone therapy for prostate cancer, but estrogenic compounds were also being used to lower testosterone (e.g., diethylstilbesterol, DES). Once LHRH analogues were deemed safer than estrogens (fewer thromboembolic side effects and cardiovascular events) and palliated advanced prostate cancer patients well, LHRH agonist therapy supplanted estrogens and bilateral orchiectomy.[6] Bilateral orchiectomy remains an option, and the side effect profile is similar to LHRH therapies (vasomotor symptoms, weight gain, mood lability, gynecomastia, fatigue, cognitive changes, and loss of libido). While bilateral orchiectomy is very efficacious and more cost effective at rapidly lowering total testosterone ($t_{½}$ 45 minutes, mean serum testosterone nadir 14 ng/dL seen in about 8.6 hours ± 3.2 hours), is not frequently performed in the modern era for a few reasons: the procedure is irreversible, and men are thought to experience significant psychological impact.[7-10] When given the choice of medication versus bilateral orchiectomy, one study noted 78% would choose medication to avoid surgery and out of convenience.[11] The reversible nature of LHRH analogues was further enhanced with the introduction of depot formulations, which last anywhere from 1-12 months before requiring re-dosing. A meta-analysis of 27 randomized controlled trials demonstrated similar efficacy between surgical and medical modalities of ADT.[12]

ADT is now standard of care in advanced prostate cancer, but it has been studied in other settings such as monotherapy for localized disease, early stage disease, neoadjuvant and adjuvant therapy in combination with surgery or radiation therapy. The practicing physician will undoubtedly encounter patients with various disease states and preferences. Below, we endeavor to summarize and review pertinent questions related to the modern accepted uses for ADT.

ADT as primary therapy

Some men may wish to avoid the side effects of definitive local therapy (radical prostatectomy or radiation therapy). Active surveillance is a valid option, particularly in men with low risk disease. The use of ADT for primary treatment is discouraged on the basis of randomized controlled trials comparing ADT alone to ADT plus radiation.[13] In one study by Widmark et al, 875 patients with either localized or locally advanced prostate cancer received either 3 months of LHRH agonist therapy plus non-steroidal antiandrogen or the same plus radiotherapy (minimum 70 Gy). After 10 years, overall mortality favored the ADT plus radiation arm (29.6% versus 39.4%).[14] The reader will note that modern ADT regimens are given for longer durations. The CAN-NCI-C-PR3 study examined men with high risk localized disease (T2 N0, PSA > 40 ng/mL or PSA > 20 ng/mL and Gleason ≥ 8) or locally advanced disease (T3/T4 N0) and randomized them to either lifelong ADT or ADT plus external beam radiation therapy. Men treated with ADT and radiation therapy had significantly lower overall risk of death (hazard ratio 0.70, 95% CI 0.57-0.85, p = 0.001).[15] Comparisons of ADT alone to ADT plus radical prostatectomy show similar poor outcomes for ADT monotherapy but are retrospective in nature.[16-18]

Despite current recommendations in the United States (U.S.) and Europe against the use of ADT as monotherapy for prostate cancer, 14.4% of patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry received only ADT as a form of therapy for prostate cancer in an analysis of the changing treatment patterns for prostate cancer between 1990 and 2007.[19] Interestingly enough, guidelines in Asia endorse monotherapy for localized prostate cancer on the basis that men have much better outcomes. One recent comparison of primary ADT patients between US and Japanese cohorts demonstrated a hazard ratio amongst all-cause mortality of 0.27 (95% CI 0.24-0.30) favoring Japanese patients.[20] The underlying reasons for these disparate outcomes is not entirely clear, but is likely multifactorial including genetics, environmental and/or dietary factors and comorbidities.

Neoadjuvant and adjuvant ADT

Investigators hypothesized that giving patients ADT prior to surgery might improve various clinical

and pathologic outcomes. A recent meta-analysis examined 10 studies comparing radical prostatectomy alone to neoadjuvant ADT followed by radical prostatectomy.[21] Overall, patients generally had T1-T3 disease with and without evidence of lymph node involvement, although the majority of patients across the studies were T1 and T2. Three of ten studies used an LHRH agonist alone, and seven studies used CAB. Overall survival was not significantly different between the two groups. Studies did demonstrate reduced positive margin rates ($p < 0.00001$), improved rates of organ confinement ($p < 0.0001$) and decreased lymph-node invasion ($p < 0.02$) when compared to radical prostatectomy alone. Longer durations (6 or 8 months) of neoadjuvant ADT versus shorter ones (3 months) improved pathologic outcomes. Currently, neoadjuvant ADT is not recommended prior to surgery.

In the adjuvant setting after radical prostatectomy, Messing et al looked at 98 men with positive pelvic lymph nodes found at time of surgery. These patients were randomized to either immediate ADT or observation. After a median follow up 11.9 years, improvements in overall survival, cancer-specific survival and progression-free survival were noted in patients who received immediate lifelong ADT.[22] Conversely, Iversen et al noted that in men with localized disease, adjuvant ADT (bicalutamide 150 mg daily) after primary therapy demonstrated no additional benefit over those who received primary therapy alone.[23] SWOG S9921 randomized 983 men with high risk features at prostatectomy (any of the following: Gleason ≥ 8, preoperative PSA > 15 ng/mL, stage T3b or greater, N1 disease, positive margin, or Gleason 7 plus PSA > 10 ng/mL) to either adjuvant ADT (goserelin plus bicalutamide) or adjuvant ADT plus mitoxantrone chemotherapy. Final treatment comparisons are not due to be reported until 2017.[24] For now, standard of care remains adjuvant RT in patients with these high risk features after radical prostatectomy. Based on the Messing data, however, adjuvant ADT does show benefit in patients with positive lymph nodes at time of surgery.[22]

With regards to patients receiving primary radiation therapy, there are a multitude of studies examining patient selection (low versus intermediate versus high risk disease), duration of therapy (6 months versus 3 years), timing of therapy (neoadjuvant versus adjuvant). Bolla et al first demonstrated benefit to adjuvant ADT for 3 years in men undergoing primary radiation therapy.[25] The most recent follow up data shows a striking difference in overall survival between those who received radiation alone (39.8%) versus radiation plus ADT (58.1%). The majority of patients had T3 disease, and the combination therapy arm overall survival hazard ratio was 0.60 (95% CI 0.45-0.80, $p = 0.0004$).[26] Other important studies have clarified other important points: adjuvant ADT does not benefit patients with low risk, localized disease;[27] intermediate risk localized prostate cancer patients do well with shorter duration of ADT (4-6 months);[28] and, high risk patients benefit from longer treatment (3 years).[29] Another study showed no difference between progression-free survival in patients undergoing radiotherapy who received neoadjuvant versus adjuvant ADT.[30]

Continuous versus intermittent ADT

Another strategy of ADT administration comes in the form of "drug holidays" wherein patients allow serum testosterone or PSA levels to recover and then repeat administration. The basis for such treatment evolved from the idea that if the time hormone-sensitive prostate cancer spent in an androgen-deficient state were drawn out, the time to castration resistant disease could be prolonged, improving patient outcomes.[31] In vitro models further showed that hormone-sensitive cells undergo repeated bouts of apoptosis in response to cyclic androgen deprivation.[32] Mouse models further demonstrated that this cyclic activity prolonged the time to a castration resistant disease state.[33,34] Other hypothesized benefits include improved quality-of-life, improved costs, and fewer adverse events associated with ADT.

A phase III trial was conducted that randomized men who had previously undergone primary therapy (radical prostatectomy or radiotherapy) to either continuous ADT (LHRH agonist with concomitant non-steroidal antiandrogen) or intermittent ADT (8 month treatment cycles, non-treatment cycle began after 8 months if there was no evidence of disease progression and PSA was < 4 ng/mL). On-therapy cycle resumed when the PSA rose to 10 ng/mL. The primary endpoint was overall survival. A total of 1,386 patients were randomized. The hazard ratio for death in the intermittent arm was 1.03 (95% CI 0.86-1.23), indicating no significant advantage. With regards to non-inferiority of the intermittent strategy, the p value was 0.01.[35] Although non-inferior, many questions with regards to intermittent ADT remain unanswered with respect to treatment schedules (PSA-based, calendar-based, or testosterone-based) and quality-of-life outcomes.

A second trial by Hussain et al recently reported results in 2013, randomizing men with newly diagnosed, metastatic, hormone-sensitive prostate

cancer to either continuous or intermittent therapy.[36] Intermittent dosing schedule was similar except the PSA-based schedule was set at 20 ng/mL before restarting ADT (or above 10 ng/mL at the investigator's discretion). Total time spent on protocol was 19 and 17 months for the intermittent and continuous arms, respectively. Patients receiving intermittent therapy spent 47% of time on ADT. Median overall survival was 5.7 years (intermittent) versus 6.4 years (continuous) after enrollment, with a hazard ratio for death in the intermittent arm of 1.10 (90% CI 0.99-1.23). With respect to non-inferiority, the study could not rule out a 20% chance of greater risk of death with intermittent therapy. This study did demonstrate intermittent therapy patients experienced better erectile function and mental health ($p < 0.001$ and $p = 0.003$, respectively) at month 3 but not at later time points.

More such trials to answer questions of different schedules are needed to fully elucidate the meaning of these two large randomized controlled trials. In fact, one study that examined different dosing scheduled noted testosterone-based dosing carried a significantly lower risk of PSA progression (hazard ratio 0.65; $p < 0.02$) as compared to continuous dosing.[37]

Disadvantages of LHRH agonists

Although LHRH agonists have been extremely successful in treating various prostate cancer disease states, they do possess some disadvantages and side effects. With regards to disadvantages, LHRH agonists will initially cause stimulation of the anterior pituitary, leading to an initial burst of LH release and subsequent testosterone flare in all patients. For about 10%, this clinical flare phenomenon can manifest itself symptomatically as acute spinal cord compression, ureteral/urethral obstruction, or bone pain. LHRH analogues take about 2-4 weeks to reach castrate levels of testosterone (defined as a serum testosterone < 50 ng/dL). Clinical manifestation of testosterone flare can be avoided by adding a non-steroidal antiandrogen that blocks downstream AR activity during the first 4-6 weeks.[40] The antiandrogen does not block the initial flare in testosterone, but rather blocks signaling activity via AR. Beyond the initial flare phenomenon, there is evidence to suggest that microsurges occur with repeat administrations of LHRH agonists in a small proportion (around 6%) of patients.[41]

Furthermore, not all patients treated with LHRH agonists will achieve a castrate level of serum testosterone of < 50 ng/dL (3.5%-17%).[41-44] The definition of castrate levels of serum testosterone remains hotly debated. The current definition of 50 ng/dL is based on the lower limit of detection for a double-dilution isotope technique to determine testosterone levels that is no longer performed.[45] Current liquid chromatography/tandem mass spectrometry (LC/MS-MS) assays have a much lower limit of detection and demonstrate that the mean serum testosterone level achieved with either surgical or medical ADT approaches 15 ng/dL.[42] As such, experts have argued that the cut off be moved to 20 ng/dL.[8] If this definition were used, up to 13%-37% of patients on LHRH agonist therapy might not have truly castrate levels of serum testosterone.[46-48]

There are suggestions from some series that inability to achieve or maintain castrate levels of testosterone confer patients worse outcomes in terms of overall survival. Morote et al examined men with non-metastatic prostate cancer receiving LHRH agonist. In men who experienced a breakthrough testosterone > 32 ng/dL during normal 3 month checks, mean progression-free survival was only 88 months versus 137 months in men who maintained serum testosterone levels < 32 ng/dL ($p < 0.003$).[49] Another retrospective study found those with higher levels of serum testosterone after 6 months of ADT had a 1.33-fold increase in cancer-specific mortality.[50] A large retrospective review of 2196 patients receiving radiotherapy with LHRH agonists showed no difference in biochemical-free survival between those who experienced any breakthrough > 50 ng/dL (73.1%) versus those who did not (62%, $p = 0.09$). The subgroup of men who experienced a breakthrough between 32 ng/dL and 50 ng/dL did show a significant difference in biochemical-free survival ($p = 0.048$). The authors note that patients who broke through 50 ng/dL were more likely to have an antiandrogen added to their regimen as opposed to those who experienced more mild breakthroughs between 32 ng/dL and 50 ng/dL. The authors note "these breakthroughs were less pronounced and, therefore, either unrecognized or presumed to be of lesser importance," perhaps explaining these data.[51]

LHRH agonist use has also been noted to result in increased risk of metabolic side effects such as diabetes and osteoporosis in addition to increased risk of cardiovascular events and stroke.[52-54] As such, in 2010, the U.S. Food and Drug Administration mandated that warnings be added to LHRH agonist labels.[55]

LHRH antagonists

To address some of these shortcomings, antagonists of LHRH receptors have been developed and have emerged from phase III clinical trials. This class of medications has the advantage of immediate downregulation of the anterior pituitary and would

not induce a flare phenomenon through initial agonistic activity like LHRH agonists. The first drug to be clinically approved for use, aberelix, was ultimately pulled from the market in the U.S. due to systemic allergic reactions secondary to histamine release and testosterone escapes. A next-generation compound, degarelix, was developed and tested in vitro and in vivo and does not have such histamine-releasing activity. As expected, degarelix abolishes gonadotropin and testosterone flare on initial administration and does not experience microsurges on repeat administration, while It suppresses PSA and testosterone faster than LHRH agonists ($p < 0.001$).[41] Further, because co-administration of an antiandrogen is not required to block flare, it avoids side effects from this class of medications. With respect to clinical outcomes, patients receiving degarelix experience fewer urinary tract infections (5% versus 8%). Biochemical control in patients with high risk disease (baseline PSA > 50 ng/mL) had better progression-free survival at 1 year versus agonist therapy (66% versus 54.7%, $p = 0.0245$).[56] No change in the rates of cardiovascular events, stroke, or thromoembolic events were noted before and after starting degarelix, implying an improvement over other forms of ADT.[57]

Effects on FSH

While most focus of LHRH agonist and antagonist activity has focused on the ability to downregulate or block the release of LH, many forget that physiologic LHRH also results in FSH release.[58,59] With LHRH agonists, FSH production is downregulated but recovers generally with time (mean levels declines 54.8% over baseline). LHRH antagonists, on the other hand, appear to have a more pronounced and persistent suppression of FSH (mean levels declines 88.5% over baseline).[41,60,61]

FSH, while not strictly germane to the testosterone axis that drives prostate cancer growth, has been shown to interact with receptors on prostate cancer cells and act as a stimulant for cellular growth.[62] FSH receptors are differentially expressed on prostate cancer cells and are expressed within blood vessels of various tumors.[63-66]

Combined androgen blockade

Greater suppression of androgenic activity is achieved when combining an LHRH agonist with a non-steroidal antiandrogen that blocks AR activity. There have been multiple studies examining clinical outcomes from CAB versus LHRH agonist monotherapy in various populations. Crawford et al compared two such populations (leuprolide versus leuprolide plus flutamide) in a large randomized controlled trial reported in 1989 with a median length in survival favoring CAB (16.5 months versus 13.9 months, $p = 0.039$).[67] A few years later, Eisenberger and colleagues reported a similar large randomized study, but with orchiectomy with and without flutamide showing no significant difference between the two arms.[68] A meta-analysis of trials comparing CAB (LHRH agonist plus one of the following: nilutamide, flutamide, or cyproterone acetate) to LHRH therapy alone showed a 2%-3% improvement in 5 year overall survival, but this was not statistically significant.[12] When examining just non-steroidal antiandrogens (nilutamide or flutamide plus LHRH agonist), there was a 2.9% statistically-significant advantage to CAB ($p = 0.005$). The number needed to treat with CAB is 35 to provide additional benefit in overall survival to one person.

Survival benefits offered by CAB are likely offset by increased rates of adverse events and reduced quality-of-life.[10] The conflicting results translate into guidelines. The American Society of Clinical Oncology (ASCO) recommends CAB for the initial management of metastatic, recurrent, or progressive prostate cancer, yet current National Comprehensive Cancer Network (NCCN) guidelines state that CAB provides no proven additional benefit over LHRH agonist therapy alone.[13,69] Certainly, these authors feel strongly that those patients who experience flare, microsurges or testosterone breakthroughs should undergo secondary hormonal manipulation, perhaps with the addition of an antiandrogen if one is not currently being used.

Role of testosterone levels in prostate cancer management

Measuring testosterone

One of the great difficulties in evaluating testosterone as a marker for prostate cancer remains our relative inability to accurately and precisely measure its value. As mentioned earlier, older techniques such as double-isotope dilution assay, radioimmunoassays, and chemiluminescence assays are imprecise at low levels of testosterone, such as those in children, women, and castrate men. These assays have coefficients of variability (CV) up to 40%. Large commercial laboratories have adopted more precise LC/MS-MS as the standard for measuring serum testosterone in hypogonadal men. CV still range from 2.7% to 25.6% on the same equipment and between equipment when measuring a single sample.[70] This variability

is influenced by differences in assay tolerances, lack of reference standards, and disparate sample preparation.[45] Given these problems, clinicians should be aware of the difficulty in interpreting individual values, particularly if testing is performed in more than one laboratory. This applies to data presented in this review as well, given varied testing platforms and variability that can occur at low levels of testosterone. There are initiatives underway to develop testing standards to allow equipment manufacturers to calibrate equipment.[71]

Current guidelines

Society guidelines regarding target serum testosterone levels in patients on ADT remain vague, likely owed to the lack of level I evidence. The 2013 National Comprehensive Cancer Network (NCCN) guidelines define "adequate suppression" of serum testosterone as < 50 ng/dL and is further reflected in the U.S. FDA insert provided with LHRH therapies for prostate cancer.[13] Additional hormonal manipulation is recommended for patients who do not achieve this level with current therapies. The American Urological Association (AUA) recently published guidelines on the treatment of castration resistant prostate cancer (CRPC) mentioning 50 ng/dL as the cut off for castrate levels.[72] The most recent European Association of Urology (EAU) guidelines question the need to redefine the cut off from 50 ng/dL to 20 ng/dL on the basis that a meta-analysis demonstrated similar outcomes between LHRH agonists and orchiectomy or DES at 2 years.[10,49] Arguably, better long term, prospectively collected evidence is still needed. Regular PSA and serum testosterone monitoring should occur for patients on ADT. An increase in PSA levels or the indication of clinical progression should trigger a testosterone level measurement in all cases to confirm CRPC. If testosterone is inadequately suppressed, secondary hormonal manipulation can be undertaken.[44]

Conclusions

Androgen deprivation continues to undergo refinement and is a mainstay in the treatment of advanced prostate cancer.

Disclosure

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Utility of LHRH antagonists for advanced prostate cancer

Judd W. Moul, MD
Division of Urologic Surgery, Department of Surgery and Duke Cancer Institute, Duke University, Durham, North Caroline, USA

MOUL JW. Utility of LHRH antagonists for advanced prostate cancer. *Can J Urol* 2014;21(Suppl 1):22-27.

Introduction: *Androgen deprivation therapy (ADT) is the lynchpin of treatment for advanced prostate cancer. Prescribing physicians and patients have a choice between orchiectomy, luteinizing hormone releasing hormone (LHRH) agonists, combined androgen deprivation (CAD) or LHRH antagonists.*

Materials and methods: *Literature relating to the use of LHRH antagonists in the management of prostate cancer was reviewed.*

Results: *Abarelix was the first-in-class LHRH pure antagonist that was Food and Drug Administration (FDA) approved in 2003. Due to a variety of concerns including hypersensitivity reactions it was withdrawn from the United States (U.S.) market in 2005. The only currently commercially available LHRH antagonist in the U.S. is degarelix available as a once-a-month depot injection. The potential clinical advantage of degarelix compared to the LHRH agonists is the very rapid and sustained testosterone suppression with no identifiable physiological or clinical testosterone surge or flare. The main disadvantage of degarelix compared to the LHRH agonists is the monthly dosing and the inconvenience for some patients and practices. Recent studies tout improved disease control for degarelix compared to monthly leuprolide acetate; however, these results remain controversial.*

Conclusions: *The rapid T-suppression achieved with degarelix may provide a clinical benefit for various groups of men with advanced or locally advanced disease.*

Key Words: degarelix, LHRH, abarelix, antagonists, prostate cancer, hormonal therapy, androgen deprivation

Introduction

For most of the last 25 years, hormone therapy (HT) or androgen deprivation therapy (ADT) for treatment of advanced prostate cancer has been based on luteinizing hormone releasing hormone (LHRH) agonists, such as leuprolide acetate or goserelin acetate.[1] LHRH agonists traditionally have been considered equivalent to bilateral orchiectomy in terms of reported testosterone suppression. Since the late 1980's another ADT strategy is combination of the LHRH agonist with an oral non-steroidal antiandrogen. Called "combined androgen blockade" (CAB) or "maximal androgen blockade" (MAB) the oral agents used include bicalutamide, flutamide, or nilutamide.[2] This combined treatment has remained controversial since its inception with some clinicians endorsing it's use and others concluding that the modest survival benefit does not outweigh the potential for increased side-effects from using two hormonal medications rather than one.

The challenge with LHRH agonists, even when administered as CAB in combination with an antiandrogen, is the possibility of periodic testosterone surges, flares and micro-surges. Gonadotropin releasing hormone (GnRH) receptor antagonism with agents such as abarelix (no longer commercially available) or degarelix represents a class of treatment that acts via immediate and competitive blockade of pituitary GnRH receptors, directly blocking release of both LH and follicle stimulating hormone (FSH).[3-6] The LHRH agonists work primarily by the competitive blockade of LH while degarelix can be classified as a GnRH antagonist since it blocks both LH and FSH. However it is recognized that the primary clinical application in prostate cancer is the LHRH antagonism. With no LH available to stimulate production of testosterone, the result is rapid testosterone suppression without an initial stimulation of the hypothalamic–pituitary–gonadal axis and the testosterone surge associated with LHRH agonists,

Address correspondence to Dr. Judd W. Moul, Division of Urologic Surgery, DUMC 3707-Room 1562, Duke South, Duke University Medical Center, Durham, NC 27710 USA

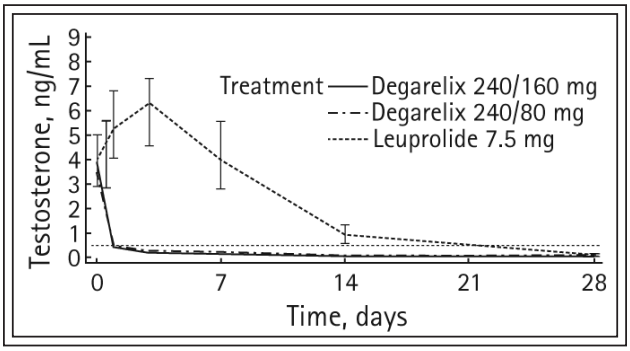

Figure 1. Comparison of serum testosterone levels during first 28 days of degarelix versus leuprolide in the Klotz et al pivotal phase III clinical trial which formed the basis for FDA approval of degarelix. Note the testosterone surge in the leuprolide patients (dotted line) compared to the rapid testosterone suppression in the degarelix treated patients. This is the key clinical data supporting degarelix use in clinical practice.[5] Reprinted with permission.

Figure 1. This mode of therapy avoids any need for concomitant antiandrogen flare protection although some clinicians prefer to continue to use oral antiandrogens even with degarelix for chronic adrenal androgen blockade.

Abarelix

Abarelix was the first-in-class LHRH pure antagonist that was Food and Drug Administration (FDA) approved in December 2003 to treat advanced prostate cancer.[3] While very effective at inducing a very rapid lowering of serum T, it was found to cause a hypersensitivity reaction in a very small percentage of patients and received a "Black Box Warning" from the FDA in late 2004. Shortly thereafter in early 2005, it was discontinued from the United States (U.S.) market. The remainder of this chapter will refer to degarelix since it is the only agent in the class that is currently FDA-approved and commercially available.

FDA approval of degarelix

A second-in-class pure LHRH antagonist, degarelix, was FDA-approved in December of 2008.[5] Now with over 5 years of clinical use, degarelix has not been associated with any serious adverse events and has steadily gained some market share as a parenteral ADT agent. More recent follow up of the degarelix pivotal phase III trial in which the agent was compared to monthly leuprolide suggests that it may be more effective than leuprolide for patients with metastatic disease at study entry.[7-9]

Degarelix (Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-hydrorootyl)-D-4Aph(carbamoyl)-Leu-Ilys-Pro-D-Ala-NH_2) is a synthetic, linear decapeptide amide analogue of endogenous GnRH. This compound is produced by insertion of seven exogenous amino acids, five of which are D-isomer amino acids. Degarelix binds to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone, and importantly this binding is reversible.

The initial dose-finding studies with degarelix suggested that 240 mg appeared to be the optimal starter dose, as this regimen resulted in castrate testosterone levels in > 96% of patients within 3 days. This led to a 1 year, multicenter, randomized, open-label, parallel-group, phase III trial (CS21) designed to demonstrate the statistical non-inferiority of degarelix versus the LHRH receptor agonist leuprolide.[5] This trial enrolled 610 patients with all stages of histologically confirmed prostate cancer and eligible for ADT. The study randomized patients to a starter dose of 240 mg sc degarelix followed by monthly maintenance doses of either 80 mg (240/80 group, n = 207) or 160 mg (240/160 group, n = 202) or to monthly leuprolide depot 7.5 mg im (n = 201). For the patients in the LHRH receptor agonist group, CAB with an antiandrogen could be added at the investigators' discretion.

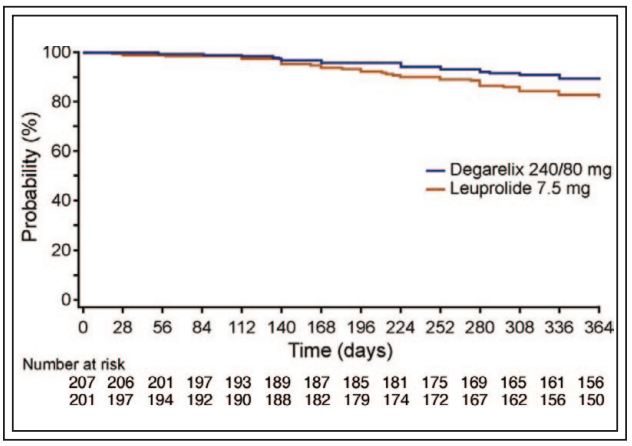

Figure 2. In follow up of the Klotz et al phase III RCT comparing degarelix versus monthly leuprolide, the disease-free survival in the patients with metastatic disease was statistically improved for degarelix-treated men compared to leuprolide-treated man at 1 year follow up. This data is in the peer reviewed literature (Tombal et al) however, the findings remain controversial. It is intriguing but must be considered hypothesis generating and is not considered valid level I evidence.[8] Reprinted with permission.

In the degarelix groups, median LH and FSH levels decreased rapidly and remained suppressed until the end of the study, whereas as expected LH and FSH levels showed an initial increase for patients in the leuprolide group, and FSH levels did not fall to the same extent as they did in the degarelix arms. In parallel with the testosterone results, the data for prostate-specific antigen (PSA) reduction showed a statistical difference at 7, 14, and 28 days, with significantly greater suppression than in the leuprolide group, and this finding correlated with a significantly lower risk of PSA failure or death. However by 1 year overall survival did not differ significantly between the degarelix 240/80 mg group and the leuprolide group (probability of death at 1 year, 2.6% versus 4.9%, respectively, NS). On the basis of these findings, the U.S. FDA approved degarelix injection on December 24, 2008 as a treatment of patients with advanced prostate cancer.

When the trial was extended beyond 1 year, the higher percentage of patients on degarelix versus leuprolide having a PSA of < 4 persisted out to about 73 weeks, Figure 2. It is important to note, however, that the patients on leuprolide were allowed to switch to degarelix after 52 weeks, with the result that between weeks 52 and 73, the curve for progression-free survival in patients on leuprolide converged with that for patients on degarelix. Therefore, by the end of the follow up period the progression-free survival results were essentially equivalent in the two arms, Figure 3.

This prostate-specific antigen (PSA) progression-free survival comparison remains very controversial especially in light that the primary endpoint of T non-

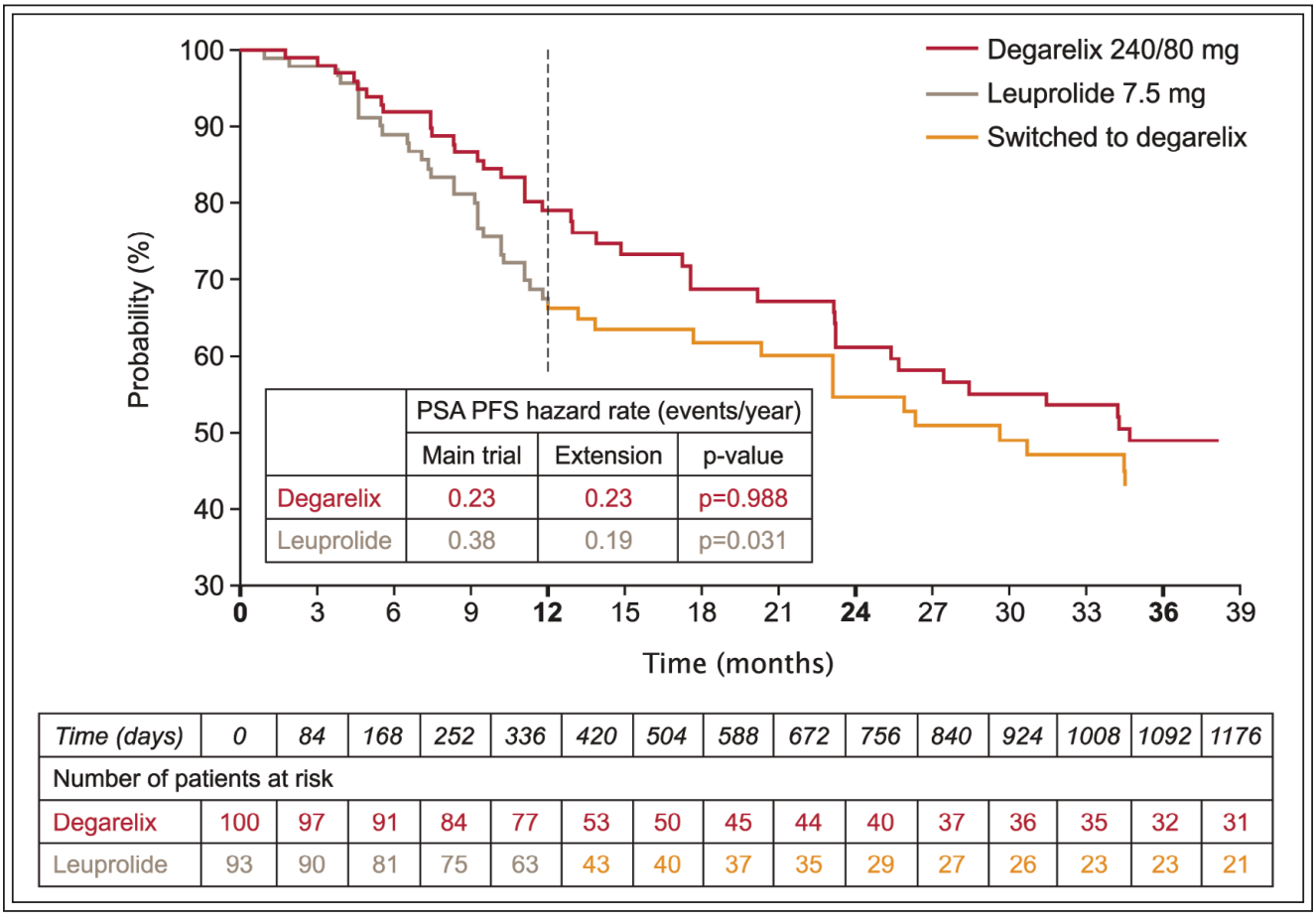

Figure 3. In the long term follow up extension study of the pivotal Klotz et al phase III RCT, the patients in the leuprolide arm could be switched to degarelix at the 1 year point (marked by the vertical dotted line). This switch from leuprolide to degarelix resulted in the survival curves converging at approximately 3 year follow up. Crawford et al suggest in the peer reviewed publication of this data that this implies that degarelix may be more effective than leuprolide. While intriguing and hypothesis-generating, this was not a pre-planned analysis and it remains speculative if degarelix is truly more effective than a comparable LH-RH agonist based on this data.[7] Reprinted with permission.

inferiority was met and in fact testosterone suppression beyond the first 28 days was similar between all three groups. A number of proposed theories to possibly explain the difference is worthy of mention such as initial rapid PSA suppression, lack of mini-flares of T with each injection, and better FSH suppression with degarelix. There are ongoing trials in Europe and North America with respect to the possible utility of degarelix in intermittent ADT. These trials may also shed more light on PSA suppression, micro surges and FSH suppression.

A final difference comparing LHRH agonists and degarelix has recently emerged- cardiovascular event rates. In the pooled global trials of degarelix recently presented by Albertsen et al, there was a substantially lower cardiovascular event rate in patients treated by degarelix.[10] This phenomenon is likely to cause significant controversy but also worthy of mention given the large patient population (pooled global trials) from which the data is obtained. Similar the findings of improved PSA control, such a finding is difficult to explain on the surface given that in general, cardiac events are felt to be exacerbated by the lowering of testosterone and in the case of degarelix, this happens at an initially faster but nonetheless there appears to a 50% decrease in cardiac events.

Clinical uses of degarelix

In theory if testosterone is lowered to castrate levels more rapidly, a patient might achieve clinical benefit more rapidly. There are certain clinical situations where degarelix is preferred or even mandated over LHRH agonists. In patients who present with metastatic prostate cancer and impending spinal cord compression, ureteral obstruction due to adenopathy or severe bone pain, the use of degarelix is of obvious utility as it avoids clinical testosterone surge or flare. In fact, LHRH agonists are specifically contraindicated in these clinical situations and either immediate orchiectomy, oral ketoconazole or degarelix would be mandated. Most patients do not desire orchiectomy and oral ketoconazole may not be properly absorbed in this acute setting making degarelix the preferred agent.

Beyond the above ideal use of degarelix, there are other clinical scenarios where clinicians might prefer degarelix over the traditional agonists. Since there is no testosterone flare/surge, some physicians prefer to start all patients on degarelix and then to switch the patient to a longer acting LHRH agonist after 2-12 months. Garnick et al showed that this practice was safe for abarelix and many clinicians extrapolate this finding to switching with degarelix.[6,11] This clinical switching is done due to the main clinical disadvantage of degarelix: the drug is currently only available as a 1 month depot injection. It is likely that if degarelix or another future GnRH pure antagonist was available in a longer acting depot (such as 3 to 6 month depot), the switching would become unnecessary.

The long term follow up of the original Klotz et al clinical trial suggest that degarelix may be more effective than monthly leuprolide acetate.[7-9] However, the cancer control outcome comparisons of degarelix versus leuprolide were not pre-specified as primary endpoints in the original Klotz et al pivotal trial so it is unclear if degarelix truly offers a survival benefit compared to LHRH agonists. If a clinician in practice feels that degarelix is more effective than LHRH agonists, then it opens clinical use to any/all patients who are placed on traditional ADT, such as high risk biochemical recurrence, newly diagnosed men with M1 disease, and in neoadjuvant/adjuvant settings. I believe it is reasonable to educate men about the option for long term degarelix noting the possible efficacy advantage versus the convenience disadvantage. In my experience, some men may want to avail themselves of the possible improved disease control and not be concerned about the monthly visits for injections. Other men choose convenience and desire longer acting depot agonists and forgo the possible efficacy difference.

In the specific setting of neoadjuvant hormonal therapy (NHT) use prior to the start of radiation, we know that degarelix provides more rapid PSA reduction over the first 56 days of use compared to monthly leuprolide in the Klotz et al clinical trial. If we believe that PSA is a general surrogate for cancer activity and prostate size, some clinicians may prefer degarelix over an agonist in this early phase. Furthermore, there is some evidence that PSA nadir while on NHT before the start of external beam radiotherapy (EBRT), predicts disease-free outcome. This would imply that using an agent with rapidity, such as degarelix, will have a better chance of lowering the PSA more robustly before radiation and might result in better long-term disease control. While speculative, there is little downside of considering degarelix for the first few months of NHT. Furthermore, in a case of intermediate risk disease where the total duration of NHT is going to be 4-6 months, there is minimal patient and physician office inconvenience of using a monthly depot for this relatively brief duration.

In addition, more rapid downsizing facilitated by the more rapidly acting degarelix might facilitate more rapid surgical scheduling in selected men with large glands prior to brachytherapy. Likewise, in the radical prostatectomy patient, there may be clinical situations where NHT is used for technical reasons. For example, NHT may also be used for prostate size considerations

or in the case of clinic T3/T4 disease where the clinician is trying to shrink the gland to facilitate a technically less-demanding operative experience. In these cases, some surgeons use degarelix in the hopes of a more rapid response.

In the setting of intermittent hormonal therapy (IHT), it is unclear if degarelix offers any advantage to the traditional LHRH agonists. There is no level I evidence to support degarelix in this setting. However, some clinicians feel the rapidity of onset may be of advantage for the first (and possibly subsequent) "on" cycles. While there have been many nuances to IHT use, most of the phase III trials have used a 6-9 month initial "on" cycle of ADT therapy. The basis for this initial duration of therapy was the time to PSA nadir on ADT. For the typical patient with M1 disease, it will take approximately 7 months to reach PSA nadir and the clinicians who designed the IHT trials felt that nadir PSA should be achieved before starting the "off" cycle. It is theoretically possible that the more rapid testosterone and PSA decline with degarelix would be an advantage to using degarelix. Furthermore, some clinicians feel that return of testosterone levels during the "off" cycle may be more rapid with degarelix compared to leuprolide and favor its use. Again, there is no level I evidence for degarelix over LHRH agonists in IHT and the concepts described are speculative.

Cost considerations

In most clinical settings, degarelix is comparably priced to commercially available branded LHRH agonists. As a result, if a prescribing physician believes there is a clinical benefit of degarelix over LHRH agonists, there would be no or little cost/price disincentive to use this agent. Two recent pharma-economic analyses have demonstrated cost effectiveness.[12,13] However, the office overhead costs, personal costs, patient travel and lost work costs of patients being seen monthly must also be considered. In my practice setting of a hospital-based clinic tertiary cancer center, many monthly patient visits for degarelix are "nurse-only" visits which does not generally impact physician workflow. However, in the first few months of administration, especially for men with more advanced disease and/or other comorbidities, the visits for degarelix also entail a provider visit which may be with a physician or an advanced practice provider.

Conclusions

Degarelix is a second-in-class pure GnRH antagonist that physiologically produces a very rapid reversible surge-free testosterone blockade. Available in the U.S. since December of 2008, it is a monthly depot androgen deprivation agent FDA-approved to treat men with advanced prostate cancer. The pivotal phase III clinical trial comparison to monthly leuprolide acetate showed equivalency in maintaining serum testosterone levels below 50 ng/dL (traditional castrate level). However, degarelix effect was much more rapid than leuprolide with over 95% of men achieving castrate testosterone within 72 hours and an overall benefit of testosterone lowering over the first 28 days of use. Longer term follow up studies of the pivotal trial patients suggest that degarelix may be more effective than leuprolide, but these data remain controversial. Various clinical situations were discussed where degarelix might be considered over agonist use. The main disadvantage of degarelix is the sole monthly depot dosing. Clinicians generally have to discuss efficacy and convenience issues with their patients when making a decision on androgen deprivation therapy.

Disclosure

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Intermittent androgen deprivation therapy for prostate cancer: translating randomized controlled trials into clinical practice

Shawn Dason, MD, Christopher Brian Allard, MD, Jing Gennie Wang, MD(c), Jen Hoogenes, MS, Bobby Shayegan, MD

Division of Urology, Department of Surgery, McMaster University, Hamilton, Ontario, Canada

DASON S, ALLARD CB, WANG JG, HOOGENES J, SHAYEGAN B. Intermittent androgen deprivation therapy for prostate cancer: translating randomized controlled trials into clinical practice. *Can J Urol* 2014; 21(Suppl 1):28-36.

Introduction: *Intermittent androgen deprivation therapy (IADT) for prostate cancer involves cycles of androgen deprivation therapy (ADT) with a period between cycles where testosterone is allowed to rise above castrate levels. A number of recent randomized controlled trials (RCTs) have compared survival and health-related quality-of-life (HRQOL) between IADT and continuous ADT (CADT). This review seeks to critically analyze these published trials for their relevance to clinical practice.*

Materials and methods: *Published trials were retrieved from a systematic search of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials databases using relevant keywords. Recent systematic reviews published on this topic were hand-searched for additional applicable references. The evidence was then synthesized for this review.*

Results: *A number of phase III trials have been recently published. IADT was found to be non-inferior in the primary setting for non-metastatic prostate cancer as well as in treatment of biochemical recurrence following radiotherapy. However, these studies overrepresented low risk patients in whom consideration may be given to deferred ADT rather than early treatment with IADT. In the metastatic prostate cancer setting, IADT was not found to be non-inferior to CADT. In most trials, castration related symptoms improved with IADT and overall HRQOL results were mixed. Little data are available on the effect of IADT on long term complications of ADT.*

Conclusions: *IADT remains a treatment with uncertain outcomes in metastatic prostate cancer and uncertain value over deferring ADT entirely in other prostate cancer clinical states.*

Key Words: health-related quality-of-life, cancer of the prostate, androgen deprivation therapy, hormonal therapy

Introduction

Androgen deprivation therapy (ADT) has been a mainstay in the treatment of advanced prostate cancer since its use was reported by Huggins and Hodges in 1941.[1] Androgen deprivation was classically accomplished surgically with bilateral orchiectomy. Although estrogen-mediated suppression of the hypothalamic-pituitary-gonadal (HPG)-axis has been adopted since the discovery of ADT, this approach has been limited by adverse cardiovascular effects.[2] The discovery of luteinizing hormone releasing hormone (LHRH) agonists made available a medical option for HPG-axis suppression without the thromboembolic effects of estrogens.[3] Today, medical ADT is usually favored over orchiectomy because of the potential for intermittent androgen deprivation, lack of surgical complications, and possible psychological benefits of testicular preservation.

Androgen deprivation therapy may be administered on a continuous or intermittent schedule. Continuous androgen deprivation therapy (CADT) suppresses

Address correspondence to Dr. Bobby Shayegan, McMaster Institute of Urology, 50 Charlton Ave E, Room G339A, Hamilton, ON L8N 4A6 Canada

testosterone to castrate levels for the duration of therapy. Alternatively, intermittent androgen deprivation therapy (IADT) involves cycles of ADT that are interrupted by injection-free intervals during which time testosterone levels are permitted to rise above castrate levels. Testosterone rises slowly during these periods and many patients will have incomplete recovery of their pre-ADT testosterone level.

The first description of IADT in clinical practice was reported by Klotz et al,[4] who reported on 20 patients with symptomatic metastatic disease treated intermittently with diethylstilbestrol (DES). Independently, Bruchovsky et al,[5] through their work with the Shionogi mouse mammary carcinoma, hypothesized that intermittent therapy could prolong time to castration resistance because CADT may preferentially enrich castration resistant stem cells.

Theories surrounding the beneficial effects of IADT prompted a number of recent phase III trials.[6] The primary hypothesis of IADT is that the testosterone rebound during treatment-free intervals of IADT may ameliorate some the adverse effects of ADT. These include castration related symptoms and their negative impact on health-related quality-of-life (HRQOL). It has also been hypothesized that IADT potentially reduces some of the bone and cardiovascular health sequelae of ADT. Finally, it has been proposed that cyclic testosterone fluctuations during IADT do not enrich cells with a castration resistant phenotype, potentially improving oncologic outcomes.[5] This review seeks to critically analyze how the available phase III trial evidence supports or refutes these theories at various prostate cancer disease states.

A disease state model of prostate cancer

Scher and Heller[7] proposed that prostate cancer may be modeled as a series of disease states through which patients may progress, ranging from localized prostate cancer to castration resistant prostate cancer (CRPC) that progresses after chemotherapy, Figure 1. Death may occur during any disease state, and therefore, does not necessarily result directly from prostate cancer due to its prolonged natural history and competing causes of death. The goals of prostate cancer therapy during any disease state include prolonging survival and optimizing HRQOL.

Prostate cancer undergoes a reduction in gland size and an increase in interglandular connective tissue during ADT.[8,9] Although residual tumor remains[9] and an inevitable progression to CRPC occurs, tumor-related symptom reduction is experienced on

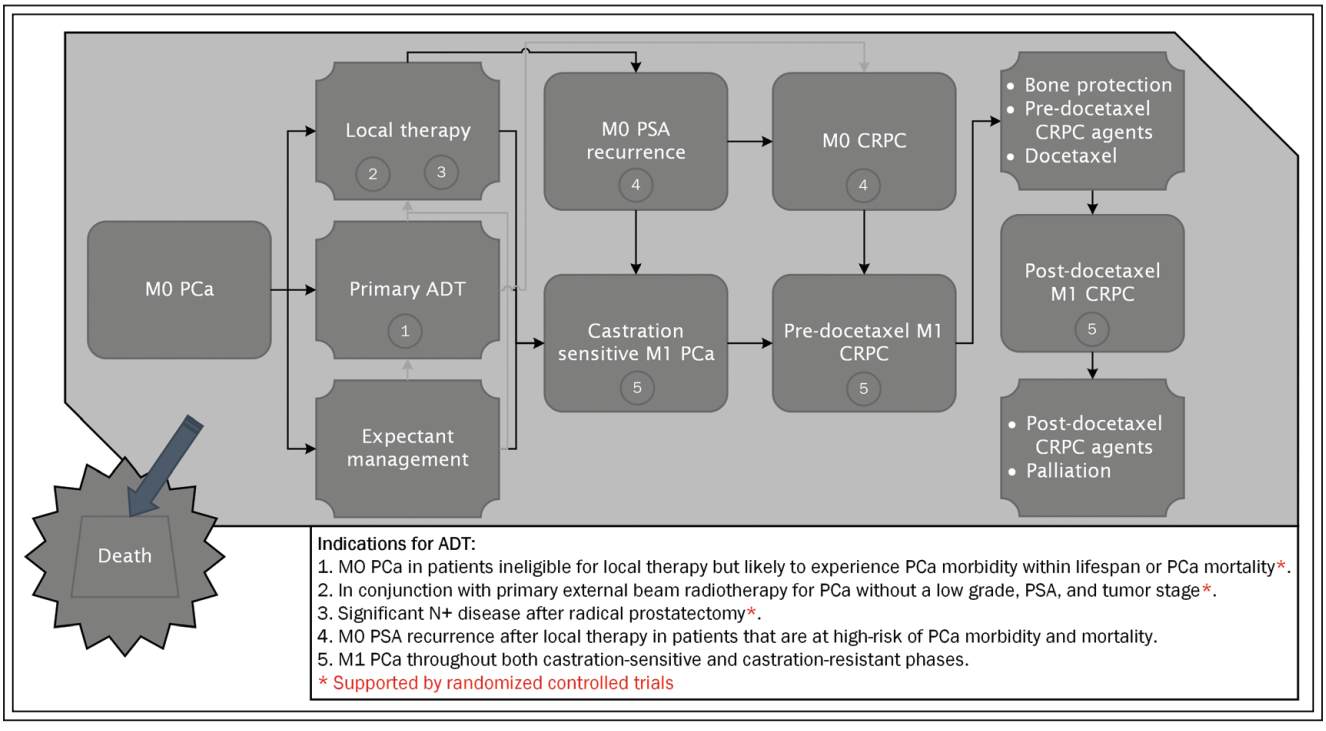

Figure 1. Indications for androgen deprivation therapy at different states of prostate cancer.[11]
PCa = prostate cancer; CRPC = castration resistant prostate cancer; ADT = androgen deprivation therapy; N+ = nodal metastases; PSA = prostate-specific antigen; M0 = non-metastatic; M1 = metastatic

initiation of ADT.[10] This effect can initially be dramatic in reducing the morbidity of symptomatic metastatic prostate cancer, including spinal cord compression, bone pain, and urinary tract obstruction. In efforts to delay the morbidity and mortality resulting from this advanced prostate cancer state, ADT is also initiated in some higher risk prostate cancer patients with asymptomatic metastases, prostate-specific antigen (PSA) recurrence after localized therapy, concurrent therapy with external beam radiotherapy, and/or patients with nodal disease after radical prostatectomy, Figure 1.[11]

Therapies for prostate cancer that are appropriate during one disease state may not necessarily be extrapolated to other disease states. As a limiting factor, the phase III IADT literature often includes heterogeneous cohorts comprised of prostate cancer patients in multiple disease states. Additionally, there is an uncertain indication for many trial patients to receive any form of ADT. This blanket approach, compounded by the publication of meta-analyses,[12,13] does not always lend itself to clinically applicable results. Multiple systematic reviews[6,12,13] thoroughly describe and tabulate the results of these phase III studies of IADT versus CADT; however, this is beyond the scope of this review. Instead, we provide suggestions for clinical practice based on a critical analysis of the IADT literature as organized by disease state, with consideration as to whether any form of ADT is indicated at all.

Primary therapy for non-metastatic (M0) prostate cancer

Local therapy is the standard of care for patients with non-metastatic (M0) prostate cancer that are not candidates for active surveillance.[14] However, given the high rates of inappropriate PSA screening,[15] a number of patients diagnosed with prostate cancer are often too old or comorbid to be candidates for local therapy. In these patients, a discussion about starting ADT is warranted when the risk of 5 year prostate cancer mortality is high.

This indication is supported by a recently published update of the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Cancers Group 30891 trial[16] which randomized patients unsuitable or unwilling to have local therapy for prostate cancer stage T0-4, N0-2, and M0 to immediate ADT (n = 492) or deferred ADT (n = 493). Only 5% of patients had known nodal metastases. Patients were followed for a median of 12.8 years with 78% of patients dying during the study, including 35% of deaths from prostate cancer and 33% from cardiovascular disease. Therapy was started in the deferred arm for new symptomatic metastases, metastases resulting in impending fracture or cord compression, pain related to prostate cancer, deterioration in performance status, and/or ureteric obstruction. Only 55% of all patients allocated to receive deferred ADT ultimately received ADT and, on average, deferred ADT required 31% of the total ADT treatment time of immediate ADT. Deferred ADT was worse than immediate ADT for time to first objective disease progression (defined as metastases or ureteric obstruction, 10 year progression rates 42% versus 30%, $p < 0.0001$). Time to castration resistant disease ADT did not differ significantly between groups ($p = 0.42$). Overall prostate cancer mortality did not differ significantly (10 year death rate of 25% versus 23%; for early and deferred ADT respectively), but overall survival was superior with immediate ADT (HR = 1.21, 95% CI 1.05-1.39, $p = 0.0085$). The authors attributed the decreased survival in the deferred ADT group to a significantly higher number of prostate cancer related deaths on deferred ADT during years 3-5 after diagnosis. PSA doubling time < 12 months served as a significant prognostic indicator of early prostate cancer death with a 3.4-fold increased risk of dying of prostate cancer with a PSA doubling time less than 12 months when compared to more than 24 months (21.0% at 5 year mortality and 46% 10 year mortality).

The EORTC 30891 trial built upon previous trials such as the Veterans' Administration Cooperative Urological Research Group (VACURG) trial,[17] which showed less progression in early ADT arms but no overall survival benefit to early ADT. The VACURG 2 trial[2] suggested a survival benefit in patients less than age 75 started on early ADT for high grade tumors. Finally, the British Medical Research Council (MRC) trial[18] of early versus deferred ADT suggested that delayed ADT was associated with more progression, complications, symptoms, and prostate cancer mortality—although there was no overall survival benefit in the final analysis.[16] The EORTC 30891, VACURG 2, and the British MRC trials can all be criticized due to inconsistent follow up resulting in an insufficient number of patients who received deferred ADT before prostate cancer mortality, bringing into question whether these trials assessed early versus no ADT instead of early versus delayed ADT.[19]

Taken together, these trials suggest that ADT may reasonably be delayed in patients ineligible for local therapy provided that patients are followed closely for disease progression. Early ADT is most beneficial in patients with more aggressive disease who are likely to

die from prostate cancer or experience prostate cancer related morbidity within their remaining years.

The most relevant IADT trial within this disease state is the South European Uroncological Group (SEUG) 9901 trial which excluded patients with prior local therapy and was comprised of 89% M0 patients.[20] A total of 918 patients were randomized to continuous or intermittent therapy with triptoreline and cyproterone acetate. At a 66 month median follow up, 525 (57.2%) of the patients had died. There was no difference in overall survival with IADT versus CADT (HR 0.90, 95% CI 0.76-1.07 – 1.21 threshold for non-inferiority).[20] The hazard ratio for prostate cancer mortality was not significantly increased with IADT.

Despite these statistical findings, it is uncertain how clinically relevant SEUG 9901 is because many patients in this trial would likely not have benefitted from any form of ADT. Approximately, 40% of patients had Gleason grade 6 or less prostate cancer and over 50% had a PSA of less than 1. This trial was not enriched with high risk patients, with only 18% of patients dying from prostate cancer between the two groups. Given such limitations, caution is still warranted in using IADT as primary therapy in patients with more aggressive disease.

Biochemical recurrence after primary therapy

There is a paucity of high quality evidence to guide which patients should receive ADT following biochemical relapse after primary therapy when there is no evidence of metastatic disease on imaging. Variables that are thought to be most important in this decision include PSA doubling time and Gleason score, as these are felt to best predict time to metastases and death.

The PR7[21] trial investigated whether IADT was non-inferior to CADT in patients who had recurred biochemically after radiotherapy. Patients with a PSA level of 3 ng/mL more than 1 year after radiotherapy for prostate cancer and no evidence of metastases were eligible for inclusion. Survival of patients in the IADT group was 8.8 years (n = 690) versus 9.1 (n = 696) years in the CADT group (HR for death 1.02, 95% CI 0.86-1.21). The trial was stopped after non-inferiority (HR < 1.25) was demonstrated at a pre-planned analysis and 524 deaths were reached (37.8%). The authors concluded that IADT was non-inferior because the HR for death was less than 1.25 and the p value for non-inferiority (HR < 1.25) equaled 0.009. In this trial, 59% of deaths were unrelated to prostate cancer and thus the authors retrospectively analyzed the data for disease-specific survival. They demonstrated a non-significant increased hazard ratio and a 7 year cumulative prostate cancer disease-related death rate of 18% and 15% in the IADT and CADT groups, respectively (p = 0.24). Time to CRPC was slightly longer in the IADT group, but the authors acknowledged that this was related to systematic biases in how CRPC was diagnosed in IADT versus CADT groups.

The PR7 trial[21] had a number of limitations in its follow up and methodology. The study group only included patients in an early clinical state of disease with a median follow up of only 6.9 years. In the National Cancer Institute's SWOG 9346,[22] a trial conducted on patients with more advanced prostate cancer, survival curves only started to separate after 5 years and 90% of patients had died after nearly 10 years of follow up. In the PR7 trial, the IADT survival curve appears to separate from CADT after approximately 9 years—without further follow up and reporting of death events, it is uncertain whether this trend would have continued. Additionally, although non-inferiority was demonstrated by the trial standards, it was defined liberally with a 1.8 year reduction in median survival required for inferiority.[22]

The PR7 trial[21] was also limited because its study population was comprised of lower risk patients. Used as a surrogate of PSA doubling time— at baseline, 78.3% of all patients enrolled in the trial had > 3 years' time since their radiotherapy. Furthermore, Gleason grade distribution was 2-6 in 42.6%, 7 in 33.0%, 8-10 in 15.2% and unavailable in 9.2%. Patients with Gleason score 8-10 disease had a 14 month poorer median survival with IADT. This poorer survival was not significant, but this was an underpowered subgroup.

The conclusion of the PR7 trial that IADT is non-inferior to CADT is thus limited to a population at lower risk of prostate cancer metastases and death. In this population, the benefit of any form of early ADT is uncertain. The PR7 trial was not appropriately designed to provide significant conclusions regarding patients most likely to experience morbidity or mortality from prostate cancer—such as those with short PSA doubling times and high initial Gleason scores. Given the limitations of this trial, IADT must be approached with caution in non-metastatic patients at risk of rapid disease progression.

Metastatic disease

For patients with metastatic disease—either on presentation or after primary therapy—SWOG 9346[22] failed to demonstrate non-inferiority of IADT. At a median follow up of 9.8 years, over 90% of the patients had died. Survival was 5.1 years in the IADT group (n = 770) and 5.8 years in the CADT group (n = 765)—

with a hazard ratio for death with IADT of 1.10 (90% CI 0.99-1.23). Prostate cancer accounted for 73% of deaths in the CADT group and 80% of deaths in the IADT group. This trial was designed such that a median survival decrease of 7 months in the IADT group was considered inferior. This required the upper limit of the 90% confidence interval to be less than 1.20 for non-inferiority, a condition that was not reached. Because the lower limit of the confidence interval included 1.0, IADT was not significantly inferior to CADT. This makes the trial statistically inconclusive, with neither the non-inferiority nor inferiority of IADT being demonstrated.

The SWOG 9346 trial performed a number of stratifications—the most interesting of which was extensive (disease in ribs, long bones, visceral organs) versus minimal disease (disease confined to spine, pelvic bones or lymph nodes). Survival with IADT versus CADT was 4.9 years versus 4.4 years (HR of 1.02, 95% CI 0.85-1.22) in the extensive disease group. However in patients with limited disease, survival was 5.4 years in the IADT group and 6.9 years in the CADT group (HR of 1.19, 95% CI 0.98-1.43). Although again statistically inconclusive—these findings suggest that caution is warranted in administering IADT for those with minimal metastatic disease.

Smaller studies with low prostate cancer mortality, mixed populations, less rigorous methodology, and shorter follow up have generally demonstrated equivalency of IADT and CADT. Since the publication of SWOG 9346, these trials may be viewed as being less significant and may therefore serve only to confound a meta-analysis.[6,23-26]

In summary, SWOG 9346 was a high quality non-inferiority trial on IADT versus CADT in patients with metastatic disease which was statistically inconclusive. IADT wasn't found to be non-inferior to CADT; but conversely, CADT was not superior to IADT. Given these inconclusive findings, CADT remains the standard of care in treatment of patients with metastatic disease.

Castration related symptoms and health related quality-of-life

Improvement in ADT-related symptomatology correlates with recovery of testosterone during off-treatment cycles which is dependent on age, baseline testosterone, number of ADT cycles, ethnicity, and the duration of induction period and length of the off-treatment period.[27] During ADT, routine testosterone measurement is currently recommended to evaluate ADT effectiveness[28] and diagnose progression to CRPC. It is also important to measure testosterone during IADT to document return of gonadal function and assess whether IADT is providing actual clinical benefit. If testosterone and symptomatic benefits are not recovered after the initial off-treatment cycles, they are less likely to return in shorter later cycles.[26] Understanding which patients will recover testosterone during the off-treatment periods is important in the decision to select IADT, particularly when employing IADT for metastatic disease, where off-treatment time is shorter (53% in SWOG 9346[22] trial versus 73% in the PR7[21] trial).

Phase III studies of IADT have confirmed patient-reported improvement in castration related symptoms during off-treatment periods as testosterone rises. Overall, study results have shown that erectile function and libido consistently improved during off-treatment periods. Hot flushes, fatigue, and headaches are also found to improve during off-treatment periods. Results concerning overall HRQOL improvements, generally measured in these trials by the multi-domain EORTC QLQ-30 questionnaire, were mixed and may relate to differences in measurement time points and in particular, blinding. Additionally, HRQOL measurement was performed with metrics not validated in this population. Unfortunately, differences in the methodology of collecting and reporting symptom and HRQOL-related data amongst phase III trials generally precluded meta-analysis of these outcomes, except for a meta-analysis of three smaller trials that reported reporting that the risk of hot flushes during IADT is lower than with CADT.[12]

In the SWOG 9346 trial,[22] patients in the IADT group received therapy for 47% of their ADT course. Reporting of HRQOL outcomes was at 3, 9 and 15 months after randomization; thereby only encompassing the first cycle off therapy. For this trial, HRQOL was divided into five domains—erectile dysfunction (ED), libido, vitality, mental health and physical functioning. Mental health, ED, and libido were improved at 3 and 9 months, vitality was improved at 9 months only and physical functioning was improved at 9 and 15 months. This equalization of HRQOL scores over time is in keeping with the fact that by the time of the 15 month analysis, 78% of men in the IADT group had resumed therapy, supporting the HRQOL benefit of IADT during off-treatment periods. HRQOL measurement in this trial was limited by a lack of blinding and the fact that that testosterone was not measured and correlated to HRQOL scores.

In the PR7 study,[21] 35% of patients had recovery of testosterone to pretreatment levels and 79% had a level of at least 5 nmol/L (144 ng/dL) by 2 years after completing the first period of treatment. Cox

regression demonstrated that men older than age 75 were less likely to return to pre-treatment testosterone level than men under age 75. Trial participants were on treatment 27% of the time. The PR7 trial authors assessed HRQOL by using a combined analysis of responses to these questionnaires at multiple fixed time points in the first 5 years of treatment. Although differences in functional HRQOL scores (physical, role, and global health) were not significant, IADT demonstrated improvements in hot flushes, desire for sexual activity, urinary symptoms and a trend towards improvement in the level of fatigue ($p = 0.07$). The functional HRQOL data in this trial is difficult to interpret because the trial was not blinded and HRQOL questionnaires were administered at fixed time points, regardless of whether IADT patients were on or off treatment.

The other smaller RCTs previously noted also generally supported improved symptomatology and sexual function during IAD. The HRQOL scores did not differ between groups in SEUG 9901,[20] although symptomatology was less frequently reported. In the FinnProstate[29] study, HRQOL scores were generally better in the IADT group in terms of activity limitation, physical capacity and sexual functioning. In the Tap 22 study,[26] which included only metastatic patients, HRQOL scores did not differ between groups, although rates of hot flushes and headache were lower in the IADT group. There was a trend towards lower rates of hot flushes in the TULP trial.[23] Improvements in hot flushes and erectile function were also suggested by de Leval et al.[24]

Long term complications of ADT

Sensitive measures of bone health outcomes were not incorporated into available phase III trials. Nonetheless, the trials did report adverse events, and fracture rates did not tend to differ. Retrospective data does support lesser bone mineral density (BMD) declines during off-treatment periods and correlates with testosterone recovery.[30,31] A recently published prospective trial analyzed the BMD declines of 56 patients on IADT without metastatic disease.[32] Patients had DEXA scans at baseline and at the start of on- and off-treatment periods. Testosterone and PSA levels were measured monthly throughout the study period. The findings of this trial demonstrated significant heterogeneity of DEXA findings but supported a decline in spine and hip BMD after the first ADT cycle and an increase in spine BMD after the first off-treatment cycle. Additionally, change in both spine and hip BMD positively correlated with testosterone levels. One post-traumatic fracture was sustained in a patient with normal BMD after a median 5.5 years follow up. This phase II trial was underpowered for the study of BMD and fractures, but does support the hypothesis that IADT may attenuate ADT-related bone loss and perhaps resultant fractures. Because testosterone recovery and off-treatment intervals are greatest when IADT is applied for non-metastatic low risk disease, if ADT is to be employed at all, this beneficial effect on bone health may be particularly significant in these patients. However, IADT may result in an increase in skeletal-related events in metastatic patients should treatment not be resumed early enough. Ultimately, bone health in the ADT population may be more readily improved by basic interventions such as periodic DEXA scans, mitigating aggravating life-style behaviors, calcium and vitamin D supplementation, and treating osteoporotic or osteopenic patients, all of which are largely underutilized by surveyed Canadian practitioners.[33]

Although ADT promotes cardiovascular disease,[11] conflicting evidence exists for its effects on cardiovascular death.[34] The use of GnRH antagonists instead of agonists may have a beneficial impact on 1 year cardiovascular events.[35] High quality data are lacking to support the effect of IADT on cardiovascular health. In adverse event reporting for published phase III trials, cardiovascular events did not significantly differ; but these trials were underpowered for these outcomes and did not describe cardiovascular risk demographics of included patients. In particular, both the SWOG 9346 and PR7 trials did not find differences in cardiovascular events.[21,22] In the SEUG 9901 trial,[20] there were 107/462 (23.2%) cardiovascular deaths in the IADT arm versus 122/456 (26.8%) in the CADT arm, but this difference was not significant. Benefits of IADT on other long term effects of ADT,[11] like mood, cognition, metabolic syndrome, acute kidney injury,[36] anemia, and stroke are also uncertain.

Summary and clinical protocol

Survival-related outcomes for IADT have been compared to CADT in a number of recent phase III trials. Local therapy or active surveillance are the standards of care for patients with M0 prostate cancer,[14] while watchful waiting with deferred ADT is appropriate for select patients with reduced life expectancy. If early primary ADT is to be administered due to higher risk prostate cancer in a patient with a reduced life expectancy, caution is warranted in administering IADT. Higher risk prostate cancer

patients were underrepresented in the SEUG 9901[20] trial which concluded non-inferiority of IADT to CADT in this prostate cancer state. Similarly, for patients with biochemical relapse after radiotherapy, there is no evidence that early ADT in lower risk relapsing patients is beneficial—and higher risk patients were a minority population of the PR7 trial,[21] which found non-inferiority of IADT to CADT in this prostate cancer state. In patients with metastatic disease, CADT remains the standard of care as SWOG 9346[22] was statistically inconclusive, finding neither the non-inferiority of IADT to CADT nor the superiority of CADT to IADT. Although meta-analyses of IADT have been published,[12,13] this approach has limited clinical relevance as it combines results from separate prostate cancer disease states and contaminates the results of very high-quality trials with low-quality trials.

Castration related symptoms including ED, low libido, hot flushes, fatigue, and headaches are improved by IADT during off-treatment periods. This likely relates to improvements in testosterone during off-treatment periods although a placebo effect remains a possible contributor.

If symptom management is unsuccessful, consideration should be given as to whether watchful waiting and deferred ADT is an appropriate option for these patients at this state of his disease—namely the patient receiving primary ADT or ADT for biochemical relapse following local therapy. If some form of ADT is still felt to be necessary, IADT has an indication here as a compromise between uncertain survival outcomes in higher risk patients and improved symptomatology.

Although there are small variations in how IADT is applied amongst phase III trials, the general principles are the same, Figure 2. As illustrated in Figure 2, IADT begins with an induction period of ADT administration. This period may be as short as 3 months (as seen in the SEUG 9901 trial, or as long as 8 months as in the PR7 trial). If, after the induction period, PSA is suppressed adequately (4 ng/mL in SWOG 9346, PR7, and SEUG 9901) then ADT administration may be halted. Prostate specific antigen levels and clinical status are closely followed, with ADT resumed on certain triggers such as symptoms or a PSA rise to 10-20 ng/mL (10 ng/mL in PR7, 20 ng/mL or baseline in SWOG 9346 and 20 ng/mL in SEUG 9901). If PSA is again suppressed to 4 ng/mL or less

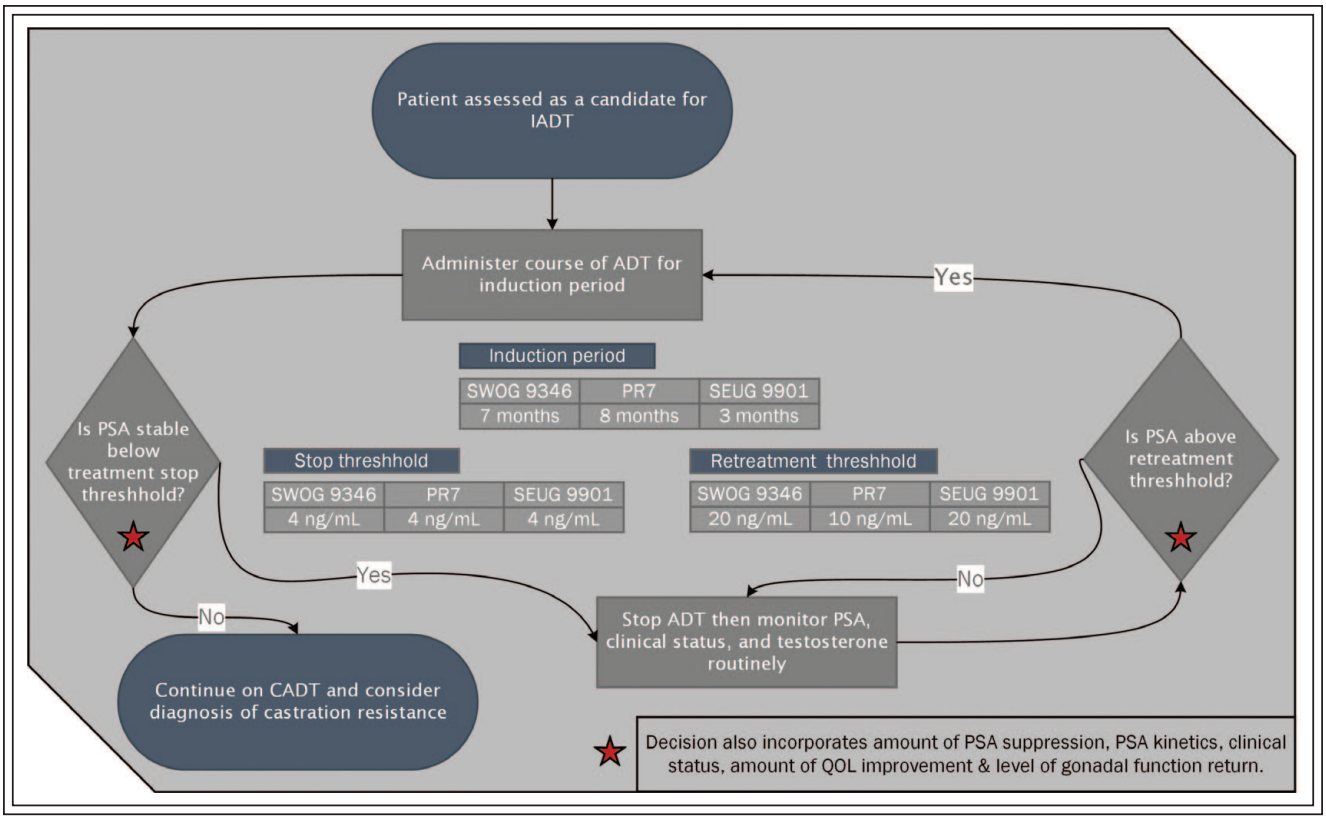

Figure 2. Clinical protocol for intermittent androgen deprivation therapy administration.
ADT = androgen deprivation therapy; IADT = intermittent ADT; CADT = continuous ADT; PSA = prostate-specific antigen. SWOG 9346, PR7 and SEUG 9901 are the three largest phase III trials comparison IADT and CADT.

TABLE 1. **Follow up of non-urologic androgen deprivation therapy complications. Modified from Grossman and Zajac.[37]**

COMPLICATION	RECOMMENDATIONS
Metabolic and cardiovascular complications	**Routinely assess:** • BMI, waist circumference, blood pressure • Screening for anemia, glucose intolerance and dyslipidemia **Manage:** • Lifestyle interventions including smoking cessation, exercise and dietary modification • Medications for control of blood pressure, diabetes and dyslipidemia
Skeletal complications	**Routinely assess:** • Risk factors for osteoporosis • Osteoporosis fracture risk stratification with tools such as FRAX (http://www.shef.ac.uk/FRAX/tool.aspx?country=19) • Assess falls risk • Measure serum calcium, creatinine, vitamin D, liver function and TSH • Measure bone mineral density with DEXA. Thoracolumbar spine x-rays in men with osteopenia (T-score <-1.5) **Manage:** • Lifestyle interventions such as smoking cessation, limiting alcohol intake, and weight-bearing exercises • Supplement calcium (1200 mg elemental calcium) and vitamin D (800 IU) intake • Treat appropriate patients with bisphosphonates or denosumab based on DEXA T-score, estimated osteoporosis fracture risk (FRAX) and history of fragility fracture

DEXA = dual energy x-ray absorptiometry

after another cycle of ADT, ADT may be halted again and the process repeated. Progression occurs when PSA or symptomatology is not suppressed by a full cycle of ADT and these patients should be considered to have CRPC. It is uncertain whether outcomes are different when a LHRH agonist or antagonist are used and whether there is benefit in adding a non-steroidal antiandrogen for combined androgen blockade. The role of LHRH antagonists in IADT are being currently examined in multiple clinical trials.

As with CADT, IADT warrants a proactive approach to ADT-related complications. Cardiovascular, metabolic, and bone complications that are ADT-related are similar to those experienced by the general population and familiar to primary care physicians. Accordingly, prescribers of ADT should ensure that patients are also following up appropriately with their primary care physicians for the diagnosis, treatment, and prevention of these complications. Grossman and Zajac[37] have suggested some ways that ADT patients should be monitored and treated with respect to these complications, Table 1. Knowledge transfer and careful care coordination with primary care physicians is needed to facilitate the comprehensive care required by patients receiving ADT.

Disclosure

The authors have no potential conflict of interest. □

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Secondary hormonal manipulation in castration resistant prostate cancer

Sohaib Al-Asaaed, MD, Eric Winquist, MD
London Health Sciences Centre and Western University, London, Ontario, Canada

AL-ASAAED S, WINQUIST E. Secondary hormonal manipulation in castration resistant prostate cancer. *Can J Urol* 2014;21(Suppl 1):37-41.

Introduction: *Castration resistant prostate cancer (CRPC) is the single common pathway to prostate cancer death. For men with symptomatic metastatic disease, docetaxel chemotherapy remains a standard of care. However, blood prostatic-specific antigen (PSA) testing allows the identification of CRPC before clinical metastases or symptoms occur, providing a long diagnostic lead time in many patients. The use of secondary hormonal manipulations (SHMs) in men not candidates for immediate chemotherapy is reviewed.*
Materials and methods: *PubMed was searched for randomized clinical trials, systematic reviews or clinical practice guidelines addressing SHMs in CRPC.*
Results: *A recent systematic review and practice guideline was identified, and used as the evidence base for this review along with reports from randomized trials over the past year.*
Conclusions: *The goals of therapy with SHMs should be discussed with patients and their preferences considered. In men without clinical evidence of metastases, gonadal androgen suppression should be maintained and generally patients should be observed. There is no clear evidence that SHMs are of benefit in these patients. Abiraterone plus prednisone is of proven benefit in men with CRPC metastases who are without significant symptoms prior to chemotherapy. Based on emerging data, enzalutamide may be of similar benefit. Use of other SHMs should be based on patient preference and consideration of possible adverse effects; with the exception of low dose prednisone, there is little evidence of benefit supporting their use. For patients accepting these uncertainties, a trial of nonsteroidal antiandrogen may be considered as an adjunct to observation, followed by low dose corticosteroid with immediate or delayed addition of abiraterone (in men with metastases) as a reasonable next step.*

Key Words: enzalutamide, hormone-dependent, prostatic neoplasms, castration resistant, abiraterone, drug therapy

Introduction

Men with castration resistant prostate cancer (CRPC) and clinically significant metastatic disease (rapid disease progression, persistent and worsening symptoms, or visceral metastases) should be assessed for palliative chemotherapy, which remains a standard of care, with docetaxel currently the agent of choice.[1,2] The diagnosis of CRPC is made when there is evidence of disease progression (biochemically, radiographically and/or symptomatically) in the presence of castrate levels of testosterone (< 50 ng/mL or < 1.7 nmol/L).[3]

Address correspondence to Dr. Eric Winquist, London Health Sciences Centre, 790 Commissioners Road East, London, ON N6A 4L6 Canada

There is no clear temporal relationship between the onset of metastatic disease and the development of CRPC, though biochemical recurrence characterized by an increasing blood prostatic-specific antigen (PSA) level alone is usually the first evidence of CRPC.[4-6] Thus the emergence of CRPC is often characterized by a lengthy "lead time" during which men without clinical evidence of metastases are observed to have rising PSA levels.

CRPC is a heterogeneous disease and consists of a spectrum of clinical states. When considering use of secondary hormonal manipulations (SHMs) it is useful to consider patients in three clinically-defined groups: 1) those with biochemical recurrence alone without any evidence of metastases, 2) those with evidence of metastatic disease and minimal or no symptoms,

and 3) those with metastases and significant cancer symptoms (who are usually candidates for palliative chemotherapy or potentially radium 223).[7] As CRPC is incurable the focus of therapy should be on optimizing a patient's quality and quantity of life, and judicious and timely use of suitable agents available in this "pre-chemotherapy" phase is important, and is the topic of this review. These goals of therapy should be discussed with the patient, and an understanding of the patient's values is essential in creating a strategy for how aggressively or conservatively they wish to pursue active therapeutics. Counseling patients about the interpretation of PSA values which may fluctuate and be misleading in CRPC, and emphasizing the goal of optimal quality of life is recommended.

Prior to considering SHMs, the question of maintaining castrative therapy may be raised. A multivariate analysis by Taylor et al[8] identified prognostic factors associated with worse survival in men with CRPC including: poor performance status (non-ambulatory), soft-tissue visceral involvement, age > 65 years-old, recent weight loss of > 5%, and discontinuation of endocrine therapy. Inadequate gonadal androgen suppression (androgen deprivation therapy—ADT) has also been associated with resistance to anticancer treatment, presumably due to anti-apoptotic effects of androgens in prostate cancer cells.[9] There is some evidence that intermittent ADT may improve side effects and result in cost savings in CRPC.[10] However, it remains the current standard of care to maintain all men with CRPC on continuous gonadal androgen suppression with luteinizing hormone releasing hormone (LHRH) agonist or antagonist if they have not been treated with bilateral orchidectomy, although these agents may be discontinued as patients near their end-of-life.[11,12]

Why use secondary hormonal manipulation in the era of newer agents?

New hormonal agents have emerged over the past 5 years and been approved for the treatment of CRPC, and are currently being studied earlier in the natural history of CRPC. This raises questions about the optimal use of these agents, and has prompted the development of clinical practice guidelines. The American Urological Association has recently published a guideline for CRPC, and the systematic review supporting this guideline provides the evidence base for this review of SHMs.[13] Men presenting with or who develop clinically significant metastatic CRPC during SHMs should be assessed for palliative chemotherapy, and may need to proceed to chemotherapy without further SHMs. In men without evidence of CRPC metastases there is no evidence available from randomized controlled trials that SHMs ultimately improve important disease outcomes, and so the risk-benefit of interventions should be considered from the view that they may merely manipulate PSA levels without other proven benefits.[13] The natural history of CRPC without metastases was studied in men enrolled in the placebo group of an aborted trial of zoledronic acid versus placebo reported by Smith et al.[14] A third of patients developed bone metastases at 2 years. Median bone metastasis free survival was 30 months, though time to first bone metastasis and overall survival were not reached. An elevated baseline PSA (> 10 ng/mL) and rapid PSA velocity (< 6 months) independently predicted shorter time to bone metastasis, metastasis free survival, and overall survival. Careful observation or offering clinical trial participation to CRPC patients without metastases may be considered reasonable standards of care.[13,15] Currently there is no high level evidence supporting the use of either SHMs or newer agents such as abiraterone or enzalutamide in CRPC patients without metastases, and clinical trials studying these are underway. In men with relatively stable asymptomatic or minimally symptomatic non-visceral metastatic disease, the use of abiraterone-prednisone may also be considered.[16] Men with bone metastases should also be considered for bone protective therapy as prophylaxis for skeletal-related events.[17]

Agents and applications

There is not sufficient data and no clinical consensus supporting an optimal sequencing of SHMs in men with early CRPC, so practical considerations including patient preferences and drug availability usually dictate treatment options. Switch to an alternate SHM should be considered if toxicity or evidence of disease progression occurs, but otherwise observation on treatment is usually continued without interruption. As mentioned ADT should be continued despite evidence of CRPC and serum testosterone level should be confirmed within the castrate range; if it is not, then a switch of LHRH agonist/antagonist or bilateral orchidectomy should be considered. A therapeutic trial of a non-steroidal antiandrogen (NSAA) is routine when biochemical evidence of CRPC is first observed on ADT monotherapy, but there is no clear evidence that this improves quality or quantity of life.[13] Generically available NSAAs include bicalutamide, flutamide and nilutamide. Although no studies have investigated optimal dosing, bicalutamide 50 mg PO

daily is often used as it is convenient and appears to have the best side effect profile in this class.[18]

The response rate to first generation antiandrogens is expected to be approximately 15%.[19,20] Switching to other NSAA such as flutamide or nilutamide has been proposed but is associated with a low and idiosyncratic response rate and the potential for exposing patients to a greater risk of adverse effects.[21] Two new agents, enzalutamide and ARN-509, are very potent antiandrogens referred to as "androgen receptor signaling inhibitors".[3,22] They not only potently bind to the androgen receptor, but also interfere with its translocation into the nucleus and with gene transcription. Both are currently under study in clinical trials as SHM in men with CRPC with and without metastases.

Some SHM agents of historical interest include estrogens (eg. diethylstilbestrol); the steroidal antiandrogen, cyproterone acetate; and the steroidal progestational drug, megestrol acetate. Diethylstilbestrol (a synthetic non-steroidal estrogen) may induce responses in CRPC and does not induce tumor flare or vasomotor hot flashes but is associated with high cardiovascular and thromboembolic complication rates and has been largely abandoned.[23,24] Evidence for the value of other estrogen formulations in CRPC is sparse. Megestrol acetate was investigated by Dawson et al[25] as a SHM in men with CRPC but demonstrated a low response rate of 14% (objective and PSA decline rates) and no dose response with higher doses was observed. Cyproterone has also been associated with PSA response in men with CRPC; however, both megestrol and cyproterone have been associated with an increased risk of cardiovascular side effects, and have generally been abandoned in practice.[26]

The phenomenon of biochemical and clinical response to discontinuation of antiandrogen ("antiandrogen withdrawal"--AAWD) has also been observed with a number of other SHM agents.[27,28] This is postulated to be due to a change in androgen receptor function in response to chronic antiandrogen therapy, with paradoxical stimulation of the androgen receptor due to receptor mutation.[29] The median antiandrogen withdrawal response duration is approximately 4-6 months.[30] If clinically appropriate for the patient, assessment for antiandrogen withdrawal response is generally recommended particularly in patients treated with NSAA for a long duration. Patients who undergo AAWD from bicalutamide should be observed for up to 8 weeks owing to this drug's longer half-life.

Currently after NSAA and AAWD, a next reasonable step is a trial of low corticosteroid with or without ketoconazole or abiraterone. Interestingly, prednisone 5 mg twice daily was associated with a PSA response rate of 24%, median PSA progression-free survival of 5.6 months, and objective response rate of 16% in a recently reported blinded placebo-controlled trial.[16] Abiraterone acetate may be considered at this juncture in suitable patients with metastatic disease, but is expensive, may not be funded or available for this indication in all jurisdictions, and is associated with incremental mineralocorticoid side effects.[16] In view of this, initiation of low dose prednisone alone with the addition of abiraterone at progression in these patients is also quite a reasonable strategy.

Historically, bilateral adrenalectomy to eliminate adrenal androgens as a method of SHM was superseded by use of aminoglutethemide and the imidazole antifungal agent, ketoconazole. The activity of ketoconazole in prostate cancer is thought to be due to inhibition of the cytochrome p450 enzymes CYP3A4 and CYP17 in the gonad and adrenal gland, with possible additional effects due to androgen receptor antagonism.[31] In a randomized trial of men with CRPC, 27% of those receiving ketoconazole 400 mg PO tid, hydrocortisone and AAWD had a PSA response, and the objective response rate was 20%.[32] Ketoconazole 200 mg PO tid was noted to elicit a comparable PSA response rate in a single arm study.[33] However, PSA response to ketoconazole should be interpreted with caution as it is confounded by use of low dose corticosteroids; low dose prednisone had similar PSA and objective response rates in the control arm of a recent randomized trial.[16] Ketoconazole may be cautiously considered as an alternative in patients who cannot afford or access abiraterone; however, ketoconazole has been banned for systemic use in the European Union due to serious hepatic toxicity, and pretreatment with ketoconazole may reduce the efficacy of abiraterone.[34,35]

Despite its limitations, ketoconazole provided inspiration for pursuing the inhibition of steroidogenesis as an additional therapeutic strategy in CRPC. At the forefront of this approach is abiraterone acetate which potently inhibits CYP17 mediated steroidogenesis in the testicle, adrenal, and in intra- and peritumoral tissues resulting in undetectable androgen levels.[36] ADT should be continued with abiraterone, and low dose prednisone is given to suppress ACTH production and mitigate the mineralocorticoid adverse effects due to accumulated steroid precursors due to CYP17 blockade. Ryan et al[16] compared abiraterone acetate 1000 mg PO daily plus prednisone 10 mg PO daily to placebo plus prednisone in mainly asymptomatic chemotherapy-naive men with metastatic CRPC. A significant improvement in

radiographic progression-free survival was observed with abiraterone (16.5 versus 8.3 months; hazard ratio: 0.53 [95% confidence interval, 0.45-0.62], $p < 0.001$), and this was concordant with improvements in multiple other clinically relevant secondary endpoints including median times to opiate use for cancer-related pain, initiation of cytotoxic chemotherapy, decline in ECOG performance score by ≥ 1 point, and PSA progression. There was a trend to improvement in overall survival (hazard ratio: 0.75) that was not statistically proven. The toxicity profile associated with abiraterone appeared very acceptable, with a low rate of grade 3 or 4 adverse events and similar rates of cardiac disorders. Mainly grade 1 or 2 adverse effects due to mineralocorticoid-related toxic effects were more common in the abiraterone-prednisone group than in the prednisone-alone group, including hypertension (22% versus 13%), hypokalemia (17% versus 13%), and fluid retention or edema (28% versus 24%). Abiraterone has been approved by the United States Food and Drug Aadministration and Health Canada, for use in men with metastatic CRPC before or after progression on docetaxel chemotherapy. A recent announcement of results from a large randomized trial indicated that enzalutamide may have similar benefits to abiraterone in this population, and presentation and publication of these data is awaited.[37]

Conclusions

SHMs in men with CRPC should consider the presence or absence of metastases, symptoms, and visceral disease; as well as patient preferences and available therapies. Maintenance of a castrate state is essential, and trials of SHMs may be considered if clinically reasonable but should not delay use of palliative chemotherapy if need becomes evident. For men without metastases, observation or clinical trial participation should be considered the standard of care. For men with metastases and minimal or no symptoms, abiraterone plus prednisone has clearly established benefit in quality and probably quantity or life given prior to chemotherapy compared to prednisone alone. Enzalutamide may provide similar benefits in this setting; high quality data is merging at the time of this report. The optimal choice or sequence of these two drugs is uncertain and will fuel future debate. The data supporting the use of other SHMs is very limited, and based more in convention than data. Taking a view, mindful of toxicity, that there may be value of these as an addition to a strategy of observation; serial therapy starting with a NSAA, with switch to low dose corticosteroid (with or without abiraterone acetate in men with metastases) in the absence of AAWD response is a reasonable approach. For other SHMs the evidence of benefit is sparse and their use cannot be recommended.

Disclosure

The authors have no potential conflict of interest. □

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Imaging approaches with advanced prostate cancer: techniques and timing

David Leung, MD, Saravanan Krishnamoorthy, MD, Lawrence Schwartz, MD, Chaitanya Divgi, MD

Department of Radiology, Columbia University Medical Center, New York, New York, USA

LEUNG D, KRISHNAMOORTHY S, SCHWARTZ L, DIVGI C. Imaging approaches with advanced prostate cancer: techniques and timing. *Can J Urol* 2014;21(Suppl 1):42-47.

Introduction: *In conjunction with biomarkers, imaging is an important component of the diagnostic work up and subsequent management of men with prostate cancer.*

Materials and methods: *The relevant literature was retrieved from a search of MEDLINE with appropriate key words.*

Results: *Osseous metastases develop in close to 90% of patients with metastatic prostate cancer, thus making bone scans (single photon, using Tc-99m labeled phosphonates) the mainstay of imaging in advanced prostate cancer. Bone scans are limited by their lack of specificity and an unclear relationship between bone scan changes and disease progression or response to therapy.*

In addition to Tc-99m bone scans, other technologies that accurately identify of sites of active disease would considerably aid castration resistant prostate cancer (CRPC) management. Accordingly, metabolic imaging, cell surface receptor targeting, and magnetic resonance imaging (MRI) are being studied for their role in evaluating metastatic disease. Due to the increasing availability of advanced imaging modalities, the optimal modality and appropriate clinical time point for its use remains unclear.

Conclusion: *A number of imaging modalities are currently or imminently available for use in advanced prostate cancer. Future research will focus on the appropriate incorporation of these modalities in prostate cancer management.*

Key Words: castration resistant prostate cancer, CRPC, molecular imaging, FDG, NaF, PET, MRI, androgen receptors

Introduction

The focus of this review is imaging in advanced prostate cancer. Imaging to identify cancer in the intact prostate gland is not currently a part of standard of care, and is achieved usually by magnetic resonance imaging (MRI).

Address correspondence to Dr. Chaitanya Divgi, Department of Radiology, Columbia University Medical Center, 722 West 168th Street, New York, NY 10032 USA

Rising PSA after definitive primary therapy

Typically, after definitive surgical or radiation therapy for primary prostate cancer, patients are followed with serial prostate-specific antigen (PSA). A rapidly rising PSA has been found to portend a poor prognosis,[2] and the PSA doubling time has been found to be predictive of positive imaging studies, typically bone scans.[3]

Bone scans, most frequently carried out using single photon scintigraphic imaging of a bone-seeking radiopharmaceutical –technetium-99m linked to a

TABLE 1. **Main differences between two imaging modalities**

	Bone scan with Tc-99m phosphonate	**Bone PET scan with F-18 sodium fluoride (NaF)**
Radionuclide	Tc-99m	Fluorine-18
Half-life	6 hours	2 hours
Radiation dose	5 milli Sievert	2.5 milli Sievert
Time for scan	Typically 30 minutes, starting 2-3 hours after injection	Typically 15 minutes, starting 30 minutes after injection
Cost	Approved imaging study	Carried out under NOPR, for Medicare patients; costs variable, typically more expensive than single photon bone scan
Accuracy	High	More sensitive and specific

suitable phosphonate (MDP most commonly) – remain the mainstay of imaging metastatic prostate cancer. Bone scans are typically carried out to identify metastatic disease. Bone is the site of metastases in 90% of patients with metastatic prostate cancer.[4] The Bone Scan Index, an estimate of metastatic bone,[5] is a metric that has shown promise as a pharmacodynamic biomarker[6] and these measurements have been automated with some success,[7] though the overall technique remains rather cumbersome to use. Sodium fluoride-18 ([18F]NaF) PET, Figure 1, is generally considered more sensitive than bone scintigraphy, though comprehensive prospective comparisons are lacking and are now being addressed in a National Oncologic PET Registry (NOPR) trial.[8] Several small studies have demonstrated the greater accuracy of NaF PET in the detection of bone metastases.[9,10] In particular, NaF has a higher specificity than conventional bone scintigraphy, leading to its higher accuracy. Table 1 illustrates the main differences between these two imaging modalities.

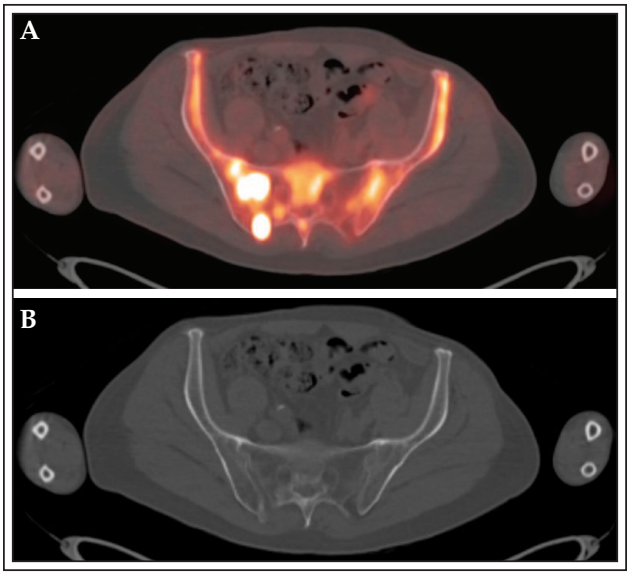

Figure 1. Bone PET with fluorine-18 (F-18) sodium fluoride in a patient with CRPC. The lesions seen on the PET/CT are not always evident on the CT alone. **A.** Fused PET/CT. **B.** CT bone window.

Computed tomography (CT) is carried out to assess extra-osseous tumor involvement, though bone lesions may also be identified as blastic or mixed lesions. Soft tissue disease is usually nodal, identified using CT scans, and does not contribute much to disease morbidity.[11]

Identification of disease outside the prostate bed by one or more of the imaging modalities described above leads to systemic therapy. Such therapy is followed with serial bone scans, though these are useful primarily to identify progression of disease. The frequency with which bone scans are carried out is highly variable, based on reimbursement as well as on patient characteristics – elderly patients with underlying bone and joint disease may have confounding results, limiting the utility of the bone scans; usually, bone scans are carried out only when PSA changes are such that treating physicians need objective evidence of osseous metastases.

Imaging of castration resistant prostate cancer

Metabolic imaging

The mainstay of imaging prostate cancer remains the bone scan, either using scintigraphy or PET/CT. However, several molecular agents are being studied, particularly with PET/CT.

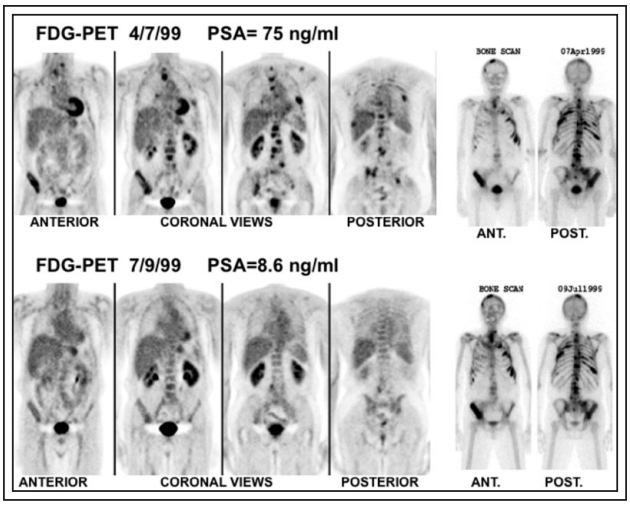

Figure 2. FDG PET and bone scans in a patient with CRPC receiving chemotherapy. Upper panel, baseline images. Lower panel, after 4 cycles of taxane therapy. Note that the lesions seen on FDG PET at baseline have largely disappeared, while conventional bone scintigraphy appears unchanged.

Metabolic imaging with fluorine-18 fludeoxyglucose (FDG) has been studied in prostate cancer, and has been demonstrated to target metastases, particularly in castration resistant prostate cancer (CRPC).[12] Moreover, at least one study has demonstrated that improvement on FDG PET/CT being concordant with PSA decreases.[13] FDG-avid cancers are probably more likely to be castration resistant, and thus FDG may be useful both for the identification of a castration resistant phenotype as well as a pharmacodynamic biomarker, Figure 2.

PET/CT with radiolabeled choline has been found to be extremely useful in the identification of prostate cancer,[14-16] in the treatment-naïve as well as the castration resistant patient, with no evidence currently of differential phenotype-specific metabolism. Choline is essential to the production of phosphotidyl choline necessary for cell membrane integrity; cancer cell membranes have elevated phosphatidyl choline levels, resulting in increased amounts of exogenous (and perhaps endogenous, detected by MRI) amounts of trapped choline in tumor cell membranes.[14] Initial studies were carried out with carbon-11 labeled choline. An Italian study[15] found that while radiolabeled choline was useful in identification of bone metastases, conventional bone scintigraphy had higher overall accuracy; positron-labeled choline PET/CT therefore is no substitute for bone scintigraphy at this time. The U.S. Food and Drug Administration (FDA) recently approved a New Drug Application filed by the Mayo Clinic for the production and use of 11 C-choline for PET imaging.[16] It is expected that the agent will have high accuracy in identification of recurrent disease after primary definitive therapy.

The 20-minute half-life of carbon-11 precludes centralized production and distribution of the radiopharmaceutical. Fluorine-18 is a positron-emitting nuclide used for PET, primarily because of its favorable imaging characteristics and its nearly 2-hour half-life. Fluorocholine has therefore been studied by numerous groups and has been shown to have utility in the detection of recurrent/metastatic prostate cancer.[17] Fluorocholine has been shown to have better accuracy than NaF bone PET in identification of bone metastases in CRPC.[18]

Another metabolic agent that has been studied in prostate cancer has been radiolabeled acetate, a fatty acid. Most studies have reported the use of carbon-11 labeled acetate,[19,20] and also shown that [11C]-acetate may have better accuracy both in detection as well as in response determination of prostate cancer metastases.[21-23]

A recent review[24] provides a comprehensive overview of the utilization of these tracers in prostate cancer, and highlights their characteristics.

Imaging of cell surface receptors

Most prostate cancers are abundant in androgen receptors (AR) at the outset. These receptors may therefore be imaged using a positron-labeled androgen.[25] These promising early results by Katzenellenbogen et al led to the clinical exploration of [18F]-labeled dihydroxytestosterone, or FDHT, in the assessment of AR expression in CRPC.[26,27] These studies have not been developed systematically to assess the utility of this novel hormone receptor imaging agent in CRPC, they have served to illustrate the continuum between AR expression and loss, and its relationship to the "castration resistant" state, in the progression of this disease.

Another receptor that is being increasingly studied in prostate cancer is the prostate specific membrane antigen (PSMA). This transmembrane receptor was first imaged with a single photon emitter, indium-111 linked via a chelate (pendetide) to a murine monoclonal antibody, capromab. Indium-111 labeled capromab pendetide was approved by the FDA for the identification of recurrent prostate cancer after primary definitive therapy.[28] However, its relatively low accuracy has restricted its use to those instances where MR is equivocal for prostate bed recurrence, and imaging with this agent is fraught with technical challenges; it is consequently not utilized in most centers.[29] It is generally believed that its low accuracy is due partly to the antibody targeting an intracellular domain of the PSMA molecule.[30]

Bander et al developed an antibody, J591, that targets the extracellular domain, and this antibody, while developed initially as a therapeutic, has shown promise as an imaging agent.[31] PSMA has several advantages as a target, since its over-expression is directly proportional to the de-differentiation of the prostate cell – it is thus expressed in greater quantities on the castration resistant than in the -sensitive cancer cell.[32] While initial imaging studies were carried out with indium-111, with the inherent limitations of single photon scintigraphy, recent reports have suggested that accuracy of detection may improve with PET using zirconium-89 labeled anti-PSMA antibody.[33]

Small molecules that target PSMA are also being evaluated. They have shown utility in detection, and an advantage compared to the macromolecular antibody is that clearance is rapid and thus imaging can be carried out the same day with more widely available positron emitters.[34,35]

Magnetic resonance imaging (MRI)

The lack of widespread utilization of whole body MRI has limited the number of studies that have evaluated the role of this imaging modality in CRPC, Figure 3. More frequent has been assessment of individual lesions, using functional parameters obtained by advanced MRI techniques including dynamic contrast enhanced or DCE MRI, and diffusion-weighted or DW-MRI. Both may have a role as pharmacodynamic biomarkers.

Bone metastases have been evaluated using both these methods.[36] DCE MRI has been used to identify marrow infiltration by prostate cancer; the abnormal marrow has higher values of a semi-quantitative parameter that measures flow.[37] Diffusion weighted imaging has been used both to characterize metastases[38-40] and as a predictive[41] and pharmacodynamic[42,43] biomarker.

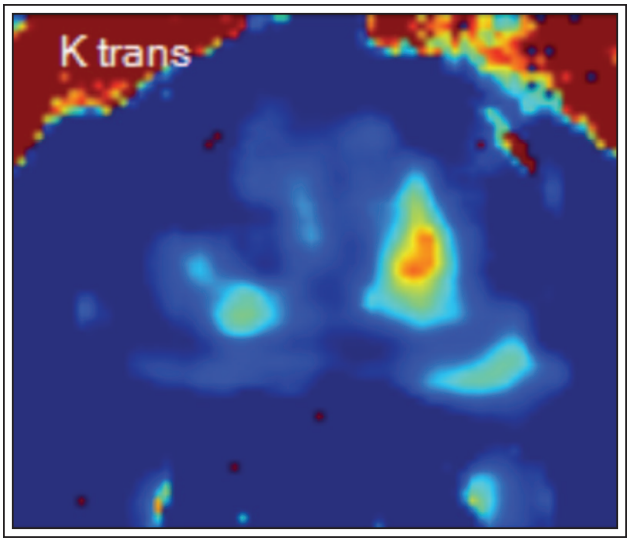

Figure 3. Parametric image of K_{trans}, a measure of vascularity in a prostate. The red area represents a high Gleason prostate cancer.

Hyperpolarized nuclei have properties that permit MRI with extremely high sensitivity, and carbon-13 is a hyperpolarized nucleus that has been successfully studied in humans labeled to pyruvate. Hyperpolarized C-13 labeled pyruvate has shown promising results in imaging prostate cancer,[44] and studies are underway to address its utility.

Timing

When should imaging be carried out? The only consensus document for CRPC in this regard is unclear.[45] Bone scans should be repeated preferably only after the end of a course of therapy. A bone scan that shows progression may represent a flare response, and thus unless there are multiple new lesions (usually two or more) that persist in a follow up scan obtained at least 6 weeks later, the scan cannot be considered to be progression. Bone scans moreover rarely demonstrate a reduction in uptake intensity or lesion number following successful therapy, and hence cannot be used to reliably document response.

Metabolic and receptor imaging, particularly with PET and MRI, may have an important role in assessment of therapy response. These techniques have been shown to be extremely promising, but there are few studies that have systematically evaluated these novel methods, and the cost constraints of most modern imaging techniques preclude their widespread utilization especially given the low cost of currently available biomarkers for estimation of extent of disease.

Biochemical change is however not rapid. The ultimate value of the novel imaging biomarkers may therefore be not in their utility as pharmacodynamic biomarkers, but as predictive or prognostic of aggressive disease, or indeed as EARLY pharmacodynamic biomarkers. This last may be particularly useful as costly and unnecessary therapy may well be avoided by an early indication of the futility of a particular therapy.

Conclusion

Imaging castration resistant prostate cancer is still in its infancy. In particular, bone metastases remain non-measurable, evaluated by bone scans that are sensitive but not specific. Novel imaging techniques that assess extent of disease in the whole body are limited to molecular imaging, particularly PET/CT. MRI can carry out assessment of individual lesions, with predictive and

pharmacodynamic potential. The development of an accurate imaging biomarker is fraught with difficulties, both economic and logistic. There is increasing necessity, however, for the development of imaging tools that can characterize the cancer phenotype, since imaging permits assessment of lesions throughout the body. Proper application and development of the range of available imaging modalities and techniques will lead to more rapid identification and appropriate modification of targeted therapies in this prevalent disease with a grim prognosis.

Disclosure

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Practical guide to immunotherapy in castration resistant prostate cancer: the use of sipuleucel-T immunotherapy

Leonard G. Gomella, MD, Francisco Gelpi-Hammerschmidt, MD, Chandan Kundavram, MD

Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

GOMELLA LG, GELPI-HAMMERSCHMIDT F, KUNDAVRAM C. Practical guide to immunotherapy in castration resistant prostate cancer: the use of sipuleucel-T immunotherapy. *Can J Urol* 2014;21 (Suppl 1):48-56.

Introduction: *New treatment options for metastatic castration resistant prostate cancer (mCRPC) have become available over the last few years should primary treatments and androgen deprivation therapies fail. While historically not considered to be amenable to immunotherapy, the treatment of advanced prostate cancer using this approach is an area of intense interest and now clinical application.*

Materials and methods: *Recent literature on castration resistant prostate cancer management with a focus on immunotherapeutic strategies was reviewed. Mechanisms of action involving the immunologic treatment of cancer were identified. Agents in clinical trials with near term application in prostate cancer were also identified.*

Results: *Numerous immunotherapeutic agents for mCRPC are in current clinical trials. The autologous, active cellular immunotherapy, sipuleucel-T, which utilizes a patient's own antigen-presenting cells, is the only Food and Drug Administration (FDA) approved agent. It provides a 4.1 month survival advantage. Other investigational agents in this area include GVAX, a whole cell irradiated vaccine, and a vaccinia-PSA-TRICOM pox virus based approach, all in phase III trials. Immune-checkpoint inhibitors that enhance T-cell activity and potentiate antitumor effects are also promising.*

Conclusions: *A first in class novel treatment modality, sipuleucel-T, is available in the United States for mCRPC. Other immunotherapies are in development and may be available in the near future. Understanding the detailed patient evaluation, initiation and administration of sipuleucel-T as described in this paper, will allow this novel cancer immunotherapy to be better understood and potentially benefit a larger group of appropriately selected patients.*

Key Words: castration resistant prostate cancer, immunotherapy, sipuleucel-T

Introduction

Prostate cancer is the most common non-cutaneous male cancer and comprises approximately 29% of all newly diagnosed cancer cases in men. While the mortality rate has significantly declined since 1994, arguably due to the introduction of routine prostate-specific antigen (PSA) for early detection and improved therapies of localized disease, at least 29480 prostate cancer related deaths are anticipated in 2014 in the United States.[1] The greatest opportunity for curing prostate cancer occurs when a patient presents with early stage localized disease. Unfortunately, 10%-20% of prostate cancer patients present with metastatic disease, and up to one-third of patients who present at an earlier stage will have disease recurrence despite surgical or radiotherapeutic treatment.[2] In over 80% of men with metastatic disease, primary androgen ablation leads to initial clinical improvement and reduction of serum PSA levels. However, almost all advanced metastatic cancers initially treated with androgen ablation will develop into castration resistant prostate cancer (CRPC), the major cause of morbidity and mortality death in these men.

A significant number of medications have been recently approved for the treatment of CRPC.[3] From 2004 until 2010 only docetaxel was approved for "androgen independent (hormone refractory) metastatic prostate cancer", now referred to as

Address correspondence to Dr. Leonard G. Gomella, Department of Urology, Kimmel Cancer Center, Thomas Jefferson University, 1025 Walnut Street, Room 1102, Philadelphia, PA 19107 USA

metastatic CRPC (mCRPC). Historically, chemotherapy using docetaxel plus prednisone was the only therapy to demonstrate a survival advantage in advanced prostate cancer, making it the "gold standard therapy" in this disease state.

The first of these new drugs approved for mCRPC was an autologous immunotherapy, sipuleucel-T.[4] Since that 2010 approval, there have been other agents with differing modes of action that have demonstrated increased survival in the setting of mCRPC. These include the hormonal agents, abiraterone acetate and enzalutamide, the chemotherapeutic agent cabazitaxel, and bone targeting agents such as the radioactive radium 223 dichloride.[3] These are reviewed in detail elsewhere in this *Canadian Journal of Urology* supplement. This article will focus on immunotherapy in the management of mCRPC.

Principles of cancer immunotherapy

Cancer is considered an immunosuppressive state that requires an intervention to boost adaptive immunity, including the antigen-specific defense mechanism. One of the key characteristics of cancer pathogenesis is the ability of the tumor cell to avoid immune destruction.[5] Mounting evidence has shown that a patient's immune system can be successfully trained to seek out and attack cancer cells by exploiting subtle differences between normal and cancer cells for use as immune recognition targets.[6] Immunotherapeutic approaches to cancer are varied and can be broadly divided into two categories—passive or active.

Passive immunotherapy typically requires direct delivery of cytokines, antibodies, and/or cells of the immune system. Notable success has been achieved in other tumors with exogenously supplied monoclonal antibodies, such as bevacizumab (specific for VEGF), and trastuzumab (specific for HER2/neu) and others which target antigens over-expressed on the surface of solid tumors with anti-tumor efficacy and less toxicity than most chemotherapies.[7] Unconjugated monoclonal antibodies as monotherapy have little or no activity on their own, and agents such as bevicuzimab and trastzumab work best in combination. There also may be the development of antibody dependent cytotoxicty with these agents. PSMA antibodies conjugated to other agents are also under investigation as an immunotherapeutic strategy. Nevertheless, the passive immunotherapeutics which target tumor antigens must be chronically administered and are not self-renewing nor do they appear to provide a sustainable anti-tumor response. Urologic examples include the use of alpha-interferon and IL-2 in the management of renal cell carcinoma.

In contrast, active immunotherapy often referred to as "vaccine therapy" is designed to elicit a host immune response that specifically targets the tumor cell through a T-cell response cascade. Active immunotherapy requires the target antigen to be processed in a manner capable of inducing an immune response that generates anti-tumor activity. T-cells do not respond to soluble or naked protein antigens but rather require peptide fragments from the antigen to be "presented" to them on the surface of antigen-presenting cells (APCs) via human leukocyte antigen (HLA) molecules. Dendritic cells, monocytes, macrophages, and Langerhan cells are all APC that possess the requisite machinery for processing internalized intact protein into peptide fragments which can then stimulate a specific tumor response with memory capabilities.

While a variety of cells can function as APCs, the pivotal steps in the induction of all active T-cell immune responses include the uptake and processing of APCs with antigen and activating the APC to express co-stimulatory molecules and induce cytokine production. APCs are present in substantial quantities in the peripheral blood, and various specialized immune compartments in the body and are the only cells endowed with the ability to stimulate naïve CD4+ T lymphocytes, which can initiate both cellular and humoral immune responses. While the main function of APCs is to internalize and/or process antigen and present antigenic peptides via HLA class I and class II molecules, they also express additional co-stimulatory molecules required for maximal T-cell stimulation. Some of these additional molecules include molecules CD80, CD86, or CD40, as well as intracellular adhesion molecules such as CD54, which are typically upregulated following activation of the APC and serve as marker of APC activation. These co-stimulatory and adhesion molecules signaling events result in T-cell proliferation and cytokine production. Ultimately, the tumor cells are killed through an apoptotic mechanism.[8,9] A common urologic example of active immunotherapy is the use of intravesical BCG for bladder cancer, recognizing that the definitive BCG mechanism of action is unclear.

A newer approach to immunotherapy involves interfering with the immune system's autoregulatory mechanisms, thereby enhancing T-cell activity and potentiating antitumor effects using antibodies targeting immunological checkpoint regulators such as CTLA-4 and PDL-1 that downregulate the immune response pathways.[10]

Prostate cancer as a target for immunotherapy

Training the host immune system to reject its own developing tumor has been a long unrealized dream. A variety of strategies were attempted in the past to stimulate an immune response in the prostate but none proved successful.[11] Based on advances in our understanding of the immune response, prostate cancer has emerged as a good target for exploring immunotherapy for a number of reasons. Mounting evidence suggests that the prostate is predisposed to inflammation, possibly owing to autoimmunity or infection, thus, the host is capable of mounting an immune response against prostate tissue.[12,13] That prostate cancer may be in fact caused by chronic inflammatory mediators adds further to the potential of immunologic therapy of the disease. The slow growth pattern of early prostate cancer also allows time to develop an immune response. Further, the prostate is a highly differentiated, gender-specific organ and prostate adenocarcinoma offers a variety of suitable antigen targets for cancer immunotherapy.[14] Many genes within the prostate are transcriptionally regulated by the androgen receptor and show highly regulated expression mostly restricted to the prostate gland or prostate cancer tissue. Included among such expressed genes are PSA, prostatic acid phosphatase (PAP), prostate-specific membrane antigen (PSMA), and prostate stem-cell antigen (PSCA).

Current leading immunotherapy strategies in prostate cancer

There are a number of investigational strategies under development for the immunotherapy of prostate and other cancers and are beyond the scope of this article. In addition to the approved autologous cellular immunotherapy sipuleucel-T, there are several viable prostate cancer immunotherapy agents that are in late stage clinical trials and have been recently reviewed by Madan and associates.[15]

Therapeutic prostate cancer vaccines

Therapeutic cancer vaccines stimulate immune cells that ultimately target tumor antigens and destroy cancer cells and the toxicity of these approaches appears minimal.

Sipuleucel-T is an example of and ex-vivo processed vaccine for mCRPC. While there are significant up front cost and logistic considerations with this approach, it appears to result in an optimal immune activation and the clinical application of this agent is presented in detail later in this article.

Vector-based vaccines deliver an immune stimulatory message in-vivo to immune cells. One such vaccine, PSA-TRICOM, is currently in phase III testing in mCRPC.[15] PSA-TRICOM consists of two poxviruses administered sequentially without the need for ex-vivo cellular processing. The poxviruses serve as vehicles to transport targeting information to the immune system and trigger an antitumor response. In addition the large poxvirus genome makes them well suited for the insertion of the genes for PSA and 3 T-cell costimulatory molecules that enhance the response.[16] Vaccinia (used in rV-PSA-TRICOM) has a well-established track record of safety in humans as it was used for the successful eradication of smallpox when used as a vaccine. Vaccinia virus has also been administered intravesically in preliminary studies to treat BCG refractory bladder cancer with no significant toxicity.[17] Fowlpox (rF-PSA-TRICOM) serves as the second virus used in this prostate cancer therapeutic combination and is considered safe as it does not replicate in humans.

A non-patient specific allogeneic cellular immunotherapy or whole-cell vaccine approach has been used. GVAX is comprised of two prostate carcinoma cell lines, PC-3 and LNCaP, genetically modified to secrete GM-CSF and radiated before injection. This approach provides multiple potential targets for the immune system. Phase III trials have been disappointing and additional work is needed to optimize this approach.[18]

Immune-checkpoint inhibitors

Immune-checkpoint inhibitors have a unique mechanism of action in cancer. This newly developed class of agents interfere with the immune system's autoregulatory mechanisms.

Anti-CTLA-4 antibodies such as ipilimumab, currently FDA approved for metastatic melanoma, and is currently in phase III testing in in a variety of settings in mCRPC. Blockade of CTLA-4 signaling with ipilimumab prolongs T-cell activation and restores T-cell proliferation, which in turn amplifies T-cell-mediated immunity and the patient's capacity to mount an antitumor response. There is concern over immune-related adverse events (skin, gastrointestinal tract are most frequent) which can be life threatening.[19]

Programmed cell death protein 1 (PD-1) and its ligand (PD-L1) are mediators of immune regulation and are similar to the action of CTLA-4. Anti-PD-1/PDL-1 antibodies are emerging as an alternative to anti-CTLA-4 antibodies. Expression may correlate with better activity of the ligand. It should also be noted that it is not clear whether PD1 or PDL

expression in the tumor or lymphocyte is necessary for an anti-tumor response. The theoretical advantage of targeting the PD-1 axis is less potential toxicity and are in early stage testing in prostate cancer.[20]

Principles of active cellular immunotherapy

One active immunotherapy approach involves APCs that are isolated ex-vivo through leukapheresis and "loaded" with the antigen of choice. This is the principle of sipuleucel-T therapy.[21] Ex-vivo isolation of APC's through leukapheresis and antigen loading provides access to a large number of APCs (10^8 to 10^9 cells). This active cellular immunotherapy offers advantages over passive immunotherapies since the target protein of interest does not have to be restricted to the cell surface. Rather, the target antigen needs only be presented as HLA molecules on cells of the target tissue recognizable by the APC-stimulated T-cells. A sampling of all the proteins produced by a tumor cell are presented as peptide-MHC I class (HLA molecules), which are delivered to the cell surface and are recognized by T-cell receptors of CD8+ T lymphocytes. In favor of autologous active cellular immunotherapy, the ability to access a large number of APCs via the apheresis source has been possible for more than a decade, suggesting that efficient targeting of antigen to these APCs would make the harnessing of the immune system to eradicate tumors tenable. In addition to sipuleucel-T prostate cancer immunotherapy other dendritic cell based therapies are being investigated in many other tumor types using different in-vivo and ex-vivo activation strategies.[22]

An evolving concept in tumor immunology is known as "antigen spreading" that has been observed in the immunotherapy of prostate cancer.[23] This enables the immune system to adapt to tumor mutations and broadens the anti-tumor response. The activated T-cell tumor kill is initially directed against a specific antigen; the release of additional tumor antigens from the lysed cell activates new tumor targeting tumor associated antigens broadening ("spreading") the anti-tumor immune response. Lastly, the concept that immunotherapy works best with lower tumor burdens cannot be underestimated.[24]

Development of sipuleucel-T

Sipuleucel-T represents the first "personalized" immunotherapy for the treatment of cancer using a patient's own immune cells to overcome the self-tolerance hurdle for the treatment of tumors. It is also important to stress that sipuleucel-T is not a gene therapy, since APCs are loaded with a purified recombinant protein and are not genetically manipulated or transfected with any form of viral or recombinant DNA or RNA. The loading of the recombinant protein is performed ex vivo where the optimal concentration of immunogen can be controlled.

PAP was chosen as the target antigen for the prostate cancer treatment because it is expressed at detectable levels in more than 95% of prostate adenocarcinomas and is highly specific to prostate tissue.[25,26] PAP was also reported to be an effective target antigen in experimental models.[27] The receptor for GM-CSF is expressed broadly on blood and bone-marrow derived APCs.[28] Engagement of the GM-CSF receptor by ligand results in the upregulation of the expression of a variety of molecules by APCs, including HLA class II, co-stimulatory molecules noted previously (CD80, CD86, or CD40), adhesion molecules (such as CD54), and a variety of secreted cytokines. Intrinsic to its design, PA2024 (the name of the recombinant fusion protein consisting of GM-CSF and PAP), can bind to the GM-CSF receptor, leading to APC activation, increased expression of adhesion and co-stimulatory molecules, and prolonged APC survival in culture. APC activation results in increased antigen uptake via multiple pathways, most prominently macropinocytosis and receptor-mediated endocytosis. These antigen uptake mechanisms target the internalization of antigen to intracellular compartments linked to HLA class I and class II processing pathways.[29] This approach is designed to be tissue-specificity and to break tolerance to the self-antigen. The final cellular product (APC8015) is suspended in lactated Ringer's and delivered for infusion within 18 hours of suspension.

Clinical evidence for immunotherapy with sipleucel-T

Two early phase III randomized, double-blind, placebo-controlled trials with sipuleucel-T, (trials D9901 and D9902A) comparing sipuleucel-T to placebo in men with asymptomatic, mCRPC demonstrated significantly prolonged survival.[30] However, these smaller initial trials were combined for an initial FDA filing which led to the need to initiate a larger randomized, double-blind, placebo-controlled Phase III clinical registration trial known as the IMPACT study (Immunotherapy for Prostate AdenoCarcinoma Treatment) (D9902B). These results have been presented previously and led to the approval of sipuleucel-T.[4] Briefly, in the 512 patient IMPACT study, the median OS was 25.8 months for men receiving sipuleucel-T

TABLE 1. **Common adverse events reported in the IMPACT trial (25% or greater incidence)[4]**

Event	Sipuleucel-T (n = 338)		Placebo (n = 168)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any	334 (98.8)	107 (31.7)	162 (96.4)	59 (35.1)
Chills	183 (54.1)	4 (1.2)	21 (12.5)	0
Fatigue	132 (39.1)	4 (1.2)	64 (38.1)	3 (1.8)
Back pain	116 (34.3)	12 (3.6)	61 (36.3)	8 (4.8)
Pyrexia	99 (29.3)	1 (0.3)	23 (13.7)	3 (1.8)
Nausea	95 (28.1)	2 (0.6)	35 (20.8)	0

and 21.7 months for patients who were treated with placebo (p = 0.03), a survival advantage of 4.1 months while possessing a relatively benign safety profile. The IMPACT study randomized patients 2:1 to active treatment versus placebo. Patients who progressed on the placebo arm had the option of participating in a companion study where they could be treated with a reactivated frozen product (APC8015F). A survival advantage was apparent despite the high percentage of subjects (75.6%) randomly assigned to APC-placebo who, following objective disease progression, subsequently received the frozen product. APC8015F was a formulation similar to sipuleucel-T consisting of APCs prepared from cryopreserved APC and loaded with PAP GM-CSF. Adverse events seen more often in sipuleucel-T treated patients than in those receiving placebo included predominantly chills, fatigue, and pyrexia that were Grade 1 or 2 in severity and of short duration (1 or 2 days), resulting in minimal discontinuation of treatment (< 2%), see Table 1.

A highly controversial report using previously unpublished IMPACT trial data has suggested that the increased overall survival in sipuleucel-T-treated men could be an artifact. The authors speculated due to age-related differences in the placebo group (more older men in the placebo group) had a higher chance of dying, because removing white cells was harmful.[31] These highly controversial findings have been definitively refuted by several other authors.[32,33]

As noted, the majority of patients on the placebo arm of the IMPACT study received salvage therapy upon progression with the frozen product. We have previously reported on an analysis of post-progression treatment with APC8015F. This trial design may have actually prolonged survival of subjects in the control arm of sipuleucel-t phase III trials potentially decreasing the absolute overall survival benefit seen with the treatment.[34] This secondary analysis suggested the absolute survival advantage of sipuleucel-T may be up to 10.9 months and possibly longer when the effect of the salvage therapy was considered in the placebo arm.

The use of PSA in the setting of sipuleucel-T requires some clarification. PSA responses may not be observed in patients who have favorable overall survival benefit form sipuleucel-T. In an exploratory analysis of the IMPACT trial, the greatest magnitude of benefit with sipuleucel-T treatment was seen in patients with better baseline prognostic factors, and in particular those with

TABLE 2. **PSA quartile data from the IMPACT study demonstrating improved survival with lower baseline PSA levels[35]**

	Baseline PSA (ng/mL), n = 128			
	≤ 22.1	> 22.1-50.1	> 50.1-134.1	> 134.1
Median OS (months)				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference	13.0	7.1	5.4	2.8
Hazard ratio (95% CI)	0.51 (0.31, 0.85)	0.74 (0.47, 1.17)	0.81 (0.52, 1.24)	0.84 (0.55, 1.29)

lower baseline PSA values. This suggests that patients with less advanced disease may benefit the most from sipuleucel-T treatment. It provides additional rationale for immunotherapy as an early treatment strategy in sequencing algorithms for mCRPC. PSA quartile data and survival is found in Table 2.[35]

Practical aspects of sipuleucel-T administration

Sipuleucel-T administration can be logistically intensive, requiring a good communication infrastructure between clinicians who perform leukapheresis, the manufacturing facility that performs the ex-vivo procedures on the patient's APCs and prepares the cells for infusion, the patient and the infusion staff. Sipuleucel-T is administered in three treatment cycles and is typically completed in 1 month. Leukapheresis is usually completed early in the week with infusion later in the work week, see Figure 1.

- Each cycle consists of two visits: leukapheresis at an approved cell collection center followed by infusion 3 days later when the product is returned from the processing center
- Each leukapheresis/infusion cycle is generally 1 week
- After the three cycles are completed, no further sipuleucel-T treatments are administered

The manufacturer of sipuleucel-T (Dendreon, Seattle, WA, USA), provides patient and physician scheduling logistical support to insure that the collection, processing and infusion are coordinated. In most cases, insurance company pre-authorization is required. Only manufacturer approved leukapheresis centers can be used for the autologous APC collection. The majority of the information presented below is based on the approved FDA label (available at www.PROVENGE.com; accessed December 15, 2013) and published clinical data.

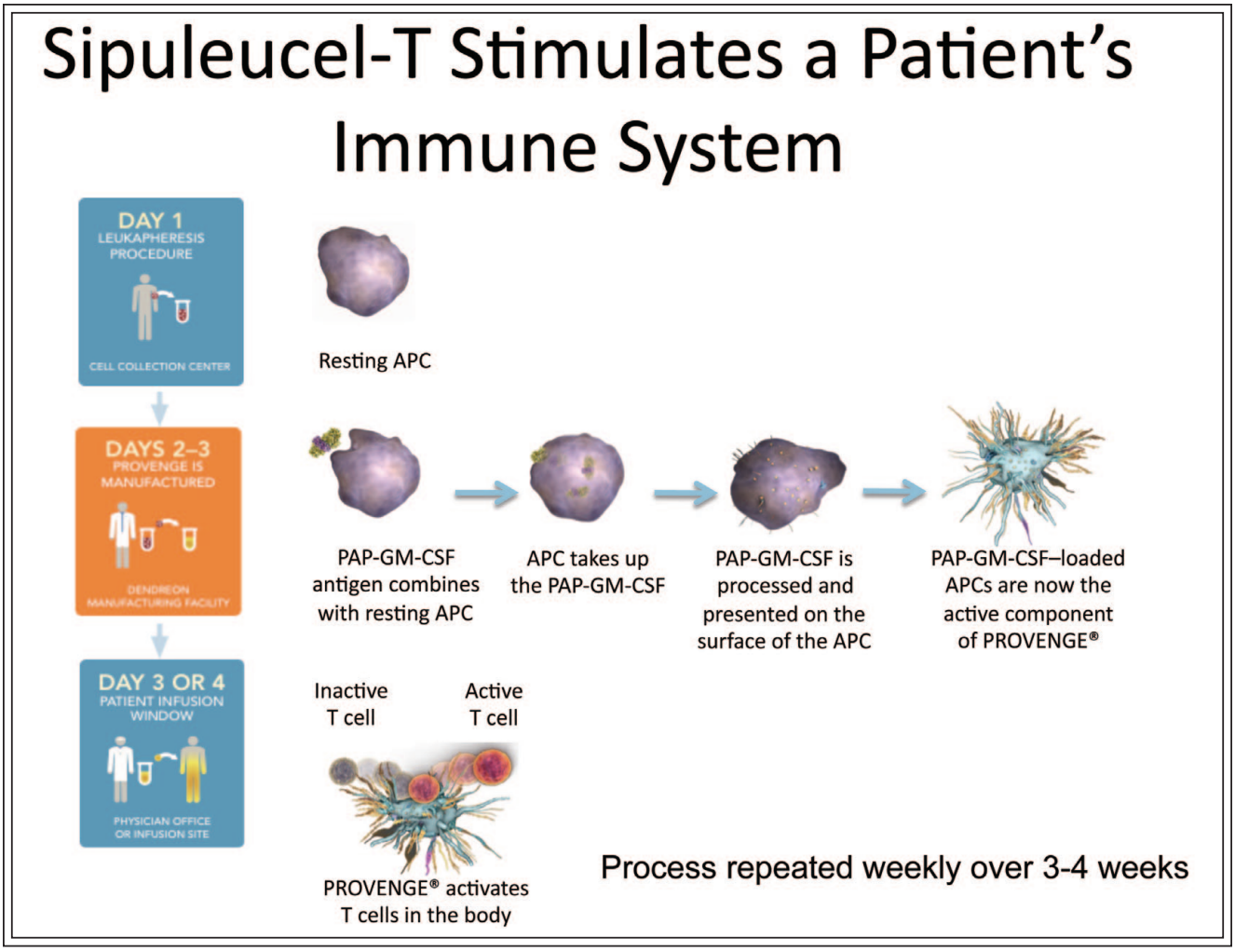

Figure 1 . Sequence of sipuleucel-T treatment (Courtesy Dendreon, Seattle, Washington).

The sipuleucel-T FDA label states the formal indication as the "treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer". These men have progressed on traditional androgen deprivation therapy (ADT), such as orchiectomy or gonadotropin-releasing hormone (GnRH) therapies with a confirmed serum testosterone of < 50 ng/dL. The progression is typically defined as a rising PSA with the identification of new or an increased number of metastasis. Imaging men with CRPC should be performed periodically to identify earliest signs if metastasis. The optimum sequence of bone scan and body imaging (CT or MRI) absent symptoms, has not been determined. Na F^{18} PET scanning to detect occult bone metastases is understudy and potentially may allow even earlier identification of metastatic disease in this and other settings.

Once metastatic lesions are noted on imaging, men with a castrate level of testosterone and usually a rising are classified as having mCRPC. Over 30% of men thought to have non-metastatic CRPC were found to have metastases when screened via imaging on a recent clinical trial.[36] However, the patient should be asymptomatic or minimally symptomatic and not require narcotic medications for cancer-related pain. According to the NCCN Guidelines (Prostate Cancer Version 1.2014, accessed December 16, 2013) sipuleucel-T is appropriate for patients with ECOG performance status 0-1 and should not be used in patient with hepatic metastasis or with a life expectancy of < 6 months. It is also listed as second line therapy for mCRPC. There are no formally noted contraindications for the sipuleucel-T therapy on the FDA label.

A CBC should be obtained 1 month before the first treatment cycle to ensure adequate hematologic parameters to undergo leukapheresis. In order to insure adequate access for leukapheresis, a "venous assessment" at least 1 week before the first cycle is required to determine whether placement of a formal apheresis catheter is needed. Peripheral IV's are the preferred method of leukapheresis collection; verify access in both arms since leukapheresis is a dual-arm procedure. However, some patients with inadequate peripheral access may require an apheresis catheter. Twenty three percent of patients in sipuleucel-T clinical trials required an apheresis catheter.[37] Apheresis catheters that provide central venous access are commonly placed by interventional radiology. Peripherally inserted central catheter (PICC) lines are usually not considered appropriate.

Patients should be informed about the nature of the leukapheresis procedure. It can last 3-4 hours and patient should be well hydrated, avoid caffeinated beverages on the day of the procedure and eat a calcium rich breakfast. Loose fitting clothing is encouraged. Side effects of the leukapheresis procedure can include perioral and digital tingling, sensation of chills, nausea and fainting. Photo ID is essential so that proper sample identification is insured at all steps in the treatment cycle. The patient should be accompanied by an adult as the procedure can cause some fatigue.

The leukapheresis product is then shipped to the Dendreon processing facility where it is treated ex-vivo with a recombinant fusion protein, PA2024 (human PAP fused GM-CSF). The activated autologous product, now officially called sipuleucel-T is usually returned within 48-72 hours to the infusion site. It contains a minimum of 50 million autologous CD54+ cells activated with PAP GM-CSF, suspended in 250 mL of lactated ringers in a sealed, patient-specific infusion bag. It should be stored refrigerated at 2°C-8°C and not frozen.

In order to minimize infusion reactions, it is recommended that patients be premedicated with 650 mg of acetaminophen and an antihistamine such as 50 mg diphenhydramine 30 minutes before. Patient identity must be verified by photo ID. After fax or e-mail confirmation from the manufacturer that the product is "approved for infusion", (post-manufacture product quality assurance and expiration date and time) it is infused through a peripheral IV (18-20 gauge needle preferred) or appropriately prepared apheresis catheter (if present). It is critical that no in-line filter or blood component infusion tubing be used in the infusion set up. Normal saline is the IV solution of choice. The product should remain in the insulated shipping container with the lid in place until the patient is ready to receive the infusion. Universal precautions should be used when handling sipuleucel-T because as an autologous product, it is not routinely tested for transmissible infectious diseases and may carry the risk of transmitting infectious diseases to health care professionals handling the product.

Post-manufacture product quality assurance verifies that the minimum requirements of activated CD54+ cell are present by measuring the increased expression of the CD54 (also known as ICAM-1), on the surface of APCs after culture with the PAP GM-CSF. The product is also approved for infusion based on the microbial and sterility results from several tests: contamination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion and will be reported to the physician with any follow up as needed.

The product should be infused over 60 minutes. Interrupt or slow infusion for acute infusion reactions, depending on the severity of the reaction. The most common adverse reactions are noted in Table 1. In controlled clinical trials, symptoms of acute infusion reactions were treated with acetaminophen, IV histamine (H1 and/or H2 blockers), and low dose IV meperidine. Do not resume the infusion if the sipuleucel-T has been held at room temperature for greater than 3 hours. The patient should be observed for 30 minutes after infusion for any adverse reactions.

This entire procedure is repeated for three cycles. If, for any reason, the patient is unable to receive a scheduled infusion, the patient will need to undergo an additional leukapheresis if the course of treatment is to be continued. Patients should be advised of this possibility prior to initiating treatment.

Sipuleucel-T treatment follow up

Routine mCRPC follow up care is indicated after sipuleucel-T therapy. Patients and clinicians should be made aware that PSA may not be used as a definitive marker for response following immunotherapy. As noted previously, PSA provides guidance concerning the men who might be optimum candidates for immunotherapy with sipuleucel-T but is not a reliable marker of response. There is no consensus as to when patient should be reimaged, and that the median time to second treatment on the IMPACT study was 6 months driven primarily by imaging studies.

Immunotherapy generally has the most benefit with early and lower tumor burden. The dynamics of immunotherapy are distinct from cytotoxic chemotherapy whereby the tumor growth rate may be significantly slowed resulting in extended survival but this can be difficult to determine in the course of routine clinical care.[38,39]

There is a pressing need to identify predictive biomarkers in the setting of immunotherapy. Recently, Sheikh et al analyzed immunological responses and overall survival through the assessment of antigen-specific cellular and humoral responses in a subset of men enrolled in the IMPACT study.[40] APC activation based on CD54 occurred in the first dose was increased with the second and third dose preparations; this increase correlated with overall survival. Interferon gamma (IFNγ) enzyme-linked immunosorbent spots (ELISPOT) also correlated with overall survival. This preliminary data provides insight on which patients may benefit from improved overall survival through induction of antigen-specific immune activation and also provides direction for future biomarker research.

Conclusions

Improved understanding of the interactions between the immune system and prostate cancer has generated renewed interest in treating prostate cancer with immunotherapy. While there are several promising immunotherapeutic agents under study, sipuleucel-T is clinically available as the first in class antigen-specific autologous immunotherapy approved for cancer treatment. Combining sipuleucel-T with other agents and further study of the optimum sequencing of immunotherapy will continue for the next few years.[41] Understanding the basic principles behind prostate cancer immunotherapy and the optimum clinical application of sipuleucel-T will potentially benefit many men with minimally symptomatic or asymptomatic metastatic castration-resistant prostate cancer.

Disclosure

Dr. Leonard G. Gomella serves as a consultant to Astellas, Bayer, Dendreon and Janssen.
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Practical guide to the use of abiraterone in castration resistant prostate cancer

Elahe A. Mostaghel, MD,[1,2] Daniel W. Lin, MD[3]

[1]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
[2]Division of Medical Oncology, University of Washington, Seattle Washington, USA
[3]Department of Urology, University of Washington, Seattle, Washington, USA

MOSTAGHEL EA, LIN DW. Practical guide to the use of abiraterone in castration resistant prostate cancer. *Can J Urol* 2014;21(Suppl 1):57-63.

Introduction: *While androgen deprivation therapy remains the primary treatment modality for patients with metastatic prostate cancer, treatment is uniformly marked by progression to castration resistant prostate cancer (CRPC). Abiraterone is the first new drug to enter clinical practice in a series of novel agents designed to potently target adrenal and tumor androgen production.*

Materials and methods: *Herein, we review the mechanism of action of abiraterone and the phase III data supporting its approval for patients with metastatic CRPC. We discuss practical treatment considerations, including the incidence and management of side effect and monitoring requirements, and conclude by discussing future directions in the use of abiraterone, including early data supporting an expanded role for abiraterone in castration sensitive disease.*

Results: *Accumulating data emphasize that 'androgen independent' or 'hormone refractory' tumors remain sensitive to hormonal activation and suggest that despite suppression of circulating testosterone (T), residual tumor androgens play a prominent role in mediating CRPC progression.*

Conclusions: *Accordingly, therapeutic strategies such abiraterone that more effectively target production of intratumoral androgens are necessary.*

Key Words: castration resistant prostate cancer, intratumoral androgen, CYP17A, abiraterone

Introduction

The efficacy of androgen deprivation therapy (ADT) is routinely based on achieving castrate levels of serum T, arbitrarily defined as T ≤ 20 or 50 ng/dL. However, tissue androgen measurements in men with either locally recurrent or metastatic castration resistant prostate cancer (CRPC) clearly demonstrate that prostate and tumor androgen concentrations remain well within the range capable activating the androgen receptor (AR).[1-4] Clinical and pre-clinical findings demonstrate that tumors remain sensitive to hormonal activation and suggest that despite suppression of circulating testosterone (T), residual tumor androgens play a prominent role in mediating CRPC progression.[5] Emerging data suggest residual intratumoral androgens are produced via the uptake and conversion of adrenal androgens, and potentially via de novo synthesis from cholesterol or progesterone precursors within the tumor.

The critical enzyme required for androgen synthesis from cholesterol is cytochrome P450 17 alpha-hydroxylase (CYP17A). Adrenal expression of this enzyme accounts for production of circulating adrenal androgens, including dehydroepiandrosterone (DHEA, which primarily circulates in its sulfated form, DHEA-S), and androstenedione (AED), and a number of studies have demonstrated expression of CYP17A in castration resistant prostate tumors. Given its central

Address correspondence to Dr. Elahe A. Mostaghel, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, MS D5-100, Seattle, WA 98109 USA

role in the production of either adrenal or tumor-derived extragonadal androgen synthesis, CYP17A has emerged as a primary target of novel therapeutics.

Mechanism of action

CYP17A is a single enzyme that catalyzes the sequential hydroxylase (required for cortisol synthesis) and lyase (required for adrenal androgen synthesis) steps that are required for conversion of C21 pregnenolone and progesterone precursors to the C19 adrenal androgens, DHEA and AED, Figure 1. Abiraterone acetate, an orally administered, rationally designed small molecule derived from the structure of pregnenolone, irreversibly inhibits both the hydroxylase and lyase activity of CYP17A with approximately 10-fold greater potency than ketoconazole.

Because adrenal inhibition of CYP17A results in blockade of glucocorticoid as well as adrenal androgen synthesis, abiraterone is co-administered with prednisone to ameliorate the secondary rise in adrenocorticotropic hormone (ACTH) that can lead to excess mineralocorticoid synthesis (discussed further below).[6]

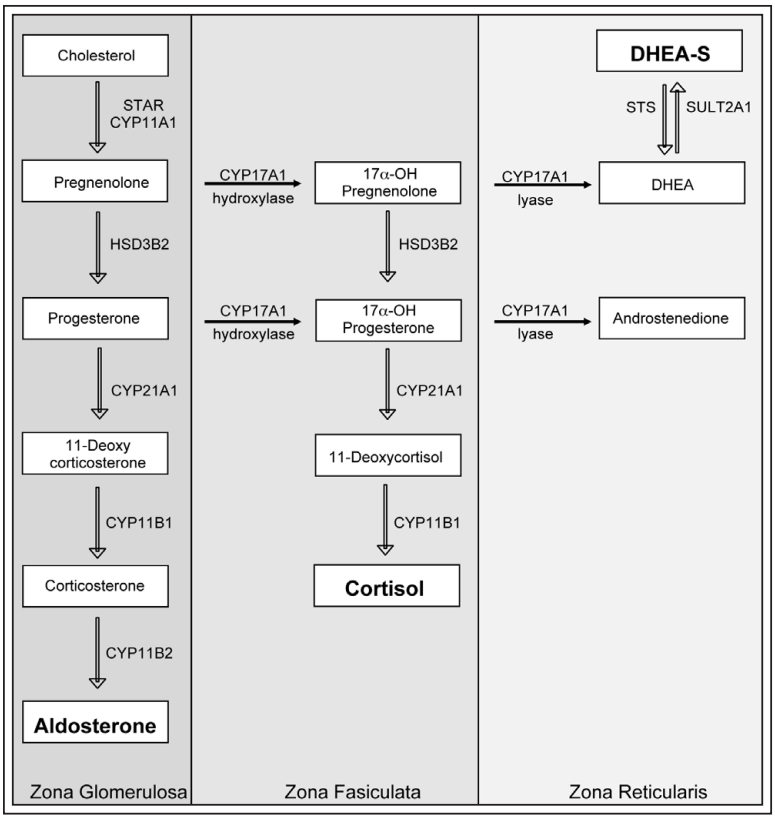

Figure 1. Steroid hormone pathways in the adrenal gland.

Efficacy data and FDA approved treatment indications

A number of phase I and II studies initially demonstrated that abiraterone suppresses serum androgen levels and achieves prostate-specific antigen (PSA) and clinical responses in chemotherapy naïve and docetaxel-treated CRPC patients. Phase III studies in chemotherapy naïve (COU-AA-302) and post-docetaxel treated men (COU-AA-301) have confirmed these findings, resulting in FDA approval of abiraterone for men with metastatic CRPC either before or after treatment with chemotherapy.

COU-AA-301

In the post chemotherapy setting, 1195 men with metastatic CRPC were randomized 2:1 to abiraterone/prednisone (n = 797) or placebo/prednisone (n = 398) with a primary endpoint of overall survival (OS). Median PSA was approximately 130 ng/dL, 90% of patients had an ECOG score of 0-1, median age was 70, and 28% were ≥ 75 years. Bone, lymph node and visceral metastases were present in approximately 90%, 40% and 10% of patients respectively, and 30% of patients had received more than one prior chemotherapy regimen. Treatment was continued until clinical or radiographic evidence of progression.

The first interim analysis demonstrated a 3.9 month OS benefit for men receiving abiraterone, prompting the independent data monitoring committee (IDMC) to recommend the study be unblinded and men on the placebo arm be offered abiraterone.[7] An updated analysis at a median survival of 20.2 months demonstrated a median OS of 15.8 months for abiraterone versus 11.2 months for prednisone (HR 0.74, $p < 0.0001$), extending the OS benefit to 4.6 months.

All secondary endpoints were statistically significant in favor of abiraterone, including median time to PSA progression (8.5 months versus 6.6 months), median radiologic progression-free survival (rPFS, 5.6 months versus 3.6 months), and proportion of patients with > 50% PSA response (29.5% versus 5.5%). The impact of abiraterone on OS was observed across all subgroups, including patients who had received one (15.4 months versus 11.5 months) or two prior chemotherapy regimens (14.0 months versus 10.3 months). Notably,

patients with a performance status (PS) of 2 had worse outcomes, with a median survival of 7.3 months versus 15.3 months for those with PS of 0-1 receiving abiraterone.[8]

In exploratory analyses abiraterone significantly increased the number of patients reporting an improvement in fatigue intensity (58.1% versus 40.3%, p = 0.0001),[9] and the number of patients reporting palliation of pain (45% versus 28.8%, p = 0.0005). Median time to first skeletal-related event was also significantly longer in abiraterone treated patients (25 months versus 20.3 months, p = 0.0001).[10] While visceral disease was associated with a poorer prognosis, the absolute benefit in OS from abiraterone was similar in those with and without visceral disease (from 8.3 months to 12.9 months in those with visceral disease, and from 12.3 months to 17.3 months in those without).[11]

COU-AA-302

In the pre-chemotherapy setting, 1088 men with asymptomatic or minimally symptomatic bone and lymph node (but not visceral) metastatic CRPC were randomized 1:1 to abiraterone/prednisone (n = 546) or placebo/prednisone (n = 542), with co-primary endpoints of rPFS and OS. The median PSA was approximately 40 ng/dL, about 30% of men were ≥ 75 years, and approximately 50% had bone-only metastatic disease.

At a median follow up of 22.2 months abiraterone doubled rPFS from 8.3 months to16.5 months (HR 0.53, p < 0.001), accompanied by a trend for increased OS from 27.3 months in the placebo arm to not-reached in the abiraterone group (HR 0.75, p = 0.01 which did not meet the prespecified p value of 0.001), again prompting the IDMC to recommend the study be unblinded and men on the placebo arm be offered abiraterone.[12] An updated analysis of OS at a median survival of 27.1 months again trended toward favoring abiraterone at 30.1 months in the placebo arm versus 35.3 months in the abiraterone arm (HR 0.79, p = 0.015).[13]

All secondary endpoints were statistically significant in favor of abiraterone, including median time to opiate use (not-reached versus 23.7 months), time to initiation of chemotherapy (25.2 months versus 16.8 months), time to performance status decline (12.3 months versus 10.9 months), time to PSA progression (11.1 months versus 5.6 months), and proportion of patients with > 50% PSA response (62% versus 24%).[12] While this study did not include patients with visceral disease or moderate to severe pain, exploratory analyses of these subpopulations in the post-chemotherapy setting (discussed above) suggest these patients are likely to benefit as well.

Also of note, although ketoconazole-treated patients were specifically excluded in the phase III studies, phase I/II data suggest abiraterone has activity in these patients. In a pre-chemotherapy phase I study PSA responses > 50% were observed in 64% of ketoconazole-naïve and 47% of ketoconazole pre-treated patients.[14] In a post-docetaxel study, PSA declines > 50% occurred in 45% of ketoconazole-naïve and 26% of ketoconazole-treated patients, with median TTP of 28 and 14 weeks, respectively.[15]

Incidence and management of side effects

Abiraterone is generally well tolerated, with 13% and 19% of abiraterone-treated patients in COU-AA-301 and COU-AA-302 (respectively) discontinuing therapy for adverse effects versus 18% and 23% of placebo-treated patients. The most common adverse events in both groups were fatigue, back pain, nausea, constipation, bone pain and arthralgia, all in the range of 25%-30%, summarized in Table 1. The incidence of urinary tract infection was statistically higher in abiraterone treated patients (12% versus 7% in placebo, p = 0.02). Here we discuss the incidence, management and monitoring of adverse events of special interest specifically associated with abiraterone therapy.

Impact of food

Phase I studies demonstrated 5-7 fold higher drug exposure when abiraterone is administered with a low fat meal (7% fat, 300 calories) as compared to the fasted state. To minimize the variability in absorption, abiraterone is administered as 1000 mg (four 250 mg tablets) daily on an empty stomach, defined as 1 hour before or 2 hours after a meal.

Mineralocorticoid and electrolyte effects

Adrenal inhibition of CYP17A results in blockade of glucocorticoid as well as adrenal androgen synthesis leading to a compensatory rise in ACTH that can lead to excess mineralocorticoid synthesis, Figure 1. Phase I and II trials demonstrated symptoms of mineralocorticoid excess occur in 50%-80% of patients treated with single-agent abiraterone.[6] Mineralocorticoid-related symptoms in the phase III studies were markedly attenuated by inclusion of prednisone 5 mg twice daily, and were generally of grade 1 or 2 in magnitude, including fluid retention (~33% versus 22%-24% in placebo), hypertension (~10% versus 8% in placebo), and hypokalemia (~18% versus 9% in placebo).[14,16,17]

Hypertension and hypokalemia should be corrected before and during therapy and patients should be

TABLE 1. **Adverse events (%) reported during treatment with abiraterone**

All grades	COU-001 (post-chemotherapy)		COU-002 (pre-chemotherapy)	
	abiraterone	placebo arms	abiraterone	placebo arms
Hematologic				
Anemia	25	28	23	26
General side effects				
Fatigue	47	44	39	34
Back pain	33	36	32	32
Arthralgia	30	24	28	24
Bone pain	27	30	20	19
Nausea	33	33	22	22
Vomiting	24	26		
Constipation	28	32	23	19
Diarrhea	20	15	22	18
Hot flash	10	9	22	18
Urinary tract infection	13	7	12	7
Mineralocorticoid effects				
Fluid retention	33	24	28	24
Hypertension	11	8	22	13
Hypokalemia	18	9	17	13
Hepatotoxicity (ALT/AST)	11	9	12	5
Cardiotoxicity				
All	16	12	19	16
Atrial fibrillation	2	1	4	5

monitored for hypertension, hypokalemia and fluid retention at least once a month. Spironolactone is avoided in patients who develop mineralocorticoid-related side effects due to its mixed AR agonist/antagonist activity. Instead, eplerenone, a second-generation mineralocorticoid receptor antagonist (MRA) in doses of 50 mg/day-200mg/day (in divided doses twice daily) can be used in combination with a salt-restricted diet.[18] Alternatively, potassium-sparing epithelial sodium channel antagonists such as amiloride and triamterene (in combination with hydrochlorthiazide if hypertension is significant) can be used in place of or added to eplerenone if necessary.[16,18] In rare instances, additional anti-hypertensive agents may be necessary in patients already receiving prednisone, eplerenone and diuretics.

Heptatotoxicity

Grade 3 or 4 hepatic transaminase abnormalities (5x upper limit of normal - ULN) occurred in approximately 4% of patients in the phase III studies, usually within the first 3 months of starting treatment, and more commonly in men whose baseline ALT or AST were elevated. Serum transaminases should be measured at baseline. Transaminases in patients with normal levels should be checked every 2 weeks for the first 3 months of therapy, and then monthly. No dose adjustment is necessary for mild hepatic impairment. For moderate hepatic impairment (Child-Pugh Class B) abiraterone should be started at 250 mg daily, and transaminases should be checked weekly for the first month, then every 2 weeks for the following 2 months, and then monthly.

If AST or ALT rise above 5 times the ULN, or bilirubin rises above 3 times the ULN, abiraterone should be held. It should be discontinued if the patient had moderate hepatic impairment at baseline, but in patients with normal hepatic function at baseline it can be restarted at 750 mg daily when LFT's decline to less than 2.5 times the ULN and total bilirubin is less than 1.5 times ULN. If hepatotoxicity recurs, a further dose reduction to 500 mg can be attempted (once levels have fallen below the thresholds given above), but recurrence of hepatotoxicity at the 500 mg dose requires discontinuation of the drug.

Cardiotoxicity

The overall incidence of adverse cardiac effects was not statistically increased by abiraterone in COU-001 (13% versus 11% in placebo), although the frequency of cardiac

failure was higher in the abiraterone group (2.1% versus 0.7% in placebo). The most frequently reported cardiac events were grade 1 and 2 tachycardia and grade 3 or lower atrial fibrillation. As patients with left ventricular ejection fraction < 50% were excluded from the phase III studies, pre-treatment assessment of cardiac status with electrocardiogram and echocardiography may warrant consideration in elderly patients with reduced cardiac function. A significant effect of abiraterone on the QT/QTc interval in patients with CRPC was not observed.[19]

Potential drug interactions

Abiraterone is a strong inhibitor of several microsomal drug metabolizing enzymes, including CYP1A2 and CYP2D6.[20] Abiraterone increased systemic exposure of dextromethorphan (metabolized by CYP2D6) approximately 2-3 fold, while the pharmacokinetics of theophylline (metabolized by CYP1A2) were unaffected. This suggests caution may be warranted when abiraterone is co-administered with known CYPD26 substrates (including beta blockers, serotonin reuptake inhibitors, anti-arrhythmics, neuroleptics, as well as codeine, tramadol, and of relevance to urologic patients, tolterodine).[21]

Practical treatment considerations

While the introduction of abiraterone has heralded a new era in the hormonal treatment of men with metastatic CRPC, there remain important questions regarding its optimal place in continuum of prostate cancer therapy. These include issues of sequencing of abiraterone with immunotherapy, chemotherapy and enzalutamide in men with metastatic CRPC, the efficacy of abiraterone in castration sensitive disease, the role of abiraterone as part of therapy in men with localized disease or biochemical relapse, whether co-administration of prednisone can be safely decreased to 5 mg/day, and whether sequential or combinatorial treatment strategies will yield the most durable responses.

In men with asymptomatic or minimally symptomatic metastatic CRPC, abiraterone is an attractive first line option given its ease of administration and relatively low toxicity profile. Similarly, the combination of abiraterone and sipuleucel T would likely be a well-tolerated regimen in this setting and is currently under clinical investigation.

The efficacy of abiraterone in men with symptomatic disease prior to chemotherapy has not been specifically demonstrated due to exclusion of these patients from the phase III trial; however, data from the post-chemotherapy trial suggest these patients are likely to benefit as well. The pace of disease may be the best guide to therapy in this setting. Patients with high Gleason scores, poor response to initial ADT, rapidly progressive disease, or poorly controlled symptoms may derive greater benefit from immediate chemotherapy, while a trial of abiraterone may be reasonable in patients with less extensive or more slowly progressing disease.[22] In this regard it should be noted that treatment with abiraterone in the phase III studies was continued until clinical or radiographic evidence of progression, thus it is reasonable to continue therapy in patients with PSA progression as long as there is evidence of ongoing clinical benefit.

While both abiraterone and enzalutamide are supported by phase III data demonstrating an OS benefit in the post-chemotherapy setting, the optimal approach to sequencing them is unknown. Retrospective evaluations of patients receiving abiraterone after enzalutamide or vice versa have shown modest response rates with median times to progression of 3-4 months.[23-25] Until biomarkers to stratify patients or clinical trial data to support combination or sequencing strategies are available, the sequencing of abiraterone and enzalutamide is likely to be dictated by insurance and regulatory approvals. From a practical perspective enzalutamide avoids the need for prednisone, although this may become less important if studies show abiraterone can be given with a lower 5 mg dose.

An emerging consideration is whether therapy with abiraterone (or enzalutamide) may influence the efficacy of subsequent chemotherapy.[22] Taxanes inhibit AR transcriptional activity by various mechanisms including induction of transcriptional corepressors and prevention of microtubule-mediated transit of AR to the nucleus, suggesting a mechanism by which development of resistance to hormonal AR pathway inhibitors may lead to cross-resistance with taxanes.[23,26,27] Notably, a small retrospective analysis of docetaxel after progression on the phase I/II studies of abiraterone showed > 50% PSA declines in only 26% of patients, compared to 45% in the TAX327 study.[28] At present these observations remain hypothesis-generating.

Conclusions and future directions

While clinical responses to abiraterone have been remarkable, not all patients respond and the majority ultimately progress with a rising PSA indicating reactivation of AR signaling. Emerging clinical and pre-clinical data similarly suggest resistance is associated with reactivation of AR signaling, including increased expression of CYP17A and induction of ligand-independent AR splice variants.[29,30] Interestingly, recent case reports describe instances of an 'abiraterone withdrawal syndrome,' in which (generally transient) PSA declines occur following discontinuation of

abiraterone, suggesting that mutations in the AR which can allow AR activation by exogenous corticosteroids may play a role.[31,32]

These observations provide a strong rationale for combining abiraterone with potent AR inhibitors such as enzalutamide rather than sequential strategies of single agents which may allow alternative pathways of AR activation to emerge. Moreover, early use of potent combined AR blockade may be particularly effective in hormone naïve tumors which have not yet had the opportunity to develop resistance. In this respect, neoadjuvant studies of multi-targeted AR blockade using LHRH agonists combined with bicalutamide, dutasteride and ketoconazole or LHRH agonists combined with abiraterone have demonstrated higher pathologic response rates than previously observed in historic studies of ADT prior to prostatectomy.[33,34]

Important clinical questions regarding the use of abiraterone in different disease settings and in combination with emerging novel agents remain to be answered. Numerous studies evaluating the sequencing and combination of abiraterone with immunotherapy, chemotherapy and other AR targeted agents in multiple disease settings are underway. Rapid accrual and completion of these studies will be imperative for determining rational treatment strategies with the highest likelihood of durable efficacy.

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Unlabeled/unapproved use of drugs or devices: Discussion of expanded indications in castration sensitive disease. □

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Practical guide to the use of enzalutamide

Jean Hoffman-Censits, MD, Wm. Kevin Kelly, DO
Department of Medical Oncology, Kimmel Cancer Center, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania, USA

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Introduction: *We summarize the development, definitive trials, and practical use of enzalutamide for practicing urologists and medical oncologists.*
The care paradigm for patients with metastatic castration resistant prostate cancer (mCRPC) is a changing landscape, with the ongoing discovery of drivers of cancer progression yielding actionable targets for drug development. Since 2010, sipuleucel-T, cabazitaxel, abiraterone with prednisone, radium 223 and enzalutamide have been Food and Drug Administration approved based upon improvement in overall survival in men with mCRPC.
Materials and methods: *A MEDLINE search for "enzalutamide or MDV3100" yielded 258 results. Prospective trials were reviewed. Abstracts from ASCO (American Society of Clinical Oncology) meetings and press release information were included where applicable.*
Results: *Enzalutamide, an oral inhibitor of the androgen receptor pathway, was approved in 2012 based upon improvement in overall survival of 4.8 months in men with mCRPC following docetaxel versus placebo. Measures of prostate-specific antigen (PSA) and radiographic response, and clinically significant endpoints such as quality of life improvement and toxicity parameters favored enzalutamide. Toxicity is modest with asthenia and fatigue being most common, with a 1% incidence of seizure reported, though patients can be selected to decrease this risk.*
Conclusion: *Enzalutamide is an effective oral therapy for mCRPC, with an overall survival benefit before and following chemotherapy. Toxicity is mild, and seizure risk can be mitigated by careful patient selection. Ongoing studies will help determine the best sequence of novel agents for prostate cancer, along with safe and effective combinations of therapies. Better understanding of tumor characteristics, particularly reliance on the androgen receptor pathway, will lead to personalized approaches to prostate cancer therapy.*

Key Words: enzalutamide, androgen receptor, metastatic prostate cancer, castration resistant, docetaxel refractory

Introduction

Enzalutamide is an oral potent inhibitor of the androgen receptor (AR) signaling pathway, with actions including inhibition of ligand/receptor binding, nuclear translocation of activated androgen receptor, and inhibition of AR regulated nuclear transcription.[1] This inhibition of the AR signaling pathway by enzalutamide is dramatically more potent than bicalutamide, and is without potential agonist properties that are sometimes acquired with bicalutamide treatment. In the phase I/II trial, the enzalutamide (formerly MDV3100) dose range was 30 mg to 600 mg daily, with ketoconazole and docetaxel naïve men experiencing the most robust responses.[2] Seizures were confirmed or suspected in one patient each at 600 mg, 480 mg, and 360 mg cohorts, suggesting dose dependency of this toxicity.

Phase III AFFIRM study: efficacy and toxicity

Based upon data from the phase I/II trial, 160 mg daily was the dose selected for the pivotal phase III AFFIRM trial, in which men with metastatic castration resistant prostate cancer (mCRPC) and disease progression following docetaxel were randomized to receive enzalutamide versus placebo.[3] Enzalutamide treatment led to a median overall survival of 18.4 months (95% CI, 17.3 months to not yet reached)

Address correspondence to Dr. Wm. Kevin Kelly, Department of Medical Oncology, Kimmel Cancer Center, Jefferson Medical College of Thomas Jefferson University, 1025 Walnut Street, Suite 700, Philadelphia, PA 19107 USA

compared to 13.6 months (95% CI, 11.3 months to 15.8 months) in the placebo cohort. This improvement in median survival by 4.8 months, corresponding to a 37% reduction in the risk of death compared with placebo, was determined when the study was stopped early at a planned interim analysis (HR for death in enzalutamide group 0.63, $p < 0.001$). Enzalutamide treatment led to superior outcomes in prostate-specific antigen (PSA) reduction > 50%, radiographic response rate, time to progression and time to first skeletal related event over placebo.

Toxicity rates between the two groups were similar, despite a significantly longer on treatment time for men in the enzalutamide cohort. More men in the enzalutamide arm experienced fatigue, diarrhea, hot flashes, musculoskeletal pain, headache and hypertension. Of note, five patients in the enzalutamide cohort experienced seizure activity, with possible predisposing comorbid brain metastasis, organic brain disease, and adverse drug interaction cited as possible contributing factors. In this and in ongoing trials, patients with history of brain metastasis, seizure, head trauma with loss of consciousness, transient ischemic attack in the last 12 months, stroke, brain arteriovenous malformation, or use of concomitant medications which could lower the seizure threshold were excluded, and thus the safety of enzalutamide in these populations is not known, see Table 1.

Which subsets of patients benefit from enzalutamide?

The cohorts in the AFFIRM study were well matched for all factors at baseline, including by Gleason grade, with median Gleason grade of 8 in each group, and Gleason grade > 7 in 50.4% and 52.4% in the enzalutamide and placebo cohorts respectively. The benefit of enzalutamide was seen across all pre-specified subgroups, including those < 65 versus 65 and older, by geographic treatment location, baseline pain score and type of disease progression at study entry (PSA or radiographic). Post-hoc subgroup analyses demonstrated similar benefit of enzalutamide in men < 75 versus 75 and older, as well as benefit in those with liver and lung metastasis when compared to placebo.[4,5] Clinical benefit, assessed by health related quality of life scores, was significantly better for men treated on enzalutamide, with improvements in physical, social, emotional and functional well-being compared to those treated with placebo.[6] Evaluation of patients who were found to be long term responders, on study agent for > 12 or > 18 months, were noted to have less baseline disease burden, longer time from cancer diagnosis to study enrollment, and improved rates of biochemical and radiographic response to enzalutamide compared to those on study < 12 months.[7] Multivariate analysis of hazard ratio for death demonstrated survival advantage for those with ECOG performance status 0 or 1 compared to 2, lower baseline pain score, PSA as compared to radiographic progression, no visceral disease, lower values of LDH and higher values of hemoglobin at study entry.[3] Gleason grade at diagnosis was not included in this multivariate analysis due to substantial missing data, thus the effect of Gleason grade upon efficacy of enzalutamide post docetaxel is not known.

Should steroids be prescribed concomitantly with enzalutamide?

Many men treated post docetaxel are on long term steroid therapy, and may represent a fundamentally different population than men not on, or who have not progressed on steroids. The authors sought to understand differences between patients with disease progression on steroids at enrollment (approximately 30% in each cohort), compared to those who were not on steroids upon outcomes in the AFFIRM study in post-hoc analyses.[8] A multivariate analysis showed median overall survival was 11 months versus median survival not met in men with baseline corticosteroid use compared to those not on baseline steroids, despite study treatment group. By study group, patients in the enzalutamide cohort on corticosteroids had a median overall survival of 12.3 months compared to 9.3 months on placebo, and this difference remained statistically significant.

Following trial enrollment, men not on steroids at baseline were also permitted to initiate corticosteroid therapy at investigator discretion, and thus the effect of all on study use of corticosteroids was also evaluated.[9] The combined baseline and on study initiation of steroids was 48% in the ezalutamide and 45% in the placebo group. The median survival in all patients treated with on study corticosteroids was 11.5 months, and not met in those not on corticosteroids. Statistically significant benefit of enzalutamide over placebo in all outcome measures was retained despite steroid use. Notably, grade 3 and 4 adverse event rates were higher in all patients on corticosteroids. Though baseline prognostic factors were reported to be slightly better in patients not on corticosteroids, the authors contend that steroid use may be associated with unmeasured or unidentified disease factors or other properties of steroid use. These may include promotion of tumor growth via aberrant mutant AR activation.[10]

TABLE 1. **Administration and strategies to manage side effects of therapy**

Toxicity (AFFIRM enzalutamide incidence)	**Strategy to manage toxicity** **Dose de-escalation/discontinuation as clinically indicated**
Seizure (0.9%)	Avoidance in patients meeting trial exclusion criteria, safety not determined: • History of seizure including febrile • Loss of consciousness or transient ischemic attack < 12 months • Conditions which may predispose to seizure –stroke, brain AV malformation, head trauma with loss of consciousness. • Brain metastasis. • Patients who experienced seizure on study were withdrawn from study. Avoidance/caution with use of concomitant medications which can lower seizure threshold (list not comprehensive): • Bronchial agents: aminophylline, theophylline • Antidepressants: tricyclics, buproprion (Wellbutrin, Aplenzin), doxepin (Silenor) • Antipsychotics: chlorpromazine, haloperidol (Haldol), perphenazine, prochlorperazine (Compazine), thioridazine, trifluoperazine (Terfluzine) • Analgesics: fentanyl, meperidine, propoxyphene, tramadol • Antibiotics: ampicillin, carbenicillin, cephalosporins, imipenem, isoniazid, lindane, metronidazole, oxacillin, penicillin, ticarcillin, pyrimethamine
Hypertension (6.4%)	Optimization of blood pressure before administration. Periodic ECG monitoring, significant increases in QT interval were not observed. Overall incidence of cardiac disorders was not different between the two treatment groups.
Fatigue and asthenia (50.6%)	High incidence in both groups, including grade 3-4 fatigue/asthenia. • Consider starting treatment at lower dose and quickly titrate to full dose as patient tolerates. 4.6% of enzalutamide and 1.3% of placebo treated patients experienced falls on study. Observe caution in this older population at risk, those with prior neuropathy, and at risk for fracture. Consideration of exercise, physical therapy and other falls prevention strategies.
Mental impairment (4.3%)	1.6% incidence of hallucinations in AFFIRM, the majority whom were on concomitant opioids. Judicious review of concomitant medications. These symptoms can improve over time.
Infections (19.4%)	Neutropenia reported in 15% of enzalutamide and 6% of placebo treated patients, death from infection in 1% and 0.3% respectively. Consideration for routine evaluation of blood counts.
Diarrhea (21.8%)	Hydration and use of anti-diarrheal as supportive measure as indicated. Consideration of volume status as contribution to symptoms of fatigue and adverse outcomes such as falls.
Drug interactions	Strong CYP2C8 inhibitors can increase plasma exposure, consider dose reduction of enzalutamide. • Strong CYP2C8 inhibitors: abiraterone, gemfibrozil (increases enzalutamide AUC by over 2x), ritonavir, sorafenib. • Moderate CYP2C8 inhibitors: celecoxib, deferasirox, felodipine, irbesartan, lapatinib, nilotinib, pioglitazone, quinine, rabeprazole, rosiglitazone, tamoxifen, teriflunomide, trimethoprim. Concomitant use of CYP3A4 or CYP2C8 inducers may decrease plasma concentration of enzalutamide. Conduct additional INR monitoring on warfarin.
Enzalutamide administration	• Recommended dose: 160 mg (in 40 mg capsules) oral once daily. • Food effect: none, take with or without food. • Renal impairment: no significant differences seen between men with normal or abnormal renal function, effect in severe renal impairment (CrCl<30 mL/min) or end stage renal disease is not known. • Hepatic impairment: effect in severe hepatic impairment (Child-Pugh Class C) is not known • Pharmacokinetics: median peak plasma concentration, 1 hour, steady state at 28 days following daily administration, metabolized predominantly by liver, half-life 5.8 days.

Does the advantage of enzalutamide oral therapy justify its use before docetaxel?

In an open label single arm phase II study of enzalutamide 160 mg daily in 67 hormone naïve non-castrate men with prostate cancer at any stage, 39% of whom had radiographic metastasis, PSA response rate of > 80% was 93% at week 25.[11] The median decrease in PSA level was -99%, with maintenance or increase in levels of testosterone. Gynecomastia, fatigue and hot flushes were the most common toxicities. These data are promising, but activity and toxicity profile of enzalutamide in large studies of docetaxel naïve men are not completely reported, and thus use prior to docetaxel is not currently endorsed. Completed and maturing, as well as ongoing studies will provide these answers.

Preliminary results from the PREVAIL study, a phase 3 trial in 1700 chemotherapy naïve men with mCRPC administered enzalutamide 160 mg daily compared to placebo have recently been completed and results updated (NCT01212991). An independent data safety monitoring board recommended the current protocol be stopped to allow all patients on the placebo arm to be treated with enzalutamide since the interim analysis showed a 30% reduction in risk of death and an 81% reduction in risk of radiographic progression or death in favor of the enzalutamide arm.[12] Abiraterone and prednisone, studied in the same mCRPC chemotherapy naïve population, was FDA endorsed based upon significant improvement in radiographic PFS and trend toward overall survival (overall survival abiraterone-prednisone not reached versus 27.2 months for prednisone alone, HR 0.75; 95% CI 0.61 to 0.93, p = 0.01). The survival benefit of enzalutamide compared to placebo is more robust, despite a smaller absolute difference in overall survival in the enzalutamide group (overall survival: enzalutamide arm: 32.4 months [range 31.5 months to limit NR] versus placebo arm: 30.2 months [range 28 months to limit NR]). The trend toward longer median survival even in the comparator arms (30.2 months for placebo on enzalutamide study versus 27.2 months for prednisone as abiraterone comparitor) is possibly explained by the increasing array of agents available for mCRPC which continue to improve upon overall survival in the post docetaxel setting. Full report of the data from PREVAIL as well as an FDA endorsement for use of enzalutamide prior to docetaxel is expected in 2014. Decisions regarding best sequence of abiraterone and enzalutamide in the pre and post docetaxel setting will require further study.

Ongoing studies are underway to assess toxicity of abiraterone and enzalutamide when combined. Phase II studies of enzalutamide compared to bicalutamide, the US STRIVE study which is enrolling men with mCRPC with biochemical as well as those with radiographic progression, and the European TERRAIN trial, enrolling mCRPC patients only, are ongoing (NCT01664923). Enzalutamide is being evaluated in smaller studies in the post-prostatectomy setting for men with high risk features, in the pre-prostatectomy space, in the localized hormone naïve space, as well as in novel combinations. A phase I combination of docetaxel every 21 days with enzalutamide 160 mg daily appeared well tolerated without demonstrable effect upon docetaxel pharmacokinetics.[13] Ongoing and planned studies of enzalutamide combinations and sequences include studies with PSA-Tricom, abiraterone acetate with prednisone (AAP), tivozanib, and sipuleucel-T.

How should enzalutamide be sequenced with other agents?

Enzalutamide following abiraterone acetate with prednisone

Though studies are ongoing, we know little about the toxicity and efficacy of novel prostate cancer agents given in sequences not previously studied. Reports from compassionate use programs for enzalutamide and abiraterone provide some insight. In Germany, 35 patients with mCRPC and progression following docetaxel and AAP received enzalutamide.[14] Rate of PSA response to enzalutamide > 50% was 28%, less than the 54% in the AFFIRM study. Those who initially responded to AAP had higher PSA response rate to enzalutamide (43% abiraterone responders versus 15% non-responders), though the numbers were small. In Britain 46 patients with mCRPC with progression following docetaxel and AAP had mean time to PSA progression on enzalutamide of 15 weeks, less than the 8.3 months in the AFFIRM study.[15] Caution should be taken for any comparison to AFFIRM however, given early reporting and small numbers, with 30 patients still on ezalutamide at the time of database publication. Rates of toxicity were similar to those reported in AFFIRM, though the authors cited an increased rate of psychiatric side effects than previously reported.

Abiraterone acetate with prednisone following enzalutamide

Thirty-eight patients from two European sites with mCRPC with disease progression on enzalutamide following AFFIRM unblinding were prospectively followed and subsequently treated with AAP.[16] Of these men, 45% did not demonstrate a PSA response of > 50% during enzalutamide treatment. On AAP, PSA response

> 50% was seen in 8% of patients, with one patient responding to AAP who had not previously responded to enzalutamide. One patient had a radiographic response. Median overall survival on AAP in this group following enzalutamide therapy on AFFIRM was 7.2 months. Toxicity of AAP following enzalutamide was consistent with previous AAP studies.

In a similar report, twenty-seven evaluable men from four centers with disease progression following enzalutamide on AFFIRM received AAP.[17] In this group where 60% experienced a 50% decline in PSA on enzalutamide, only 3% had a > 50% PSA response to AAP. There were no radiographic responses and the median overall survival was 50.2 weeks. Toxicity was not reported, though no patient discontinued study drug due to toxicity.

Conclusion

Enzalutamide is another agent in the expanding therapeutic field for men with mCRPC. Current labeling supports use following docetaxel, though soon data should be available from the PREVAIL study regarding clinical benefit and safety in men with mCRPC prior to docetaxel. The lure of an oral agent like enzalutamide for convenience and possible toxicity benefit over cytotoxic chemotherapy may not reflect actual outcomes, particularly for those at risk for toxicities unique to enzalutamide. Findings in the small study of hormone naïve patients indicate that monotherapy in non-castrate individuals may lead to short term response without suppressing testosterone levels, but the long term rates of control, toxicity and survival will need to be determined. The survival benefit of enzalutamide for men following docetaxel is clear, but whether this benefit will be potentiated for docetaxel naïve men with mCRPC, and if enzalutamide will lead to response improvement relative to bicalutamide in docetaxel naïve men, is yet to be determined. Steroids are required for the safe administration of abiraterone acetate, are routinely used with docetaxel, and are frequently used as a comparator in randomized trials thus better understanding the effects of corticosteroids in men with mCRPC is warranted. Small series of patients that have been treated with enzalutamide on the AFFIRM study and those patients followed in the compassionate use programs for enzalutamide, have reported a decrease in the overall response to subsequent treatment with abiraterone acetate with prednisone. This preliminary data indicate that a cross resistance mechanisms does exist to enzalutamide and abiraterone, highlighting another area of future research to improve the care of men with mCRPC.

Disclosure

Dr. Jean Hoffman-Censits has no potential conflict of interest.
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Practical guide to the use of radium 223 dichloride

Robert B. Den, MD,[1,2,3] Laura A. Doyle, MS,[2] Karen E. Knudsen, MD[1,2,3,4]

[1]Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA
[2]Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA
[3]Department of Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA
[4]Department of Urology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

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Introduction: *Bone seeking radiopharmaceuticals have been used for decades in the palliation of pain from bone metastases emerging from prostate cancer. Recent clinical evidence has demonstrated an improved survival in men with metastatic castration resistant prostate cancer (CRPC) with radium 223.*

Material and methods: *A review of the literature was performed to identify the role of radiopharmaceuticals in the management of prostate cancer. We focused on prospective trials in order to identify the highest level of evidence describing this therapy. Further, we focused on providing a clinical guide for the use of radium 223.*

Results: *The phase III ALSYMPCA trial which compared radium 223 to placebo in men with symptomatic CRPC demonstrated a statistically significant improvement in median overall survival of 3.6 months and an improvement in time to first skeletal related event. There were higher rates of myelosuppression and diarrhea with radium 223, however, no clinically meaningful differences in the frequency of grade 3 or 4 adverse events were observed between the study groups.*

Conclusion: *Radium 223 is a safe and effective therapy in men with symptomatic CRPC providing a survival advantage on par with novel antiandrogens, CYP-17 inhibitors, and chemotherapy. Radium 223 has huge potential in combination strategies as well as for use earlier in the natural history of metastatic prostate cancer.*

Key Words: radium 223, castration resistant prostate cancer, alpha particle, radiopharmaceuticals

Introduction

Prostate carcinoma is the most common non-cutaneous malignancy diagnosed in US men and the second leading cause of cancer related death with approximately 29480 men succumbing to the disease in 2014.[1] Primary therapy for localized disease consists of either surgical resection or radiation therapy,[2] however, for patients with recurrent or metastatic prostate cancer, treatment consists of androgen deprivation therapy through depletion or blockage of circulating androgens.[3] While initially effective, most men develop resistance as manifested by either clinical, radiographic or most commonly biochemical progression (increase in prostate-specific antigen despite "castrate" [< 50 ng/dL] levels of testosterone).[4] The development of castration resistant prostate cancer (CRPC) signals an inappropriate reactivation of the androgen receptor (AR) axis resulting in growth and proliferation.[5] Further, targeting of the AR pathway, through either the disruption of adrenal production of androgens with abiraterone acetate,[6,7] or inhibition of ligand binding using the second generation antiandrogen enzalutamide,[8] results in increased survival for this population of men. Other Food and Drug Administration (FDA) approved modalities which have increased survival for men with CRPC include chemotherapy[9,10] and immunotherapy.[11]

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Address correspondence to Dr. Robert B. Den, Department of Radiation Oncology, Thomas Jefferson University Hospital, 111 South 11th Street, Philadelphia, PA 19107-5097 USA

TABLE 1. **Physical characteristics of radiopharmaceuticals used in prostate cancer**

Radionuclide	Half-life	Decay particle	Tissue penetration
Radium 223	11.4 days	alpha	< 0.1 mm
Strontium 89	50.5 days	beta	5.5 mm
Samarium 153	1.9 days	beta, gamma	2.5 mm
Rhenium 186	3.8 days	beta, gamma	4.5 mm

Prostate cancer frequently metastasizes to the bone primarily within the axial skeleton (vertebral bodies, pelvis, ribs, and skull) but may also occur in the long bones.[12] Radiographically, osseous metastases are most often noted on ^{99}technetium methylene diphosphonate bone scintigraphy scans. However, newer modalities such as ^{18}sodium fluoride PET and ^{18}fluorodeoxyglucose PET are more frequently being utilized given their increased sensitivity for detection.[13]

Clinically, bone metastases are the primary cause of morbidity and mortality for men with metastatic CRPC,[14] with 80%-90% of patients eventually developing metastatic disease.[15] Bone lesions may cause pain or skeletal related events such as spinal cord compression, fractures, or hypercalcemia. Further, the extent of osseous involvement is associated with overall survival.[16] Given the systemic and complex nature of managing painful bone metastases, radiopharmaceuticals have emerged as a promising modality.

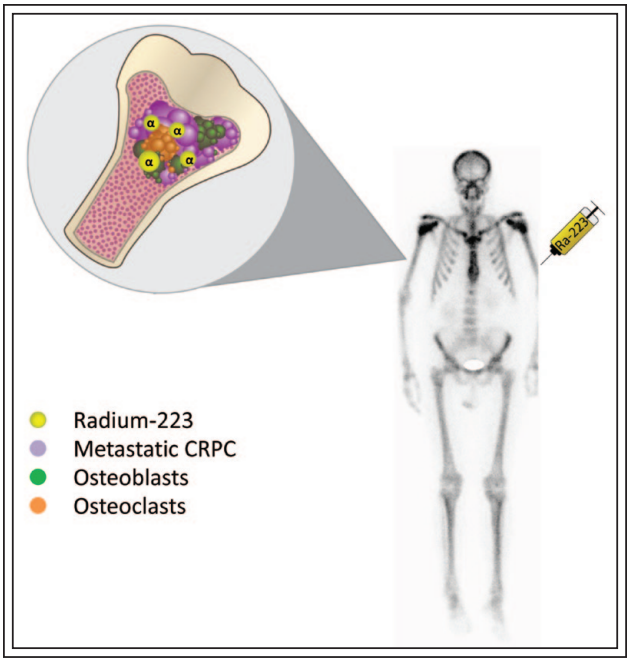

Figure 1. Overview schematic of radium 223 mechanism of action.

The current radiopharmaceutical agents used against metastatic prostate cancer include strontium-89, samarium-153, rhenium-186, and radium 223. The physical characteristics of these agents are shown in Table 1. Multiple randomized controlled trials have been conducted with these agents for the management of prostate cancer patients with bone metastases.[17-33] Historically, primary outcomes included pain response, decrease in analgesic consumption, and quality-of-life. Radium 223 is the first radiopharmaceutical agent to demonstrate improved survival among patients with symptomatic bone-metastatic CRPC.[32]

This review will provide an overview of radiopharmaceuticals in prostate cancer with a focus on the mechanism of action of alpha and beta emitters. Further, it will highlight radium 223, Figure 1, including the indications based on the clinical trials,[29-33] administration, and strategies to manage the side effects of therapy.

Alpha, beta, and gamma emission

Radioactive decay, also known as radioactivity, is the process by which the nucleus of an unstable isotope loses energy through emission of particles of ionizing radiation. Radiation may be emitted in the form of an alpha (α) or beta (β) particle, a gamma (γ) ray or any combination. An α particle consist of two protons and two neutrons, a β particle is a high energy electron, while a γ ray is described as ionizing electromagnetic radiation. Each type of radiation has different advantages and disadvantages.

Alpha particles have the shortest range of these particle types, resulting in a dense deposition of energy close to the origin of the particle emission. Thus, α particles provide more dense ionizing radiation over a shorter distance < 100 μm (approximately 2-10 tumor cell diameters), resulting in the induction of DNA double-strand breaks with minimized myelotoxicity.[30] Alpha particles can be stopped by a sheet of paper, eliminating the need for any radiation shielding. Radium 223, as an alpha emitter, administered intravenously requires no radiation safety precautions

such as particular sleeping arrangements, limited time or specified distance from children or pregnant women.

In contrast to alpha particles, β emitters have track lengths that consist of up to a few millimeters which results in collateral bone marrow toxicity. Further, β particles require increased shielding as they can penetrate paper, but can be stopped by a thin layer of high Z material depending on the energy of the particle. Consequently, β emitters are often stored in lead-shielded containers to reduce radiation exposure; however patients still have little to no radiation precautions or restrictions.

Bone physiology and cancer

Bone homeostasis is a complex cellular process consisting of osteoblasts, which function in bone production and mineralization, and osteoclasts, which function in bone resorption.[34] Bone matrix is initially organic osteoid whose calcium hydroxyapatite mineralization occurs through alkaline phosphatase function. Cancer cells cause inappropriate osteoblastic or osteoclastic activity resulting in either blastic or lytic lesions respectively.[35] Blastic function can be monitored clinically via alkaline phosphatase levels. The current radiopharmaceuticals either mimic calcium (radium, strontium) or bind as an attachment to the hydroxyapatite components of the bone matrix (samarium, rhenium).[36]

Current radiopharmaceuticals: indications and benefits

Strontium-89

Strontium-89 is a calcium analog approved by the FDA in 1993 for the treatment of painful bone metastases.[37] It decays as a pure β emitter with only 0.01% γ emission and is incorporated into bone when intravenously administered. Strontium has a 10-fold uptake increase into bone containing metastatic tumor as compared to normal healthy bone.[38] There have been multiple randomized trials evaluating the efficacy of strontium-89 with most focused on pain reduction. However, inter-study comparison is limited given the various grading systems utilized. A systematic review of strontium-89 reported a complete pain response varying from 8% to 77% with a partial pain response in 44% of patients.[39] In addition, use of analgesic decreased by 70%-80% and duration of clinical response varied from 3-6 months. The common toxicities include leukopenia, thrombocytopenia with nadir in counts occurring approximately 4-8 weeks post injection.

Samarium-153 lexidronam

Samarium-153, a β emitter with 28% γ emission, was approved by the FDA in the 1997 for the treatment of bone metastases. The radionuclide has a half-life of 1.9 days and is complexed with ethylene diamine tetramethylene phosphonate (EDTMP) which rapidly localizes to bone in association with hydroxyapatite. It has a five times greater affinity to tumor than normal bone. It is delivered intravenously and has a complete renal clearance within 6 hours of administration.[40] Multiple randomized phase III trials have consistently demonstrated an improvement in bone pain and reduced analgesic use.[24-26] As with strontium-89, myelosuppresion, particularly thrombocytopenia, is the most common side effect.

Rhenium-186 etidronate

Rhenium-186 hydroxyethylidene diphosphonate (HEDP) a β and γ emitter, has a half-life of 3.7 days. Its γ emission allows for bone metastases localization though imaging, making it both diagnostic and therapeutic. Rhenium has efficacy in pain reduction with thrombocytopenia and leukopenia being the most common toxicities.[27,28]

Comparison of beta emitters

These compounds have been compared in the management of patients with osteoblastic lesions to determine their relative efficacy. While all effective, there was no statistical significance between the various agents in terms of pain palliation, analgesic use, or bone marrow toxicity.[41-43]

Radium 223

Radium 223 was recently approved by the FDA in 2013 for the management of men with metastatic castrate resistant prostate cancer after the publication of a randomized phase III trial which showed an overall survival benefit.[32] Table 2 provides the indications, administration, and strategies to manage side effects. Radium 223, an alpha particle emitter, was originally selected given its half-life (11.4 days) that allowed convenient dosing, safe radon daughter isotope and high skeletal uptake in patients with osteoblastic metastases.[44]

The phase I dose escalation study of radium 223 consisted of 25 breast and prostate cancer patients with osteoblastic lesions who were injected with a single dose of the agent.[30] Pharmacokinetic studies demonstrated that within 24 hours < 1% of administered dose remained in circulation and was predominantly eliminated via the gastrointestinal tract. Pain relief was reported by 52%, 60%, and 56% of patients after either 1, 4, or 8 weeks respectively. Twenty-eight percent of patients

TABLE 2. **Administration and strategies to manage side effects of therapy for radium 223**

Indication	• Radium 223 is indicated for the treatment of patients with castration resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease
Administration	• Radium 223 is administered by slow intravenous injection over 1 minute • Prior to administration, the intravenous access line or cannula should be flushed with isotonic saline
Strategies to manage side effects	
Hematologic	• Hematologic evaluations should be performed at baseline and prior to every injection of radium 223 • Before the first administration ▸ absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L ▸ platelet count should be ≥ 100 x 10^9/L ▸ hemoglobin ≥ 10g/dL • Before subsequent administration ▸ ANC should be ≥ 1 x 10^9/L ▸ platelet count should be ≥ 50 x 10^9/L • If counts do not recover to the above values within 6-8 weeks of administration, despite supportive care, treatment should be discontinued • Supportive care includes transfusions and growth factors • Radium 223 should be discontinued in the event of life threatening complications despite supportive care for bone marrow failure • Patients are instructed to report signs of bleeding or infection
Non-hematologic	• Patients are instructed to remain well hydrated and to monitor oral intake • Patients are instructed to report signs of dehydration, hypovolemia, urinary retention or renal failure/insufficiency • Patients are instructed to follow good hygiene practices for at least 1 week post injection including: ▸ flushing the toilet several times after use ▸ promptly washing soiled clothing separately • Caregivers are instructed to use universal precautions including: ▸ hand washing ▸ using gloves and barrier gowns when handling bodily fluids ▸ patients are instructed to use condoms when sexually active and female partners are instructed to use birth control up to 6 months from last radium 223 injection

did experience a "flare" phenomenon. There was a significant decline in alkaline phosphatase amongst the prostate patient cohort. No dose limiting toxicities (defined as platelets < 20 x 10^9/L, or neutrophils < 0.5 x 10^9/L) were experienced. Myelosuppression was mild and reversible with a nadir 2-4 weeks after drug administration. However, nonhematologic toxicity consisting of transient diarrhea (40% of patients), fatigue (25% of patients), and nausea or vomiting (20% of patients) occurred.

The phase II double blind placebo control trial randomized 64 men with CRPC to receive four intravenous injections of either 50kBq/kg of radium 223 or placebo every 4 weeks. The primary endpoints were change in bone-alkaline phosphatase and time to skeletal related events (SREs).[29,45] At 4 weeks alkaline phosphatases levels were -65% in the radium 223 arm and +9.3% in the placebo arm ($p < 0.0001$). Time to skeletal related events was not statistically significant (14weeks versus 11 weeks, $p = 0.26$). There was a statistically significant change in time to PSA progression of 26 weeks versus 8 weeks and median change in relative PSA (-24% versus +45%). There was a trend to improvement in overall survival (65.3 weeks versus 46.4 weeks, $p = 0.066$), suggesting a potential survival advantage. Hematological toxicity was comparable in the two arms and noted only in the first 4 weeks of treatment with radium 223.

The phase III placebo controlled trial randomized 922 men with symptomatic bone-metastatic CRPC using a 2:1 ratio to receive six injections every 4 weeks of either radium 223 (50 kBq/kg) or placebo.[32] Entry criteria included at least two bone metastases without visceral metastases and either prior docetaxel treatment or inability to receive docetaxel. The primary endpoint was overall survival, with secondary endpoints of time to first SRE, time to alkaline phosphatase progression, alkaline-phosphatase response, alkaline-phosphatase normalization, time-to-PSA-progression, safety, and quality-of-life. The study was designed with 90% power to detect a hazard ratio for death of 0.76 at 5% significance level. The trial was halted at interim analysis after 809 patients (541 on radium 223 and 268 on placebo) had been randomized. The two arms were well balanced in terms of baseline demographics. At interim analysis, 50% of the patients receiving radium 223 had received all six injections in comparison to 35% of placebo while 21% and 19% were still undergoing therapy. Median survival was significantly increased from 11.2 months to 14.0 months with a hazard ratio of 0.695 in favor of radium 223.

Subset analysis revealed that the survival advantage was primarily seen in those patients who had not previously received docetaxel (hazard ratio 0.611; 95%CI: 0.423-0.883) as opposed to those who had received docetaxel (hazard ratio 0.755; 95%CI: 0.565-1.009) and those with ECOG performance of 0-1 (hazard ratio 0.691; 95%CI: 0.535-0.892) as opposed to those with a score ≥ 2 (hazard ratio 0.731; 95%CI: 0.398-1.343). Use of concurrent bisphosphonate did not impact the survival advantage. In addition, there was significant improvement in median time to SRE (13.6 months versus 8.4 months), time to alkaline phosphatase progression, and time to PSA progression (hazard ratio 0.671) favoring the treatment arm.

Adverse events (AEs) were determined for any man who received > 1 injection in 762 patients. AEs were observed in 88% of the radium 223 patients and 94% of placebo-treated patients. Serious AEs were higher in the placebo group (43% versus 55%) and treatment discontinuation due to AEs was higher in the placebo group (13% versus 20%). Grade 3/4 hematologic toxicities were comparable between the two arms (neutropenia 3% versus 1%, thrombocytopenia 6% versus 2%, anemia 13% versus 13%). Nonhematologic Grade 3/4 toxicities included bone pain (21% versus 26%), nausea (2% in either cohort), diarrhea (2% in either cohort), vomiting (2% in either cohort), fatigue (5% versus 6%), and bone pain (21% versus 26%). A statistically higher percentage of patients had meaningful improvement in quality-of-life with radium 223 over placebo.

Assessment and management

Prior to initiation of radium 223 therapy, baseline hematologic evaluation must be performed at which the absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L, platelet count of ≥ 100 x 10^9/L, and hemoglobin ≥ 50 x 10^9/L. Before subsequent treatments, the ANC should be ≥ 1 x 10^9/L, and platelet count of ≥ 50 x 10^9/L. If recovery to the values mentioned above does not occur within 6 to 8 weeks after administration, despite supportive care, radium 223 should be discontinued. Further, in patients with life threatening complications from bone marrow failure should have their treatments halted.

Given, that radium 223 is excreted via the intestinal system, which can manifest as diarrhea, nausea or vomiting, careful monitoring of the patient's oral intake and fluid status is crucial to prevent dehydration. There are no contact restrictions for patients receiving radium 223 and patients are instructed to follow good hygiene during the 6 months of therapy and 1 week after completion of treatment to minimize radiation exposure to household members and caregivers.

Future directions

Radium 223 is the first radiopharmaceutical to provide a prolongation in overall survival in men with castration resistant prostate cancer. The safety profile of radium 223 is encouraging, in comparison to the β emitters, which may allow for increased dosing (phase I study planned), integration with myelosuppressive chemotherapy (NCT01106352, phase I/IIa study of safety and efficacy of radium 223 with docetaxel in patients with bone metastasis from castration resistant prostate cancer), or novel AR targeting agents (phase I study planned with enzalutamide and abiraterone acetate). The long term safety data of radium 223 are still unknown and are of particular importance when considering integration of this agent in the setting of non-metastatic or micro-metastatic disease especially in terms of potential secondary malignancy. However, this agent provides another beacon of hope in the management of this disease.

Disclosure

Dr. Robert B. Den is a speaker for the Bayer Algeta Oncology Speaker Bureau.
Dr. Karen E. Knudsen and Laura A. Doyle have no potential conflict of interest. □

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Practical guide to the use of chemotherapy in castration resistant prostate cancer

Daniel P. Petrylak, MD
Department of Medicine (Medical Oncology) and Urology, Yale Cancer Center, New Haven, Connecticut, USA

PETRYLAK DP. Practical guide to the use of chemotherapy in castration resistant prostate cancer. *Can J Urol* 2014;21(Suppl 1):77-83.

Introduction: *Chemotherapy, once thought to be toxic and ineffective in men with castration resistant prostate cancer (CRPC), has a significant impact on survival and quality-of-life in these patients. This article summarizes recent studies performed with two Food and Drug Administration (FDA) approved agents which have improved survival in men with CRPC, docetaxel and cabazitaxel.*

Materials and methods: *The literature on cytotoxic chemotherapy for castration resistant prostate cancer was reviewed. The individual efficacy, mechanisms of chemotherapeutic action, and appropriate disease states of administration were identified. Recent clinical trial results of chemotherapy combined with targeted agents was also reviewed.*

Results: *Front line cytotoxic therapy consists of docetaxel combined with prednisone. In two randomized trials, docetaxel based therapy demonstrated a 20%-24% improvement in survival over the palliative standard of care, mitoxantrone combined with prednisone. Eight randomized trials combining docetaxel/prednisone with other antiangiogenic, bone targeted, vaccine or metabolic therapies failed to demonstrate an improvement in survival over docetaxel alone. Cabazitaxel, an analogue of docetaxel which has activity in taxane resistant cell lines, is approved by the FDA, for use in CRPC patients who have previous exposure to docetaxel.*

Conclusions: *Docetaxel combined with prednisone remains the standard of care as first line cytotoxic therapy for CRPC. Cabazitaxel is an effective second line cytotoxic agent that improves survival; studies are underway comparing cabazitaxel to docetaxel as first line chemotherapy. Given its lack of survival benefit, as well as the emergence of new treatments for prostate cancer, mitoxantrone has a diminished role in the treatment of CRPC.*

Key Words: castration resistant prostate cancer, docetaxel, cabazitaxel, chemotherapy

Introduction

It is estimated that more than 29000 men will die from metastatic prostate cancer in 2014, making it the second leading cause of male cancer death.[1] The initial treatment for metastatic disease is surgical or medical castration; reduction in testosterone to levels of less than 50 ng/dL can rapidly and dramatically result in prostate tumor regression.[2] Clinical response to androgen blockade is manifested by a relief in pain from boney metastases, improvement in neurologic symptoms from spinal cord compression, and a decline in serum prostate-specific antigen (PSA). Despite initial clinical and symptomatic improvement, nearly all men will progress to castration resistant prostate cancer (CRPC). This state of disease is defined as progression of face of castrate testosterone levels, historically have a dismal prognosis with median survival times of 9-12 months. In addition, the morbidity associated with CRPC is significant as metastases to bone can lead to spinal cord compression, fractures, pain, cachexia, anemia, and ultimately death.

In the 1990s, the management of CRPC was limited to palliation of symptoms, due to a lack of effective

Address correspondence to Dr. Daniel P. Petrylak, Department of Urology and Medical Oncology, Yale University Cancer Center, 789 Howard Ave, FMP 312, New Haven, CT 06519 USA

treatments. Historically, chemotherapy for advanced prostate cancer was viewed as toxic and ineffective. Two reviews of single agent cytotoxic therapy in men with CRPC demonstrated that objective responses to chemotherapy were 6.5% to 8.7%, with no improvement in survival.[3,4] The combination of mitoxantrone-prednisone was approved by the Food and Drug Administration (FDA) based on palliation of bone pain; three randomized trials also demonstrated modest improvements in time to progression when mitoxantrone combined with corticosteroids was compared to corticosteroids alone.[5-7] Until 2004, CRPC was considered a chemotherapy resistant disease with no randomized study demonstrating a survival of chemotherapy.

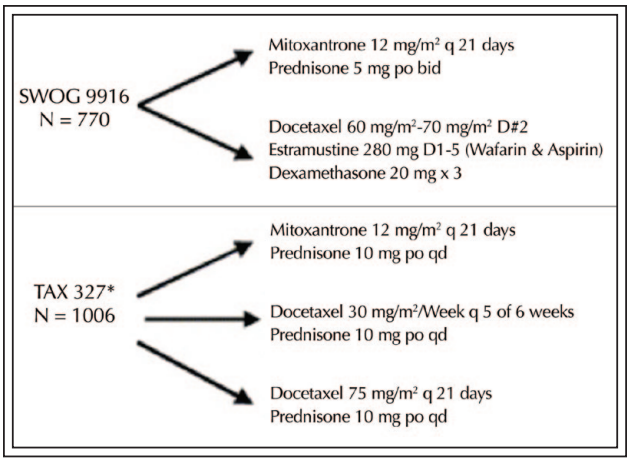

Figure 1. Study designs of SWOG 99-16 and TAX 327.

Docetaxel for CRPC

A semisynthetic taxane derived from the needles of *Taxus baccata*, docetaxel. Docetaxel reversibly stabilizes microtubules and prevents depolymerization.[8] Apoptosis results from accumulation of microtubules, as well as through phosphorylation of an oncoprotein, Bcl-2.[9] Both in vitro and in vivo studies found docetaxel to be effective against a wide range of human cancer cell lines, including the prostate cancer cell lines DU 145, PC-3 and LNCaP.[10,11] Phase I and II trials of docetaxel administered as a single agent or in combination with estramustine phosphate demonstrated PSA decline rates of > 50% in 36%-69% of treated patients, objective response rates of 17%-38% and median survivals of 20-23 months.[12-15] Two phase III trials compared docetaxel-based combination regimens with standard mitoxantrone/prednisone in men with progressive CRPC, Figure 1 and Table 1.

TAX327 was an international multi-center study that compared two different dosing schedules of docetaxel/prednisone with mitoxantrone/prednisone for metastatic CRPC.[16] No history of any prior chemotherapy in these CRPC patients was permitted except for estramustine. One thousand six patients were randomized to one of three arms: 1) docetaxel 75 mg/m^2 every 3 weeks; docetaxel 30 mg/m^2 weekly for 5 of 6 weeks or mitoxantrone 12 mg/m^2 every 3 weeks. Prednisone at 5 mg PO bid was given to all patients at 5 mg PO BID.

The median survival was superior to mitoxantrone only in the 3 week docetaxel arm (18.9 months versus 16.4 months) (p = 0.009). Weekly docetaxel did not result in a statistically significant survival advantage (17.4 months versus 16.4 months, p = 0.36). When compared to the mitoxantrone/prednisone group, the reduction in the risk of death was 24% and 9% for the every 3 week and weekly docetaxel arms, respectively. An updated survival analysis found that more patients survived 3 years when treated with docetaxel either every 3 weeks or weekly (18.6% and 16.6% when compared to mitoxantrone (13.5%).[17] PSA declines of > 50% were significantly higher (45% and 48%) in patients treated on the 3 week and weekly docetaxel groups, respectively, than in the patients treated with mitoxantrone (32%). No significant differences in

TABLE 1. **Docetaxel based phase III trials**

Study	Treatment regimen	Objective measurable response rate (%)	PSA response rate (%)	% with palliative response	Time to progression	Survival (months)
SWOG 9916	Docetaxel/estramustine	17	50	17*	6	18
	Mitoxantrone/prednisone	10	27	11	3	16
TAX 327	Docetaxel (q 3 wks)/prednisone	12*	45	35	7.9*	18.9
	Docetaxel (q wk)/prednisone	8*	48	31	8.2*	17.4
	Mitoxantrone/prednisone	7*	32	22	7.8*	16.5

*did not reach statistical significance

objective response rates were observed in the three treatment arms. Docetaxel therapy was associated with superior palliation of bone pain (33% and 31% in the docetaxel every 3 weeks and weekly regimens as compared to 21% in the mitoxantrone group). Quality-of-life, in general, when using the FACT-P instrument was significantly better in the docetaxel groups as compared to the mitoxantrone group.

Neutropenia was more frequent in the Q3 week docetaxel group (32% compared to 21.7% in the mitoxantrone group). Grade 3 and 4 neutropenia occurred in 3% of patients in the docetaxel Q3 week group, with 2.7% experiencing febrile neutropenia. Neuropathy and alopecia were also more frequent in the docetaxel arms; however the patterns of toxicity were not significantly different between the docetaxel and mitoxantrone groups.

SWOG lead an intergroup study comparing docetaxel/estramustine to mitoxantrone/prednisone.[18] Men randomized to the experimental arm received estramustine at 280 mg PO tid on days 1-5, docetaxel at 60 mg/m^2 IV on day 2 every 21 days, and dexamethasone 60 mg PO in 3 divided doses prior to docetaxel. In contrast to TAX 327, patients did not receive prednisone. Men randomized to the control mitoxantrone arm received mitoxantrone at the same dosage and schedule as in TAX 327. Dose escalation to docetaxel 70 mg/m^2 or mitoxantrone 14 mg/m^2 was permitted for those patients who did not experience grade 3 or 4 toxicity in the first cycle of therapy. Docetaxel combined with estramustine improved median survival (17.5 months compared to 15.6 months, $p = 0.01$), progression-free survival (6.3 months compared to 3.2 months, $p < 0.001$). A greater percentage of patients demonstrated a > 50% PSA decline (50% as compared with 27%, $p < 0.0001$) with docetaxel/estramustine than mitoxantrone/prednisone. A trend towards an improved rate of objective responses in measurable soft tissue disease was noted in favor of Q 3 week docetaxel (17% versus 11%, $p = 0.030$). In addition, palliation of bone pain was not found to be statistically different in the two arms. Overall, the relative risk of death was reduced by 20% with docetaxel and estramustine as compared to mitoxantrone and prednisone (HR for death, 0.80; 95% CI: 0.67-0.97).

Grade 3 and 4 toxicities was reported at higher rates in the docetaxel prednisone arm compared to mitoxantrone/prednisone. The incidence of grade 3 or 4 cardiovascular (15% versus 7%, $p = 0.001$), neurological (7% versus 2%, $p = 0.001$), neutropenic fever (5% versus 2%, $p < 0.001$), gastrointestinal (20% versus 5%, $p < 0.001$), and metabolic disturbances (6% versus 1%, $p < 0.001$) were increased in the experimental arm. However, there was not a higher rate of discontinuation from the study and there was no increase in toxic deaths in the docetaxel/estramustine arm. Prophylactic anticoagulation with Coumadin and aspirin was added to the experimental arm approximately half way through the trial. A post-hoc analysis of toxicity revealed that anticoagulation decreased the rate of cardiac ischemia but not the rate of thrombosis. However, the evaluation of the use of anticoagulation is limited as the trial was not designed to detect a difference in vascular events for patients using anticoagulation as compared to those who did not receive Coumadin and aspirin.

Docetaxel based investigational therapies

A number of novel agents have been investigated for combination with docetaxel in an attempt to improve survival and response in patients with CRPC. The results with docetaxel-based combination therapy have been disappointing. Although serum VEGF levels correlate inversely with survival, antiangiogenesis agents (bevacizumab,[19] aflibercept,[20] lenalidomide,) combined with docetaxel/prednisone have not been a therapeutic advance. Combinations of bone targeted agent such as atrasentan,[21] dasatinib,[22] and ZD4054[23] with docetaxel have also had disappointing results. Vitamin D (calcitriol, DN-101 combined with weekly docetaxel also demonstrates no survival advantage over docetaxel/prednisone.[24] Reasons for the failure of combination therapy include marginal activity of the agents that were combined with docetaxel, as well as dose reduction of docetaxel due to overlapping toxicities.

Cabazitaxel

Granted fast track designation in November of 2009, cabazitaxel combined with prednisone was approved by the FDA in June 2010 for the treatment of men who had previously received a docetaxel-based regimen for CRPC. Cabazitaxel is the third cytotoxic agent to be approved by the FDA for castration resistant disease, and the second to demonstrate a survival benefit over mitoxantrone combined with prednisone.

Mechanism of action

Similar in structure and antitumor mechanism to paclitaxel and docetaxel, cabazitaxel is a novel second-generation, semisynthetic taxane that induces cell

death by microtubule stabilization through inhibition of disassembly. Cabazitaxel binds the N-terminal amino acids of the beta-tubulin subunit, and promotes stabilization of microtubules and the mitotic spindle. In addition to activity against paclitaxel and docetaxel sensitive human cervical, breast, and leukemia and prostate cancer cell lines, cabazitaxel demonstrates activity in taxane resistant cell lines.[25] The explanation for this pattern of activity stems from cabazitaxel's effect on the efflux pump of p-glycoprotein, known to be responsible for the multidrug resistance phenotype. Expressed in a variety of human tumors including prostate cancer, p-glycoprotein is responsible for the adenosine-5′-triphosphate (ATP) dependent extrusion of natural product chemotherapeutic agents such as doxorubicin, vinca alkaloids, as well as paclitaxel and docetaxel. The extra methyl groups found on cabazitaxel are more effective against the ATP dependent efflux pump of p-glycoprotein than similarly placed hydrol groups on docetaxel and paclitaxel. This phenomenon may also be responsible for the disproportional increase CNS accumulation of cabazitaxel with increasing plasma concentrations, demonstrated in rodent models; p-glycoprotein is known to be expressed in the capillary endothelium of the brain and may be responsible for the blood-brain barrier.[26]

Phase I study of cabazitaxel

Mita et al conducted a phase 1 study in 25 patients with chemotherapy refractory solid tumors. Cabazitaxel was administered at four dose levels (10, 15, 20, and 25 mg/m^2) as an intravenous (IV) infusion every 3 weeks. Of the eight CRPC patients entered on the trial, two, previously treated with mitoxantrone and docetaxel, demonstrated partial responses in soft tissue lesions to 15 mg/m^2 and 25 mg/m^2, of cabazitaxel, respectively. Both also manifested > 50% declines in PSA. A third prostate cancer patient demonstrated a minor response. Neutropenia was the major dose limiting toxicity observed, with two patients demonstrating prolonged grade 4 neutropenia at 25 mg/m^2, and another demonstrating febrile neutropenia at the same dose level.[27] In contrast to patients treated with docetaxel, fluid retention was not observed with cabazitaxel treatment. The commonest non-hematologic toxicities observed were diarrhea (52%), nausea (40%), and vomiting (16%). The authors concluded that 20 mg/m^2 of cabazitaxel administered every 3 weeks as the recommended phase II dose. It is to be noted that prophylactic granulocyte colony stimulating factor (GCSF) was not administered.

Phase III studies of cabazitaxel in docetaxel pretreated CRPC patients

The activity of cabazitaxel demonstrated against taxane resistant cell lines, as well as the responses observed in phase I lead investigators to study cabazitaxel in men with castration resistant prostate cancer previously treated with docetaxel. The TROPIC trial randomized 755 men to either cabazitaxel 25 mg/m^2 Q 3 weeks or mitoxantrone 12 mg/m^2 Q 3 weeks. Prednisone 5 mg PO BID was administered in both arms.[28] All patients were required to have progressive disease as evidenced by RECIST criteria or two consecutive rising PSAs at least 1 week apart in patients with non-measurable disease. The median age of patients entered in the metastatic study was 68. A median dosage of 529.2 mg/m^2 and 576.6 mg/m^2 of docetaxel were administered in the cabazitaxel and mitoxantrone/prednisone arms, respectively. Two or more cytotoxic regimens were previously administered to 29% and 31% of the patients entered on the mitoxantrone and cabazitaxel arms, respectively. Nearly half of the patients entered in the trial had symptomatic bone pain, with 25% of patients demonstrating visceral metastases.

After a median follow up of 12.5 months, a 3.1 month improvement in median survival was noted in favor of cabazitaxel treatment, with a hazard ratio of 0.7. At a median follow up of 25.5 months, 15.9% of the cabazitaxel patients survived > 2 years compared to 8.2% of patients treated with mitoxantrone. A subgroup analysis demonstrated that the survival benefit of cabazitaxel over mitoxantrone was maintained in patients who discontinued docetaxel for disease progression compared to those who stopped docetaxel due to toxicity, completion of 10 cycles of treatment, or for other reasons.[19] Although patient selection may play a role, the median survival from the time of the first docetaxel dose in the cabazitaxel group was 29 months (95% CI 27-31) versus 25 months (95% CI 23-28) in the mitoxantrone group. PSA declines of > 50% and objective response rates were superior (39.2% and 14.4%) in the cabazitaxel arm when compared to the mitoxantrone arm (17.8% and 4.4%). The palliation rates using the PPI, were similar in both arms.

Neutropenia was the most commonly encountered toxicity, with grade 3 or higher events occurring in 82% of patients treated with cabazitaxel. Febrile neutropenia was observed in 8% of patients. The prevalence of cabazitaxel induced neutropenia increases with age, and was observed at a 6.6% higher rate in patients over the age of 65. Grade 3 diarrhea was observed in 6% of patients on the cabazitaxel arm

TABLE 2. **Common toxicities of Docetaxel and Cabazitaxel and their management**

Drug	Dose/schedule	Toxicity	Management
Docetaxel Contraindications: Baseline neutrophil count less than 1500 cells/μL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80, severe hepatic dysfunction (bilirubin >Upper limit of normal (ULN), SGOT and/or SGPT >1.5XULN concomitant with alkaline phosphatase >2.5XULN	75 mg/m^2 Q 3 weeks	Neutropenia	Per ASCO guidelines, risk of febrile neutropenia <20%, use Colony Stimulating Factors (GCSF, GmCSF) based on age, medical condition, history, disease characteristics. Monitor CBC at least weekly
		Fluid retention	Prophylactic administration of steroids, monitor with daily weights, diuretics as needed
		Hypersensitivity reaction	Corticosteroids, antihistamines, H2 antagonists
		Neuropathy	No standard treatment
Cabazitaxel Contraindications: Baseline neutrophil count less than 1500 cells/μL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80	25 mg/m^2 Q 3 weeks	Neutropenia	GCSF prophylaxis recommended for age > 65, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation, poor nutritional status, other comorbidities. Monitor CBC at least weekly
		Diarrhea	Hydration, treat with antidiarrheals (loperamide). If ≥ grade 3, dosage should be modified
		Hypersensitivity reactions	Corticosteroids, antihistamines, H2 antagonists

compared to < 1% of patients on the mitoxantrone arm. As with neutropenia, diarrhea was more frequently observed in patients over the age of 75. Diarrhea also was observed at a 8.6% higher rate in patients who had a prior history of radiation therapy. A higher rate of death due to adverse events was noted in patients treated on the cabazitaxel/prednisone arm when compared to mitoxantrone/prednisone. Of the 18 patients on the cabazitaxel arm who died of adverse events, 7 patients died of neutropenic sepsis, in contrast to 1 patient on the mitoxantrone arm. It is to be noted that prophylactic colony stimulating factors were not administered during the first cycle of therapy, which could possibly reduce the risk of neutropenic death. This pattern of toxicity has lead the FDA to recommend administration of prophylactic growth factors in patients treated with cabazitaxel who are older than 65, have had extensive prior radiation, poor nutrition, previous febrile neutropenia, poor performance status or other serious comorbidities. In a report of a global early access program performed in Italy, CRPC patients treated with six cycles of cabazitaxel experienced neutropenia (33.9%), leukopenia (15.6%), anemia (6%), and asthenia.[29] Table 2 shows common toxicities of docetaxel and cabazitaxel and their management.

Two relevant questions regarding sequencing of cabazitaxel and dosage are being answered by randomized clinical trials. Given cabazitaxel's efficacy in docetaxel pretreated patients, it would be logical to evaluate cabazitaxel as front line chemotherapy in men with castration resistant prostate cancer. An international randomized trial of docetaxel combined with prednisone versus cabazitaxel (20 mg/m^2 or 25 mg/m^2)/prednisone is underway, clinical trials.gov NCT01308567. To further define the optional dose, a second study is randomizing patients to either 20 mg/m^2 or 25 mg/m^2 of cabazitaxel, clinical trials.gov NCT01308580.

Sequencing of treatments

With the recent approvals of abiraterone,[30] radium 223,[31] sipuleucel T[32] in the pre-docetaxel space, given the relative lack of toxicity of the aforementioned treatments, chemotherapy potentially could be administered later in the course of disease. It is unclear whether administration of any of these agents before either docetaxel or cabazitaxel affects efficacy and toxicity of these cytotoxic agents. Retrospective studies have been performed in small, select groups of patients and are difficult to apply to individual treatment decisions. For example, the preclinical observation that docetaxel may actually have cross resistance with hormonal agents due to docetaxel inhibition of androgen receptor translocation theoretically could make taxanes less effective after administration of abiraterone or enzalutamide.[33,34] Pond et al found that patients previously treated with ketoconazole/hydrocortisone in a randomized trial of docetaxel+/- AT-101, a novel bcl-2 inhibitor, trended towards bursting overall survival, objective response rates, and PSA declines compared to those patients who had not received prior ketoconazole/hydrocortisone.[35] In a retrospective evaluation of 35 patients who received docetaxel after abiraterone treatment, the median survival was 12.5 months, significantly lower than what was observed in TAX 327. Patients refractory to abiraterone were also refractory to docetaxel. In a small subgroup of patients treated with cabazitaxel after abiraterone alone, abiraterone followed by enzalutamide, or in enzalutamide alone, 16/41(39%) of patients demonstrated a > 50% PSA decline, with a median survival of 15.8 months.[36] Clearly, prospective randomized trials are needed, utilizing biomarkers, to determine the optimal sequence of these agents for both survival and toxicity.

Conclusions

Both docetaxel and cabazitaxel have antitumor activity in chemotherapy naïve and chemotherapy pre-treated patients, respectively. Combination therapy with docetaxel has not resulted in increased survival. Although randomized trials are currently underway to define which of these two agents should be administered as front line therapy, the optional sequences of these agents with newer agents such as abiraterone, enzalutamide and radium 223 have yet to be defined.

Disclosure

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Practical guide to bone health in the spectrum of advanced prostate cancer

Valentina Butoescu, MD, Bertrand Tombal, MD
Cliniques universitaires Saint-Luc, Institut de Recherche Clinique Université catholique de Louvain, Brussels, Belgium

BUTOESCU V, TOMBAL B. Practical guide to bone health in the spectrum of advanced prostate cancer. *Can J Urol* 2014;21(Suppl 1):84-92.

Introduction: *In the advanced stage of prostate cancer, bone is consistently the first and, later on, the dominant extra-nodal metastatic site. Bone metastases account for most of prostate cancer's morbidity.*
Materials and methods: *We have performed a literature review using the MEDLINE database for publications on: 1) bone metastases (androgen deprivation therapy); 2) cancer treatment induce bone loss; 3) skeletal related events; 4) denosumab; 5) zoledronic acid.*
Results: *Prostate cancer cells disrupt the normal bone remodeling process, invade the skeletal environment, and ultimately weaken the bone structure. This may result in skeletal complications, also known as skeletal related events (SREs), including pain, fractures, spinal cord compressions requiring surgery, radiotherapy or change in anti-cancer treatments. SREs negatively impact quality-of-life and survival and represent a major cost for the healthcare system. The bone metastases conundrum is further aggravated by the fact that androgen deprivation therapy (ADT), the reference systemic treatment of advanced prostate cancer, profoundly affects the skeletal integrity as well. ADT accelerates the physiological bone resorption, leading to osteoporosis and fragility fractures.*
Conclusion: *The concept of "bone health" or "skeletal heath" refers to the diagnostic, prevention, and treatment of cancer treatment induced bone loss (CTIBL) and metastasis, and their respective complications, osteoporotic fractures and SREs.*

Key Words: prostate cancer, androgen deprivation therapy, osteoporosis, skeletal related events, bisphosphonates, denosumab

Introduction

Advanced prostate cancer is characterized by a very high tropism to bone.[1,2] Less than 10% of men diagnosed with prostate cancer will ultimately die of the disease.[3] In those progressing to lethal stage prostate cancer, the skeleton is the first metastatic extra-nodal landing site in 80% of patients and, overall, 90% of patients will have bone metastases.[4,5] The metastatic tissue replaces the normal bone marrow content, leading to anemia. But more importantly, metastases alter the normal bone remodeling processes and invade the surrounding structures, resulting in complications such as pathologic fractures, pain, spinal cord compression. Registration authorities have aggregated these complications and coined the term of skeletal-related events (SREs), mostly for the purpose of proper evaluation of new pharmacological entities.[6] SREs are common in all "osteotropic" cancers, such as breast, prostate, and lung cancer.

In breast and prostate cancer, skeletal integrity is also compromised by hormonal treatments, androgen deprivation therapy (ADT) in prostate cancer patients. ADT increases bone resorption and is a known risk factor for osteoporosis and osteoporotic fractures.

The concept of "bone health" or "skeletal heath" refers to the diagnostic, primary and pharmacological prevention, and treatment of cancer treatment induced bone loss (CTIBL) and metastasis, and their respective complications, osteoporotic fractures and SREs. Bone health is a major issue in prostate cancer because it impacts quality and duration of life of the patients. The

Address correspondence to Dr. Bertrand Tombal, Service d'Urologie, Cliniques universitaires Saint Luc, Avenue Hippocrate, 10, B-1200 Brussels, Belgium

TABLE 1. **Observed changes in bone mineral density at 12 months in patients treated with androgen deprivation therapy**

Study	Patient number	Treatment	BMD changes at 12 months
Eriksson et al[7]	27	Orchiectomy or oestrogens	Hip: -9.6% Radius: -4.5%
Maillefert et al[8]	12	LHRH agonist	Hip: -3.9% Lumbar spine: -4.6%
Daniell et al[10]	235	Orchiectomy or LHRH agonist	Hip: -2.4%
Berrutti et al[50]	35	LHRH agonist	Hip: -0.6% Lumbar spine: -2.3%
*Higano et al[51]	19	LHRH agonist	Hip: -2.7% Lumbar spine: -4.7%
Mittan et al[13]	15	LHRH agonist	Hip: -3.3% Radius: -5.3%

*9 months of androgen deprivation therapy
BMD = bone mineral density; LHRH = luteinizing hormone releasing hormone

aim of this review is to understand the basic facts and figures of CTIBL and bone metastasis and to provide some guidance on when and how to administer preventive or curative measures. This review will not include information on recent developments in diagnostic techniques or data on radionuclides.

ADT induced CTIBL in prostate cancer patients

The association between surgical castration and accelerated bone loss was first described more than 15 years ago and confirmed since then by several prospective studies.[7-12] After 12 months of ADT, men would usually lose between 2% and 10% of their bone mineral density (BMD), measured by dual-energy x-ray absorptiometry (DXA) at their hip or radius, Table 1. CTIBL begins very early in the course of treatment with ADT, as suggested by the concentration of urinary bone resorption marker N-telopeptide that already increases after 6 months of ADT.[13] Large epidemiological surveys have demonstrated that ADT induced CTIBL increases the risk of fragility fracture, modestly but significantly, Table 2.[14-16] This risk may although become significant when added to other traditional risk factors such as a low or high body mass index, a history of a prior fracture at more than 50 years of age, a parental history of hip fracture, being a current smoker, receiving corticosteroid treatment for > 3 months, an excessive alcohol use, and a history of rheumatoid arthritis.[17] These additional risk factors are important to decide if a patient requires treatment. In addition, the impact of ADT should be modulated according to the age of the patient and the duration of treatment. In one of the aforementioned surveys, the relative risk of any fracture was 1.07 for patients receiving ≤ 4 monthly doses of luteinizing hormone releasing hormone (LHRH) agonists and 1.45 for ≥ 9 doses, the relative risk increasing by 1.21 for each age 5 year categories.[15]

TABLE 2. **Risk of fracture associated with chronic administration of androgen deprivation therapy (ADT)**

Study	Patient number	ADT duration	Fracture risk (%)					
			All sites		Hip		Hospitalization	
			ADT	No ADT	ADT	No ADT	ADT	No ADT
Shahinian et al[15]	50613	1 yr-5 yr	19.6	12.6	4.06	2.06	5.19	2.37
Smith et al[16]	11661	> 12 yr	7.88*¶	6.51*¶	1.26*	0.98*		
Alibhai et al[14]	19079	6.7 yr	17.2¶¶	12.7¶¶	2.6	2	8	5.7

*rate per 100 person-years; ¶relative risk 1.21; p < 0.001 ¶¶hazard ratio 1.65, 95% CI 1.53-1.78

Monitoring and prevention of CTIBL in ADT treated patients

DXA can be used to monitor spine, hip, or total body BMD. The spine is the preferred site of densitometry for serial measurement of bone mass to monitor changes in BMD.[18] The European Association of Urology (EAU) guidelines recommend performing a DXA every 2 years after initiation of castration, provided there are no other risk factors, and every year if there are risk factors.[19] Patients should be encouraged to make specific lifestyle changes: quit smoking, reduce alcohol and caffeine consumption, engage in regular weight-bearing exercises, and favor a healthy diet of foods and beverages containing calcium (dairy) and vitamin D (fatty fish).[20] The National Comprehensive Cancer Network (NCCN) guidelines recommend assessing fracture risk using the FRAX algorithm (www.shef.ac.uk/FRAX/index.htm) by considering CTIBL as "secondary osteoporosis".[21]

Pharmacological prevention and treatment of ADT induced CTIBL

One of the most important questions for the physicians is when to initiate preventive treatment in ADT treated patients.

Physicians should make the difference between osteopenia and osteoporosis. This can be evaluated using the T-score on DXA and the WHO classification. The T-score is the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient. Osteopenia is defined by a T score <-1 and >-2.5; osteoporosis by a T score ≤ -2.5, and severe osteoporosis by a T score ≤ -2.5 with history of 1 or more fragility fracture. Osteoporosis is a condition that must be corrected notwithstanding initiation of ADT. The question is more about the benefit of treating osteopenic patients before they are really osteoporotic, as an alternative to monitor BMD during ADT.

The EAU guidelines recommend treating osteoporotic patients (DXA T-score ≤ -2.5) with denosumab or bisphosphonates, but provide no guidance for osteopenic patients.[19] NCCN guidelines recommend treatment with zoledronic acid (ZA) (5 mg IV annually), alendronate (70 mg PO weekly), or denosumab (60 mg sc every 6 months) for men with a 10 year probability of hip fracture ≥ 3% or a 10 year probability of major osteoporosis-related fracture ≥ 20% on the FRAX algorithm.[21]

Denosumab (denosumabis) a fully human monoclonal antibody that specifically inhibits the receptor activator of nuclear factor-KB (RANK) ligand (RANKL), which is produced by osteoblasts and progenitor cells and plays a central role in the maturation of pre-osteoclasts into osteoclasts.[22] Denosumab, administered subcutaneously (sc) every 6 months at the dose of 60 mg, is currently the only agent approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the prevention of osteoporotic facture in non-metastatic ADT treated patients. Inclusion criteria of the registration trial were: ≥ 70 years old, or a DXA T-score <–1.0 at baseline, or a history of osteoporotic fracture.[23] These criteria actually describe a mixed population of osteopenic and osteoporotic patients. In the registration trial, denosumab significantly increased BMD and decreased the incidence of new vertebral fractures at 36 months (1.5% versus 3.9% with placebo; p = 0.006).[23] In that setting, the incidence of side effects was low.

Although not registered for that specific indication, bisphosphonates zoledronic acid (4 mg IV every 3 or 12 months) and alendronate (90 mg oral weekly) have been studied in that indication, in smaller shorter studies not powered to detect a reduction of the incidence of fracture, Figure 1.[24-26] Although recommended by guidelines, prescription of bisphosphonates in osteopenic patients not supported by specific registration should be left to the discretion of the physician.[19]

Prevention of complications of bone metastases

With the widespread use of prostate-specific antigen (PSA), most patients are diagnosed with localized or locally advanced disease and ADT is usually started in absence of any radiological evidence of metastases. Similarly, most patients will progress and become resistant to castration with no detectable metastasis.[27] But ultimately, the skeleton will be the first metastatic site in 80% of patients and, later on, 90% of patients will have bone metastases.[4,5]

Prostate cancer cells disseminating in the bone marrow do not destroy the bone on their own. Instead, they alter the functions of osteoclasts and osteoblasts, and hijack signals coming from the bone matrix, thereby disrupting physiological bone remodeling.[28] Specifically, there is a 'vicious cycle' whereby metastatic cells residing in the bone marrow secrete factors that stimulate osteoclast-mediated bone resorption whereas growth factors released from resorbed bone stimulate tumor growth. Taken together, this leads to an imbalance between bone resorption and bone formation, resulting in enhanced skeletal destruction and occurrence of SREs.[29] SREs are present at diagnosis of bone metastasis in 10% of

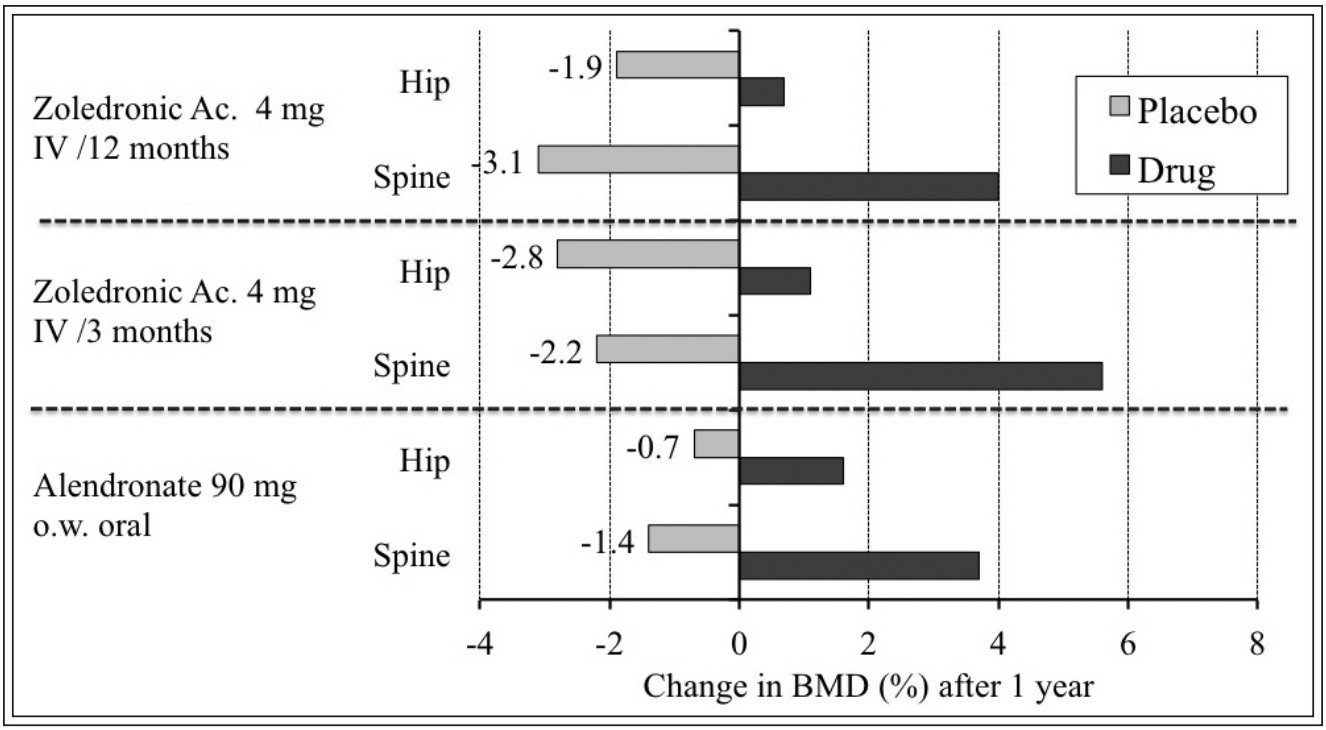

Figure 1. Benefit of bisphosphonate of prevention of androgen deprivation therapy induced cancer treatment induced bone loss in prostate cancer patients.

prostate cancer patients. Later on, 50% of bone metastatic castration resistant prostate cancer (CRPC) patients will experience one or more SREs.[30,31] In the ZA registration trial, the mean annual incidence of SREs in the placebo group was 1.47.[32] The presence of SREs is significantly associated with worse survival, poorer quality-of-life in CRPC patients, and a significant cost for the healthcare system.[33,34]

Pharmacological prevention of SREs, Table 3

The bisphosphonates clodronate and pamidronate were tested against placebo in three trials with palliative endpoints, both failing to provide significant clinical benefit, explaining why these drugs have never been widely prescribed by urologists in metastatic patients. Triweekly clodronate (intravenous (IV) 1500 mg) has

TABLE 3. **Summary of studies evaluating bone targeted agents in the prevention of SRE in bone metastatic CRPC patients**

Drugs	**Pamidronate versus placebo[36]**	**Zoledronate versus placebo[32]**	**Denosumab versus zoledronate[31]**
Number of patients	320	422	1701
Study duration	Fixed at 27 weeks	Fixed at 24 months	Event-driven, maximum 41 months treatment
% patients with SRE (p)	25 versus 25 (NR)	38 versus 49 (0.009)	36 versus 41
Median time to first on-study SRE (months)	Not tested	16.0 versus 10.5; p = 0.009	20.7 versus 17.1 p = 0.0002 non-inferiority, 0.008 superiority
Benefit on time to first and subsequent SREs	Not tested	HR = 0.64; p = 0.002	HR = 0.82; p = 0.008

SRE = skeletal related event; CRPC = castration resistant prostate cancer; HR = hazard ratio

been tested in a randomized controlled trial (RCT) on 209 symptomatic bone metastatic CRPC patients scheduled to receive mitoxantrone and prednisone.[35] There was no difference in palliative response, symptomatic progression free survival (PFS), overall survival (OS), and health related quality-of-life (HRQoL).

Triweekly pamidronate (IV 90 mg) has been tested in two similarly designed RCTs on a total of 378 symptomatic CRPC patients.[36] The pooled analysis did not detect significant differences in self-reported pain score, analgesic use, incidence of SREs, and mobility between pamidronate and placebo.

Zoledronic acid (ZA) was the first bisphosphonate to be approved for the prevention of SREs in bone metastatic CRPC. The 3 arms randomized controlled registration trial compared triweekly ZA IV, at a dose of 4 mg or 8 mg or placebo for 15 months.[32] The endpoints included proportion of patients with SREs, time to first SRE, skeletal morbidity rate, pain and analgesic scores, and disease progression. Excessive nephrotoxicity lead to a dose-reduction to 4 mg in the 8 mg treatment arm and to an increase in the infusion time from 5 minutes to 15 minutes. At the dose of 4 mg, ZA reduced the incidence of SREs by 11% compared to placebo (44.2% versus 33.2%; p = 0.021).[37] In the long term report, the median time to the first on-study SRE was 488 days for the ZA 4 mg versus 321 days for the placebo (p = 0.009); the annual incidence of SREs was 0.77 with ZA versus 1.47 with placebo (p = 0.005).[32] The study failed to show an OS improvement, although there was a trend toward a longer survival in patients receiving ZA (546 days versus 469 days for placebo; p = 0.103).[38]

Denosumab has been developed for the prevention of SRE in various cancer types at the monthly dose of 120 mg sc, 12 times higher than the dose used in osteoporosis treatment. The dose was optimized to achieve sustained suppression of bone markers; patients on less frequent dosing schedules showing evidence of escape.[39] Denosumab has been directly compared to monthly ZA (4 mg IV) in 1904 bone metastatic CRPC patients.[31] The primary endpoint was time to first on-study SRE and was assessed for non-inferiority. Secondary endpoints included assessment for superiority in time to first SRE and OS. Denosumab delayed by 18% the time to the first on-study SRE (20.7 months denosumab versus 17.1 months ZA, HR = 0.82, 95% CI 0.71-0.95; p = 0.0002 for non-inferiority and 0.008 for superiority). Denosumab also significantly delayed the time to first and subsequent SRE and reduced the total number of SRE observed in the trial (494 with denosumab versus 584 with ZA). There was no difference in OS and time to disease progression.

The impact of ZA and denosumab on pain and HRQoL has been also documented. In the ZA registration trial, mean least-squares in the bone pain index (BPI) change from baseline value at 18 months was 0.58 for ZA and 0.95 for placebo (p = 0.075); at 24 months it was 0.58 and 1.07 (p = 0.024), respectively.[32] The additional benefit of denosumab over ZA has been measured on a denosumab pooled analysis of the three similar trials in breast cancer, metastatic CRPC, and other solid tumors, for a total of 5544 patients.[40] Onset of moderate/severe pain was 4.7 months with ZA and increased to 6.5 months with denosumab (HR = 0.83; 95%CI 0.76-0.92; p < 0.001). Strong opioid use and worsening of health related quality-of-life were less common with denosumab.

Timing of administration of bone protecting agents

EAU and NCCN treatment guidelines recommend that bone metastatic CRPC patients should receive ZA or denosumab and recognize the superiority of the latter in delaying SRE.[19,21] None of the guidelines however provides practical recommendation on when to start, when to stop, and the interest of switching between agents. A supplementary analysis of the ZA registration trial indicated that ZA was more efficacious when initiated before the onset of pain.[41]

Noteworthy, EMA and FDA have granted regulatory approvals for ZA and denosumab in patients with hormone naïve prostate cancer with bone metastases, although published studies have been conducted only in CRPC patients. Since metastatic prostate cancer is unique in that it is so frequently responsive to first-line disease-modifying therapy, we believe that ZA and denosumab prescription should be restricted to CRPC patients.

Toxicity of bone targeted agents in metastatic CRPC

The most common expected toxicities are summarized in Table 4. In contrast to ZA, there is no need for denosumab dose-adjustment in case of renal impairment, a common problem in prostate cancer patients. In the denosumab registration trial, a dose adjustment for creatinine clearance at baseline and a dose withhold for serum creatinine increases occurred in 22% and 15% of patients receiving ZA, respectively.[31]

Hypocalcemia is a known adverse effect of anti-remodeling agents, which is more frequent in CRCP than other cancer type and with denosumab than with ZA (all grades: 12.8% denosumab versus 5.8%

TABLE 4. **Safety results of interest in a pooled analysis of the denosumab registration program. Adapted from Lipton et al[52]**

Patient incidence, n (%)	Zoledronic acid n (%)	Denosumab n (%)
Total patients	2386	2841
Infectious AEs	1218 (42.9)	1233 (43.4)
Infectious serious AEs	309 (10.9)	329 (11.6)
Acute phase reactions (first 3 days)	572 (20.2)	246 (8.7)
Cumulative rate of ONJ	37 (1.3)	52 (1.8)
Year 1	15 (0.5)	22 (0.8)
Year 2	28 (1.0)	51 (1.8)
Hypocalcemia	141 (5.0)	273 (9.6)
New primary malignancy	18 (0.6)	28 (1.0)
AEs leading to study discontinuation	280 (9.9)	270 (9.5)

AEs = adverse effects; ONJ = osteonecrosis of the jaw

ZA).[31,42] Grade 3 hypocalcemia (corrected serum calcium (CSC) < 7.0 mg/dL-6.0 mg/dL; ionized calcium < 0.9 mmol/L-0.8 mmol/L; hospitalization indicated) or 4 (CSC < 6.0 mg/dL; ionized calcium < 0.8 mmol/L; life-threatening consequences) has been reported in 5.1% of patients with denosumab and 1.4% with ZA. The risk of developing hypocalcemia is mainly increased among patients with impaired renal function (creatinine clearance < 30 mL/min).[43] This is likely due to reduced renal calcium reabsorption, insufficient conversion of vitamin D to its active metabolite and impaired phosphorus excretion. Pre-existing hypocalcemia must be corrected before starting denosumab or ZA. Initial monitoring of calcium levels is recommended. All patients but those with hypercalcaemia should be given calcium (≥ 500 mg/d) and vitamin D oral supplements (≥ 400 IU/d) and should have their serum calcium concentration checked on a monthly basis for instance. Should hypocalcemia occur, denosumab should be held until correction of hypocalcemia has been achieved.[44]

Osteonecrosis of the jaw (ONJ) was observed in 1%-2% of the study cohort (12 cases with zoledronic acid, 22 cases with denosumab; p = 0.09). Although ONJ may also occur spontaneously, local invasive dental procedures and concomitant oral disease have been identified as the most important local risk factors.[45] The cornerstone of ONJ prevention is thus traditionally to improve dental care and avoidance of invasive dental procedures once therapy has been started.[46,47] We must agree however that such recommendations are based on position papers and case reports, while evidence-based treatment recommendations are lacking.

The "Holy Grail" of metastases prevention

Non-metastatic (M0) CRPC patients are usually strictly asymptomatic and it has become a major challenge to cherish this asymptomatic health state as long as possible by extending bone metastasis free survival (BMFS).[27] This has consequently been the subject of several clinical trials, most of them being negative or inconclusive, Table 5. The tested agents include bisphosphonates clodronate and ZA, endothelin receptor type A inhibitors atrasentan and zibotentan, and denosumab. One of the reasons for failure is clearly the heterogeneity of that patient group and the usual very prolonged BMFS. In the first trial evaluating the benefit of ZA in M0 CRPC, median BMFS was 30 months and at 2 years, only 33% of the patients had developed bone metastases.[48]

Smith et al have recently reported the results on denosumab in a placebo-controlled trial in M0 CRPC patients with PSA ≥ 8 ng/mL and/or a PSA doubling time (DT) ≤ 10 months.[49] Denosumab significantly prolonged BMFS by a median of 4.2 months compared with placebo, but the benefit/side effects ratio was deemed insufficient to grant registration in that setting. There was indeed a significant risk of osteonecrosis of the jaw (5% in the denosumab arm versus 0% in the placebo arm) and hypocalcemia (2% in the denosumab arm versus < 1% in the placebo arm).

Prevention of bone metastasis is therefore still a major issue to be tackled.

TABLE 5. **Summary of bone metastasis prevention trial in non-metastatic prostate cancer patients treated with androgen deprivation therapy**

Study	Patients	Treatment arms	Endpoints	
MRC PR04[53]	T_{2-4}	Clodronate versus placebo	Time to symptomatic BM or prostate cancer death, OS	Primary not met
Zometa 203[48]	M0 CRPC	ZA versus placebo	Time to first BM, OS, BMFS	Terminated early
RADAR	T2a (Gleason ≥ 7, PSA ≥ 10 ng/mL); or T_{2b-4}, N_0	EBRT + ADT ± ADT	PSA, PFS, OS, BMFS	Ongoing
STAMPEDE	High risk patients starting ADT	ADT + placebo or ZA or docetaxel or combination	OS, QoL, SREs, PFS	Ongoing
ZEUS	Gleason 8-10; pN_+ or PSA ≥ 20 ng/mL	ZA versus standard treatment	BM rate, OS, PSA DT	Primary not met
M00-244[54]	M0 CRPC	Atrasentan versus placebo	BMFS, PSA, PFS, OS	Primary not met
Enthuse M0[55]	M0 CRPC	Zibotentan versus placebo	BMFS, OS	Terminated early
Study 147[49]	M0 CRPC	Denosumab versus placebo	BMFS, OS	BMFS + 4.2 months for denosumab

BM = bone metastasis; BMFS = bone metastasis free survival; EBRT = external beam radiotherapy; PFS = progression free survival; ZA = zoledronic acid; , DT = doubling time; OS = overall survival; QoL = quality-of-life; SRE = skeletal related event
STAMPEDE includes M0 and M+ patients

Conclusions

Preserving skeletal integrity is a key component of the management of advanced prostate cancer. Indeed, the skeleton is the primary dissemination site for metastatic cells and ADT, the reference systemic treatment, profoundly affects bone physiology.

The bone mineral density of patients receiving ADT should be periodically checked by DXA scan, especially if they carry additional risk factors for osteoporosis. Lifestyle adjustments, including weight-bearing exercises, and appropriate calcium-vitamin D intake should be recommended to every ADT patient. Bisphosphonates or denosumab should be discussed in case of osteoporosis.

In CRPC patients, bone is the most frequent metastatic site. Bone metastases can grow rapidly and cause debilitating complications. Bisphosphonates or denosumab effectively delay these complications and should be part of the standard armamentarium in progressing metastatic CRPC patients. A careful monitoring of patients, with a special attention on calcium/vitamin D intake and oral hygiene, their safety, is required to secure an acceptable toxicity profile.

Based on the current evidence, there is no indication of bisphosphonates or denosumab in bone metastatic hormone naïve or hormone responsive patients, or in non-metastatic CRPC to prevent the onset of bone metastases.

Disclosure

Dr. Valentina Butoescu has no potential conflict of interest. Dr. Bertrand Tombal has received honoraria from Amgen and Ferring. □

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How to approach sequencing therapy in patients with metastatic castration resistant prostate cancer

Robert Dreicer, MD
Department of Solid Tumor Oncology, Cleveland Clinic, Cleveland, Ohio, USA

DREICER R. How to approach sequencing therapy in patients with metastatic castration resistant prostate cancer. *Can J Urol* 2014;21(Suppl 1):93-97.

Introduction: *Rapid progress has recently been made in understanding the biology of advanced prostate cancer. This has translated into the development of a number of novel agents to treat metastatic castration resistant prostate cancer (mCRPC).*
Materials and methods: *The relevant literature was retrieved from a search of MEDLINE with appropriate key words.*
Results: *Therapeutic approaches to mCRPC include chemotherapy, hormonal manipulation, immunotherapy and radioisotope therapy. Docetaxel and cabazitaxel are cytotoxic agents which have demonstrated a modest impact on survival. Hormonal manipulation with abiraterone and enzalutamide have also been reported to be beneficial in mCRPC. The radioisotope radium 223 utilizes a novel approach in treating mCRPC and was recently described in a positive phase III trial. Finally, sipuleucel-T is an immunotherapy that has a demonstrated overall survival benefit in mCRPC.*
Conclusions: *A number of phase III trials have been published that describe agents which are beneficial in treating mCRPC. Future research will focus on sequencing these agents in a clinically rational and economically viable manner.*

Key Words: radium 223, docetaxel, enzalutamide, cabazitaxel, castration resistant prostate cancer, abiraterone

Introduction

Prior to the availability of docetaxel, management of men with metastatic prostate cancer was relatively uncomplicated. Patients received testosterone suppressive therapy either surgically or medically and then ultimately progressed to "hormone-refractory" disease subsequently managed with palliative intent second-line hormonal therapy or cytotoxics and died shortly thereafter. The introduction of docetaxel into the management paradigm, provided a therapeutic option that provided real palliative benefit and a modest impact on survival.[1] However, after several decades with only modest changes in the therapeutic paradigm, rapid progress in understanding the biology of advanced prostate cancer with a focus on androgen receptor biology has translated over the last few years into a period of unprecedented development of novel agents that have moved through the regulatory process in what is now termed metastatic castration resistant prostate cancer (mCRPC).[2-7]

Given the high degree of bone tropism in advanced prostate cancer rendering standard objective response measures problematic, the absence of validated

Address correspondence to Dr. Robert Dreicer, Department of Solid Tumor Oncology, Cleveland Clinic, 9500 Euclid Avenue, R35, Cleveland, OH 44195 USA

surrogate end points, and the Food and Drug Administration (FDA) requirement of a survival end point for drug approval, rapidly led to a paradigm of testing new agents in the post docetaxel setting given the shorter time lines for read outs.

The initial approval of abiraterone in the post-docetaxel setting led to a broad discussion of the optimal timing of initiating next generation androgen receptor (AR) targeting therapies, given the somewhat arbitrary nature of the timing of docetaxel administration and the critical nature of the androgen receptor as a therapeutic target.[8] Subsequent level 1 evidence of abiraterone's clinical utility in the "pre-docetaxel setting, led to regulatory approval of this agent for use in mCRPC irrespective of prior therapies.[9] Data from the phase III pre-chemotherapy trial of enzalutamide is anticipated within the year. The phase III trial for the recently approved alpha emitter radium 223 included men with mCRPC both docetaxel pre-treated and docetaxel naïve.[6] Of interest, the FDA approved label for radium 223 makes no mention of docetaxel.

The elephant in the room for any discussion of the role of sequencing therapy in mCRPC is the issue of cost. The role of pharmacoeconomics will without question ultimately influence management decisions in many clinical settings, however for the purposes of this review, the clinical utility not the costs of the agents will be the primary consideration.

The concept of moving the management of mCRPC towards a chronic disease paradigm has increasingly become a goal of clinicians heavily involved in both the management and investigation of therapies in patients with mCRPC. Goals of managing chronic disease typically requires clinicians to optimize the timing for therapies taking into consideration issues of risk and benefit from level 1 evidence or in some cases evolving clinical experience/expert opinion.

The extraordinary speed of the introduction of novel therapies into the clinical armamentarium (sipuleucel-T and cabazitaxel in 2010, abiraterone in 2011, enzalutamide in 2012, radium 223 in 2013) has provided important new therapeutic options for patients, but without any opportunity to prospectively address sequencing questions.

Initial therapy options: asymptomatic mCRPC

The role of subsequent therapeutic intervention for patients with castration resistant prostate cancer, biochemically defined is undefined, and beyond the scope of the current discussion. Although the optimal therapeutic paradigm for patients with mCRPC remains undefined, a number of clinical parameters help guide the decision making process. Immunomodulatory therapy appears best utilized in asymptomatic patients with a less aggressive disease phenotype. Symptomatic patients, those with progressive fatigue, appetite loss or pain require intervention with agents with overt anti-tumor activity such as docetaxel or next generation androgen receptor targeted agents, such as abiraterone or enzalutamide. Selected patients with bone only metastatic disease with progressive symptoms may be appropriate candidates for early use of radium 223.

Sipuleucel-T remains the only FDA approved therapeutic vaccine in oncology. Utilization of this agent in the United States has remained modest for a variety of reason, including the poorly understood mechanism of action, and its lack over objective anti-tumor activity in most patients.[10] Although in the phase III trial that led to its regulatory approval, 18.2% of patients received sipuleucel-T post chemotherapy, recent evidence provides evidence that the optimal timing is much earlier in the disease process.[5,11] In a post hoc analysis of the phase III IMPACT study of sipuleucel-T, Schellhammer and colleagues evaluated a range of clinical factors and assessed their association with overall survival. In this analysis, baseline prostate-specific antigen (PSA) was divided in quartiles, with patients in the lowest PSA quartile (< 22.1 ng/mL) having a median survival of 13 months compared to 2.8 months in the highest PSA quartile (> 134 ng/mL).[11] Among the controversies surrounding the potential timing of administration of sipuleucel-T is the theoretical concern that even the low doses (5 mg-10 mg) of prednisone that are used along with abiraterone acetate, may impair an immune response to this dendritic cell vaccine. Recently Small and colleagues presented a preliminary analysis of randomized phase II trial of sipuleucel-T with concurrent or sequential administration of abiraterone acetate and prednisone. In this small trial (63 patients) no significant differences were seen between arms in median cumulative antigen presenting cell activation or total counts. Increased CD54 up-regulation with the 2nd and 3rd treatments were indicative of a prime boost effect in both arms.[12] This data provides some evidence that 5 mg-10 mg of prednisone has no "significant" effect on the ability to mount an immune response to sipuleucel-T.

Given the lack of overt anti-tumor activity and compelling evidence that patients with lower volume disease may derive greater benefit, if sipuleucel-T is to be part of an individual patient management paradigm, it should be used early in the management of patients with mCRPC, optimally in essentially asymptomatic patients with biochemical, not symptomatic progression.

Next generation androgen receptor signaling agents

As remains the case even for docetaxel, the optimal timing for the initiation of therapy with abiraterone remains undefined. In the pre-docetaxel phase III trial, patients receiving abiraterone + prednisone had a median PSA of 42.0, with nearly two-thirds of patients reporting essentially no pain and only 2% of patients with moderate or greater pain, presumed to be disease related.[9]

While the pre-chemotherapy phase III trial failed to meet pre-specified end points to demonstrate a survival advantage, there was a highly statistically and clinically significant improvement in time to radiographic progression free survival: 16.5 months for patients receiving abiraterone + prednisone in contrast to 8.3 months in patients receiving prednisone alone (0.53; 95% confidence interval [CI], 0.45 to 0.62; $p < 0.001$).[9]

Concerns among some clinicians regarding the tolerability of 10 mg of prednisone which is typically prescribed to minimize the mineralocorticoid side effects of abiraterone acetate have not been realized with broad use of this agent in the United States and around the world. Studies are ongoing to evaluate lower doses of steroids to further mitigate steroid related complications i.e. blood sugar control etc.

Setting aside issues of availability/affordability of abiraterone + prednisone which will always to some extent influence therapeutic decision making, with the exception of patients who present with significant disease related symptoms, i.e. hydronephrosis from nodal disease progression or moderate-significant bone pain, where the high clinical response rate of docetaxel may be preferred, abiraterone + prednisone both mechanistically and from a patient preference perspective appears to have become a front-line therapy for patients with mCRPC and objective disease progression (PSA or radiographic progression).

At the time this manuscript was being prepared, a press release indicated that the phase III trial comparing enzalutamide and placebo in patients with chemotherapy naïve mCRPC was stopped early. Patients treated with enzalutamide demonstrated both a statistically significant overall survival advantage and reduction in risk of radiographic progression or death compared with placebo. To what extent the impact of enzalutamide' s ability to improve overall survival (in contrast to the pre-chemotherapy abiraterone) in this setting alters the initial sequence of these agents remains to be seen.

In the early phase of the development of next generation androgen receptor targeted therapies i.e. lyase inhibitors and second generation antiandrogens there was hope that given the divergent mechanism of these two classes of agents that sequential use or combinations of these agents would provide significant therapeutic benefit.

Although we are still early in the experience with these agents, there is increasing, albeit limited observations of some degree of cross resistance to these classes of agents. Noonan and colleagues recently reported on 30 patients from a number of centers treated with enzalutamide on the phase III AFFIRM study who were subsequently managed (off study) with abiraterone + prednisone.[13] Of the 27 evaluable patients, the median prior enzalutamide treatment duration was 41 weeks (6-95 weeks). Subsequent abiraterone + prednisone treatment duration was 13 weeks (1-52). No objective radiographic responses were observed, and the median abiraterone time to progression (PSA, objective or symptomatic) was 15.4 weeks with a median overall survival of 50.1 weeks.

Schrader et al reported on 35 patients with mCRPC treated on an expanded access program of enzalutamide. All patients had previously received abiraterone and docetaxel. In this group the median duration of prior abiraterone treatment was 9 months (2-19 months) with 16 patients demonstrating greater than a 50% decline in PSA as their best response. The median duration of subsequent enzalutamide therapy was 4.9 months. Seven of 16 patients who were initially abiraterone-sensitive (44%) and 3 of 19 patients who were initially abiraterone-insensitive (16%) experienced a > 50% PSA decline while taking enzalutamide.[14]

Loriot and colleagues reported the utility of abiraterone in 38 mCRPC patients previously treated with docetaxel and enzalutamide. In this experience only three patients (8%) attained a greater than ≥ 50% decline in PSA. The median progression-free survival (PFS) was 2.7 months. Of 12 patients assessable radio logically, only 1 (8%) attained a confirmed partial response.[15]

In the near term, decisions regarding treatment sequence of next generation androgen receptor targeted agents will remain empiric, informed by issues such as drug availability both approval status and cost as well as physician experience with the individual agents. Prospective studies are planned, including a United States Intergroup study that will randomized patients to the combination of enzalutamide plus abiraterone + prednisone versus enzalutamide.

Cyotoxics

Among the questions regarding therapeutic sequence in the management of mCRPC is the evolving role of the approved cytotoxic agents that have evidence of

providing survival benefit, docetaxel and cabazitaxel.[7,16] As abiraterone moves into the pre-docetaxel space in a number of countries around the world, docetaxel and subsequently cabazitaxel's use moves further to the right in the disease course. Although there are some reports questioning whether prior abiraterone impacts on the response rate to docetaxel, this remains a preliminary observation, worthy of prospective evaluation.[17] The question of taxane sequencing is also under investigation, with an ongoing phase III trial randomizing patients with mCRPC to receive either docetaxel or cabazitaxel (NCT01308567).

Radium 223

Among the most intriguing questions of drug sequencing involves the novel alpha emitter, radium 223, which recently gained FDA approval for treatment of patients with mCRPC with symptomatic bone metastases and without known visceral disease. In the phase III trial patients treated with radium 223 had a median survival of 14.9 months compared to 11.3 months in patients receiving a placebo (hazard ratio, 0.70; 95% CI, 0.58 to 0.83; $p < 0.001$).[6] Of interest, patients were eligible for this trial if they had received docetaxel, were not healthy enough or declined to receive it, or it was not available. Of the 614 patients randomized to radium 223, 262 (43%) did not receive prior docetaxel. The authors noted that this trial incorporated patients that represent a substantial number of similar patients who for one reason or another do not receive docetaxel.[6,18]

In addition to the impact on survival, patients receiving radium 223 had a significantly prolonged time to the first symptomatic skeletal event (defined as first use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or non-vertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention) median, 15.6 months versus 9.8 months.[6] Radium 223 was relatively well tolerated with relatively modest myleosuppression, presenting intriguing opportunities for combination therapy.

Conclusions

With the rapid introduction of multiple new agents, the lack of clarity regarding the optimal integration of these drugs into the management paradigm of patients with advanced prostate cancer is unsurprising. Prospective studies designed to inform clinicians regarding the optimal sequence of new drugs are uncommon in oncology and in the near term clinicians will use best evidence and clinical experience along with pragmatism i.e. is the drug approved in the clinical setting and "can my patient afford it" to make management decisions.

The emerging evidence of clinically meaningful cross resistance in some patients between lyase inhibitors such as abiraterone and next generation androgen receptor antagonists such as enzalutamide requires prospective assessment to better understand from a clinical perspective optimal sequencing and to improve the understanding of the molecular biology of resistance to these agents.

The optimal timing of radium 223 administration remains undefined, although it seems clear that some patients with bone predominant disease may benefit from its use prior to docetaxel administration.

Other drugs such as cabozantonib, ipilimumab and custirsen are in late stage evaluation and may in the near term add to the armamentarium and quandary of managing patients with advanced prostate cancer.[19-21]

Disclosure

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Emerging therapies in castration resistant prostate cancer

Gregory R. Thoreson, MD, Bishoy A. Gayed, MD, Paul H. Chung MD, Ganesh V. Raj, MD

Department of Urology, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA

THORESON GR, GAYED BA, CHUNG PH, RAJ GV. Emerging therapies in castration resistant prostate cancer. *Can J Urol* 2014;21(Suppl 1):98-105.

Introduction: *Prostate cancer continues to be the second leading cause of cancer related mortality in men within the United States. Despite a consistent decline in prostate cancer mortality over the past two decades, the prognosis for men with metastatic prostate cancer remains poor with no curative therapies. In this article, we review the recently approved and emerging therapeutics for patients with castrate resistant prostate cancer.*

Materials and methods: *An advanced search was conducted on the clinicaltrials.gov database, using search terms "metastatic prostate cancer", and limiting results to phase II-IV clinical trials. Clinically relevant emerging therapeutics were selected and a Medline search for supporting documents was performed. An emphasis was placed on newly approved and promising new therapeutics.*

Results: *A total of four Food and Drug Administration approved medications and eight investigational agents were chosen for review. The background and role of these therapeutics in the treatment of prostate cancer treatment is discussed.*

Conclusions: *The past few years have yielded a near exponential increase in treatments for metastatic prostate cancer, many of which have a unique mechanism of action. The estimated median survival for patients with metastatic prostate cancer remains dynamic as we begin to integrate these therapeutics into clinical practice and determine the optimal sequence and timing of treatment.*

Key Words: CRPC, emerging therapies, castration resistant prostate cancer

Introduction

In 2014 alone, it is estimated that there will be 233000 new cases of prostate cancer in the United States. With an estimated 29480 deaths, prostate cancer is the second-leading cause of cancer-related death in men.[1] Although many patients present with organ confined disease, there continues to be a subset of patients that progress or present with metastatic prostate cancer. Until 2009, there were only four drugs approved for the treatment of castration resistant prostate cancer, with only one, docetaxel, that showed improvement in overall survival. The median survival of patients with advanced metastatic prostate cancer, who have failed androgen deprivation therapy, was typically 16 to 20 months in 2009.[2,3] Since 2009, work building on decades of research, dissecting molecular pathways involved in prostate cancer, has resulted in five novel Food and Drug Administration (FDA) approved therapeutic agents, each of which has shown an improvement in overall survival. Although the survival improvements in these recently approved medications are modest, nearly all of them have a distinct mechanism of action, Table 1. The potential for combining therapies or optimally sequencing therapies may offer further improvements in the survival of patients with metastatic prostate cancer.[4] As newer drugs progress through the development pipeline, Table 2, there is real hope for decreasing the mortality from metastatic prostate cancer.

Address correspondence to Dr. Ganesh V. Raj, Department of Urology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390-9110 USA

TABLE 1. **Therapeutic agents and mechanism of action**

FDA approved agents	**Mechanism of action**	**Sponsor**	**Delivery**	**Prednisone supplement**	**Approval date**
Sipuleucel-T	personalized antigen presenting cell-based immunotherapy	Dendreon	IV	no	4/29/2010
Abiraterone	CYP17 inhibitor	Cougar Biotechnology	oral	yes	4/28/2011
Enzalutamide	AR antagonist	Medivation	oral	no	8/31/2012
Radium 223 (Alpharadin)	alpha-particle emitting radiopharmaceutical	Algeta ASA	IV	no	5/15/2013
Investigational agents	**Mechanism of action**	**Sponsor**	**Delivery**	**Prednisone supplement**	
ARN-509	AR antagonist	Aragon Pharmaceuticals	oral	no	
TAK-700	CYP17A1 inhibitor	Millennium Pharmaceuticals	oral	yes	
TOK-001	CYP17 inhibitor, AR antagonist	Tokai Pharmaceuticals	oral	no	
OGX-111	second-generation ASO with a high affinity for CLU RNA	OncoGenex Technologies	IV	yes	
OGX-427	second-generation ASO with a high affinity for Hsp27 expression	Hoosier Oncology Group	IV	yes	
Prostvac	prostate cancer vaccine	Bavarian Nordic	SQ	no	
Ipilimumab	monoclonal antibody blocking CTLA-4	Bristol Myers Squibb	IV	no	
Cabozantinib	tyrosine kinase inhibitor	Exelixis	oral	no	

Androgen axis

In 1941, Huggins and Hodges performed a series of experiments that showed a relationship between metastatic prostate cancer growth and testosterone levels.[5] Since this pioneering study, androgen deprivation therapy (ADT) has been the cornerstone of metastatic prostate cancer therapy. The emergence of gonadrotropin releasing hormone (GnRH) analogues has enabled effective chemical castration of patients with metastatic prostate cancer.[6] In addition, antiandrogens such as bicalutamide offer direct competitive antagonism of the androgen receptor.[7] Metastatic prostate cancer is typically responsive to castration: a vast majority of patients respond to ADT with declines with their tumor burden, as evidenced by decreased serum prostate-specific antigen (PSA) levels.[8] Importantly, ADT is effective in relieving symptoms from metastatic prostate cancer but does not improve overall survival.[9-11] Despite an initial response of prostate cancer to ADT, ADT inevitably fails and disease recurs. Prostate cancer refractory to ADT is termed castration resistant prostate cancer (CRPC).[12] In 2004, a landmark study established that CRPC is still driven by the androgen receptor,[13] and

TABLE 2. **Clinical trials evaluating new therapeutics in patients with metastatic prostate cancer**

	Phase I	Phase II	Phase III	FDA approval	
Androgen receptor					
MDV3100			NCT00974311 (AFFIRM)	8/31/12	Completed, has results
ARN-509		NCT01171898			Active, not recruiting
Androgen production					
Abiraterone			NCT00638690 (COU-301)	4/28/11	Completed, has results
TAK-700			NCT01193257 (ELM-PC 5 (C21005))		Completed, has results
TOK-001		NCT01709734 (ARMOR2)			Active, recruiting
Targeted therapy					
OGX-111			NCT01578655 (AFFINITY)		Active, recruiting
OGX-111			NCT01188187 (SYNERGY)		Active, not recruiting
OGX-111			NCT01083615		Active, not recruiting
OGX-427		NCT01681433 (Pacific)			Active, recruiting
Immunologic					
Sipuleucel-T			NCT00065442 (IMPACT)	4/29/10	Completed, has results
Prostvac			NCT01322490 (BNIT-PRV-301)		Active, recruiting
Ipilimumab			NCT01057810		Active, not recruiting
Ipilimumab			NCT00861614		Active, not recruiting
Radiopharmaceuticals					
Radium 223			NCT00699751	5/15/13	Completed, has results
Tyrosine kinase inhibitors					
Cabozantinib			NCT01605227 (COMET-1)		Active, recruiting
Cabozantinib			NCT01522443 (COMET-2)		Active, recruiting

established the rationale for more effective therapeutic agents targeting the androgen receptor. In addition, despite castrate levels of circulating serum androgens, the local tumor milieu was noted to be replete with androgen.[14,15] These studies led to the development of therapeutic agents targeting both systemic and intratumoral synthesis of androgens. Since the androgen receptor signaling is active in CRPC, several new agents recently FDA approved or in development target the androgen receptor activation by one of three mechanisms:

1. Direct androgen receptor antagonists: Enzalutamide (FDA approved) and ARN-509 (in clinical trials)
2. Androgen biosynthesis inhibitors: Abiraterone (FDA approved), TAK-700 (in clinical trials)
3. Androgen receptors coactivators: OGX-111 and OGX-427 (in clinical trials)

Direct androgen receptor antagonists

Enzalutamide

Enzalutamide is an oral androgen-receptor–signaling inhibitor that inhibits nuclear translocation of the androgen receptor hormone complex, DNA binding, and coactivator recruitment, and induces cell apoptosis. Enzalutamide has a higher affinity for the androgen receptor than bicalutamide.[16] Phase II clinical studies showed antitumor effects at all doses, but maximum tolerated dose was set to 240 mg per day, with a higher frequency of seizures and grade 3 fatigue noted at the 320 mg per day dose.[17] In the AFFIRM phase III clinical trial (NCT00974311), enzalutamide showed an improvement in overall survival by 4.8 months over placebo (18.4 months versus 13.6 months, $p < 0.001$) in patients with metastatic prostate cancer previously

treated with docetaxel [NCT00974311].[18] Enzalutamide does not require concomitant steroid administration. At the dosage of 160 mg per day seizures were encountered in 0.9% of patients receiving enzalutamide.[19] Based on the data from the AFFIRM trial, enzalutamide received FDA approval for administration in the post-docetaxel setting. A second phase III study (PREVAIL) was developed to investigate the utility of enzalutamide in a docetaxel naïve setting [NCT01212991]. The study showed a 29% reduction in risk of death (HR = 0.706, $p < 0.0001$) and an 81% reduction in the risk of radiographic progression (HR = 0.186, $p < 0.0001$) when enzalutamide was compared to placebo. Enzalutamide also delayed time to chemotherapy by 17 months (HR = 0.35, $p < 0.0001$) when compared to placebo.[20] Currently, enzalutamide is awaiting FDA approval for the pre-docetaxel setting.

ARN-509

Like enzalutamide, ARN-509 is an oral competitive androgen receptor antagonist that impairs androgen receptor binding to DNA and androgen receptor target gene modulation, and induces cell apoptosis. ARN-509 has a slightly higher affinity for the androgen receptor than enzalutamide[21] and showed a greater efficacy than enzalutamide in a murine xenograft model of human CRPC.[16] In a phase I clinical study, ARN-509 was safe and well-tolerated across all dose levels, with a minimum effective dose projected to be > 180 mg/day. Unlike enzalutamide, no seizures were noted. Dosage of 240 mg/day was selected for phase II studies, with a primary endpoint of PSA response at 12 weeks, and secondary endpoints evaluating antitumor effects and changes in circulating tumor cells (CTC) [NCT01171898]. The three treatment arms in the phase II study included: 1) non-metastatic CRPC which is chemotherapy and abiraterone naïve; 2) metastatic CRPC which is chemotherapy and abiraterone naïve; 3) metastatic CRPC recurrent after abiraterone treatment. A second phase II clinical trial is underway with an estimated primary completion date in 2015 [NCT01790126] that will evaluate the utility of ARN-509 dosed at 240 mg/day in the setting of hormone sensitive prostate cancer with the primary quality-of-life endpoint measures.

Androgen biosynthesis inhibitors

Abiraterone

Abiraterone-acetate, a prodrug for abiraterone, is a cytochrome P450 c17 (CYP17) inhibitor, blocking androgen synthesis by the adrenal glands, testes, and within the prostate tumor in a ligand-dependent fashion.[22] In the initial phase III clinical trial [Cou-301, NCT00638690], abiraterone in combination with prednisone showed an improvement in overall survival by 3.9 months over placebo-matched controls in a post-docetaxel setting (14.8 months versus 10.9 months, $p < 0.001$) and all secondary endpoints confirmed superiority.[23] Abiraterone required concomitant administration of steroids. These data led to FDA approval for abiraterone for the post-docetaxel setting. A follow up phase III clinical trial [Cou-302: NCT00887198] in the pre-docetaxel setting also showed that abiraterone improved radiographic progression-free survival (16.5 months versus 8.3 months, $p < 0.001$), showed a trend toward improved overall survival (median not reached, versus 27.2 months, hazard ratio, 0.75; 95% CI, 0.61 to 0.93; $p = 0.01$) and significantly delayed initiation of chemotherapy in patients with metastatic CRPC.[24] Currently, abiraterone is FDA approved in the pre-docetaxel setting.

TAK-700

TAK-700 selectively inhibits the 17,20-lyase activity of CYP17A1, and generally does not lead to secondary mineralcorticoid excess that is seen in abiraterone-acetate, and may permit steroid-free dosing. In a phase I/II study [NCT00569153], 96 patients with metastatic CRPC in a chemo-naïve setting received TAK-700 at various dosing intervals with and without prednisone supplementation. The study was limited by a large percentage of patients (50%) due to either adverse events (AEs) or disease progression. In decreasing order of frequency, the most common AEs were fatigue (72%), nausea (44%), and constipation (31%).[25] PSA response rates (≥ 50% decrease) at 12 weeks were significant with 63% (300 mg BID), 52% (400 mg BID + prednisone), 41%(600 mg BID + prednisone), and 62% (600 mg QD) in their respective groups.[26]

In a July 2013 press release, Takeda Pharmaceuticals announced that the ELM-PC 5 phase 3 study [NCT01193257] was unblinded based on the recommendation of the Independent Data Monitoring Committee (IDMC). Overall survival would likely not be significant in the Orteronel plus prednisone when compared to the control arm (HR 0.894, $p = 0.23$). There was, however, a significant improvement in radiographic progression-free survival (rPFS) in the Orteronel plus prednisone arm over the control arm (HR 0.755, $p = 0.0003$).[27] Currently, there are four active phase III clinical trials investigating TAK-700.

TOK-001

TOK-001, formerly known as VN/124-1, inhibits prostate cancer growth by 17A-hydroxylase/17,20-lyase (CYP17) inhibition and down-regulation of

wild type and mutant androgen receptor protein expression.[28-30] Phase I clinical studies [NCT00959959] resulted in > 50% PSA decline in 11/49 patients (22%) and an additional 13/49 (26%) had 30%-50% declines. Thirty-six of 49 (74%) patients completed 12 weeks of the study but early discontinuation was seen in 13 of 49 (26%) patients for toxicity (6/13), progression (5/13), or withdrawal of consent (2/13). The maximal tolerated dose was not reached in this study. TOK-001 is currently being reformulated with potential phase II clinical trials planned in the near future.[31] Additional modifications to exploit the chemical framework of TOK-001to create novel potent/efficacious androgen receptor degrading agents (ARDAs) are underway.[32]

Targeted therapy against androgen receptor coactivators

OGX-111

Clusterin (CLU) is a stress-induced androgen-receptor regulated cytoprotective chaperone that is upregulated in cell death. Increased concentrations confer treatment resistance in experimental and clinical studies.[33,34] Custirsen, a second-generation antisense oligonucleotide (ASO), has high affinity for CLU RNA, and has been shown to suppress CLU levels.[35,36] Treatment with custirsen increased tumor cell death and improved chemosensitivity to multiple drugs, including docetaxel and mitoxantrone, in preclinical CRPC prostate cancer models. In a phase II clinical study [NCT00258388], men with metastatic CRPC with disease progression after two or more cycles of first line docetaxel-based therapy showed improvements in overall survival, although not statistically significant, when custirsen was combined with docetaxel and prednisone, compared to docetaxel and prednisone alone (23.8 months versus 16.9 months).[37] Currently, there are three randomized phase III clinical trials underway evaluating the utility of OGX-111 in combination with chemotherapy.

OGX-427

Heat Shock Protein 27 (Hsp27) is a chaperone protein that regulates cell signaling and survival pathways involved in cancer progression and is uniformly expressed in metastatic CRPC.[38] Its expression is induced by hormonal withdrawal and/or chemotherapy, and inhibits treatment induced apoptosis through multiple mechanisms.[39,40] In prostate cancer, Hsp27 complexes with androgen receptor and enhances transactivation of androgen receptor-regulated genes.[41] OGX-427 is a 2nd generation antisense oligonucleotide that inhibits Hsp27 expression. Phase I clinical studies showed that the drug was well tolerated [NCT00487786]. In a phase II clinical study investigating the utility of OGX-427 in chemotherapy-naïve patients, patients with minimal symptoms were randomized to receive OGX-427 weekly with prednisone or prednisone only [NCT01120470]. In the OGX-427 plus prednisone arm, 71% of patients were progression-free at 12 weeks, compared to 33% in the prednisone only arm. 41% of patients who received OGX-427 plus prednisone experienced a > 50% decline in PSA, versus 20% of patients who received prednisone alone.[42] A separate phase II clinical trial is investigating the utility of OGX-427 in combination with abiraterone versus abiraterone alone, and is in active recruitment with estimated completion date listed as June 2015 [NCT01681433].

Immunologic therapies

Immunologic therapies offer an alternative approach for patients with CRPC. Indeed, sipuleucel-T was the first of the new generation of FDA-approved agents against metastatic CRPC in April 2010. These immunomodulatory agents offer the potential for long term therapeutic responses against CRPC.

Sipuleucel-T

Sipuleucel-T is a personalized antigen presenting cell-based immunotherapy product that showed a 4.1 month improvement in overall survival (25.8 months versus 21.7 months, hazard ratio for death in the sipuleucel-T group, 0.78; 95% confidence interval [CI], 0.61 to 0.98; p = 0.03) in a phase III clinical trial [NCT00065442].[43] Sipuleucel-T is FDA approved for metastatic prostate cancer across all stages. However patients treated with sipuleucel-T show an absence in significant difference of objective tumor disease progression,[44,45] Despite early approval of sipuleucel-T, it has failed to gain widespread traction and marketshare.[46]

Prostvac-VF

Prostvac-VF is a prostate cancer vaccine approach consisting of a recombinant vaccinia vector as a primary vaccination, followed by multiple recombinant fowlpox booster vaccinations.[47] Phase II studies showed an increase in OS (25.1 months versus 16.6 months, p = 0.0061), but no statistically significant difference in the median progression-free survival (3.8 months versus 3.7 months, p = 0.60). These results mirror those seen with sipuleucel-T and follow a trend of improved overall survival without a change in measurable tumor response.[48] A phase III trial with an estimated primary completion date at the end of 2015 is investigating the use of Prostvac-VF in 1200 men

with chemotherapy-naïve metastatic prostate cancer allocated to one of three treatment arms; (Arm V+G) PROSTVAC-V/F plus adjuvant dose GM-CSF, (Arm V) PROSTVAC-V/F plus GM-CSF placebo, (Arm P) double placebo [NCT01322490].

Ipilimumab

Ipilimumab is a monoclonal antibody blocking the immune checkpoint molecule cytotoxic T-lymphocyte antigen-4 (CTLA-4). Ipilimumab has shown a survival advantage in melanoma,[49] but the utility in prostate cancer has yet to be established. Several phase I/II clinical studies have evaluated ipilimumab in combination with GVAX, PROSTVAC, docetaxel, and radiotherapy, with promising results.[50-53] Currently, there are two phase III clinical trials investigating the utility of ipilimumab. The first study [NCT00861614] evaluated ipilimumab versus placebo following radiotherapy in post docetaxel metastatic CRPC patients. Preliminary results were released by Bristol-Myers Squibb showing that the primary endpoint of overall survival was not met (HR = 0.85; 95% CI = 0.72-1.00; p = 0.053).[54] The final results were released at the 2014 Genitourinary Cancers Symposium which showed that an improvement in progression free survival (HR = 0.70; 95% CI = 0.61-0.82) and a reduction in the PSA level by 50% or more (13.1% versus 5.3%).[55] The second [NCT01057810] is comparing the efficacy of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naïve castration resistant prostate cancer.

Tyrosine kinase inhibitors

The utility of tyrosine kinase inhibitors (TKI) and vascular endothelial growth factor (VEGF) inhibitors have been shown to improve survival in many different types of cancers.[56-58] The utility of this modality of treatment is currently being investigated in the field of metastatic CRPC.

Cabozantinib

Cabozantinib is an oral tyrosine kinase inhibitor with specific activity against MET and VEGF receptor 2 (VEGFR2). In a phase II randomized discontinuation trial, progression free survival was improved in the cabozantinib arm when compared to placebo (23.9 weeks versus 5.9 weeks, $p < 0.001$). Using response evaluation criteria in solid tumors (RECIST) criteria, 5% of patients showed a partial response, 75% showed stable disease, and 11% showed disease progression to treatment. One hundred forty-nine patients showed evidence of bone metastases at baseline and of these patients, 12% showed complete resolution, 56% showed partial resolution, 28% showed stable disease, and 3% showed progressive disease in response to treatment with cabozantinib.[59] Currently, there are two phase III studies evaluating the utility of cabozantinib in metastatic CRPC. The first trial [COMET-1; NCT01605227] is a randomized double-blind trial of patients with metastatic CRPC who progressed on docetaxel and either abiraterone or MDV3100 independently. The study will compare cabozantinib to prednisone with the primary endpoint being overall survival and secondary endpoints being bone scan response. This study has completed accrual and is currently awaiting planned analyses. The second trial [COMET-2; NCT01522443] is another randomized double-blind trial of patients with metastatic CRPC who progressed on docetaxel and either abiraterone or MDV3100. The study will compare cabozantinib to mitoxantrone plus prednisone with the primary endpoint of pain response. Secondary endpoints include bone scan response and overall survival. The study has an estimated primary completion date in June 2014.

Radiopharmaceuticals

Radiopharmaceuticals such as strontium-89 (89Sr) and samarium-153 (153Sm) ethylene diamine tetramethylene phosphonate (EDTMP), are beta-emitting radioisotopes and have long been used for palliation of bone pain in metastatic prostate cancer.[60] This mode of treatment is governed by the dose-limiting toxicity of myelosuppression. In comparison to a beta-emitting radioisotope, an alpha-emitting radioisotope has a much higher linear energy transfer (LET) and subsequently has a smaller influence on the surrounding bone marrow and an increased anti-tumor effect. These phenomena explain the decreased bone marrow toxicity and improved overall survival recently exhibited in alpha-emitting radioisotopes.[61]

Radium 223

Radium 223 is a novel alpha-particle–emitting radiopharmaceutical targeting bone metastases. In a phase III clinical study of patients with progressive, symptomatic metastatic CRPC with ≥ 2 bone metastasis, radium 223 showed improvement in overall survival when compared to placebo by 3.7 months (14.9 months versus 11.2 months, $p < 0.001$)[NCT00699751]. Additionally, time to first skeletal related event was significantly delayed in the radium 223 treatment arm when compared to placebo (15.6 months versus 9.8 months, $p < 0.001$).[62] Radium 223 represents a unique therapeutic option for metastatic prostate cancer and will likely find a role in the management in CRPC patients with metastatic bone lesions.

Conclusion

Building on decades of research, the past few years have yielded a near exponential increase in treatment modalities for patients with metastatic prostate cancer. Individually, these improvements in overall survival may appear modest, however, nearly all of them have a distinct mechanism of action and the possibility of synergistic effects have yet to be established. Going forward, the promise of a durable impact on the mortality from metastatic prostate cancer will likely stem from further elucidation of molecular pathways involved in prostate cancer, as well as defining the optimal sequence of treatment for patients with metastatic prostate cancer.

Disclosure

Drs. Gregory R. Thoreson, Bishoy A. Gayed and Paul H. Chung have no potential conflict of interest.
Dr. Ganesh Raj has served on Speaker/Advisory boards of Bayer, Janssen, Medivation, Astellas and Merck. He has several patent applications on potential therapeutics (not discussed in this article) in prostate cancer. He also receives research funding from Janssen and C-diagnostics Corp. □

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Release Date:	April 7, 2014
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1. Which of the following is the definition of castration resistant prostate cancer (CRPC)?
   a. Castration resistant prostate cancer is defined by disease progression despite androgen deprivation therapy and requires evidence of new metastases by imaging.
   b. Castration resistant prostate cancer is defined as disease progression despite androgen deprivation therapy and may present as either a continuous rise in serum PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases.
   c. Castration resistant prostate cancer is defined by rising PSA prior to androgen deprivation therapy.
   d. Castration resistant prostate cancer is defined by three rising PSA's with a castrate level of testosterone.

2. A 55-year-old male presents to you after receiving a diagnosis of prostate cancer. His PSA is 4.6 ng/mL, Gleason score 3+3=6 in 3 of 12 cores with 25% involvement of each core. He mentions that he has a strong family history of prostate cancer (brother diagnosed at 62 years old, father and grandfather). He is strongly considering radiation therapy, but also wonders about the role of "hormone treatment" in his case. Which of the following statements BEST describes the utility of androgen deprivation therapy in this patient?
   a. Androgen deprivation therapy is commonly used as monotherapy in patients with clinically localized prostate cancer.
   b. Androgen deprivation therapy does have side effects, but it should be reserved for men with metastatic disease only.
   c. Although androgen deprivation therapy is useful as adjuvant therapy to radiation treatment for prostate cancer, there is little to no benefit in men with low grade disease.
   d. Neoadjuvant androgen deprivation therapy is superior to adjuvant therapy when considering radiation treatment for prostate cancer.

3. After initiation of degarelix therapy, castrate levels of testosterone are achieved in over 90% of patients within:
   a. 24 hours.
   b. 3 days.
   c. 7 days.
   d. 28 days.

4. Regarding degarelix, which statement is TRUE:
   a. Degarelix is a competitive antiandrogen peptide.
   b. Degarelix competitively blocks the GnRH receptor.
   c. This agent causes a surge in serum T for up to 28 days after initial administration.
   d. Co-administration of a non-steroidal anti-androgen is recommended with the initial dose of degarelix.

5. Which of the following statements BEST describes the significant findings SWOG 9346 clinical (intermittent versus continuous androgen deprivation therapy in metastatic prostate cancer)?
   a. Intermittent androgen deprivation therapy has demonstrated non-inferior survival in the metastatic setting.
   b. Health-related quality-of-life scores in the domains of mental health, erectile dysfunction and libido were improved at early time points (3 and 9 months) in patients treated with intermittent androgen deprivation therapy.
   c. Cardiovascular health outcomes are improved in patients on intermittent androgen deprivation.
   d. Bone health is improved in patients on intermittent androgen deprivation.

6. A 70-year-old man with metastatic CRPC involving bone presents to the emergency department unable to function at home with fatigue, nausea and vomiting, and anorexia. He is receiving treatment with depot goserelin, hydrocortisone 20 mg po qam and 10 mg po qpm, zoledronic acid 4 mg IV every 3 weeks, and started ketoconazole for rising PSA 2 weeks ago. Routine complete blood count and serum biochemistry are normal except for mild anemia, mild elevation in BUN, and AST 3 x ULN, ALT 4 X ULN. PSA is 78 ng/mL and was 69 ng/mL 2 weeks ago. The most likely explanation is:
   a. Hepatic metastases due to CRPC progression have developed.
   b. Hepatic toxicity of ketoconazole.
   c. Nausea and vomiting due to zoledronic acid therapy.
   d. Hypoadrenalism secondary to ketoconazole.

7. Bone scans with either technetium-99m labeled phosphonate or fluorine-18 labeled fluoride are useful for:
   a. Evaluating bone metastases.
   b. Measuring response to therapy.
   c. Both a and b.
   d. Neither a or b.

8. PET/CT with fluorine-18 labeled FDG is useful for:
   a. Evaluating bone metastases.
   b. Measuring response to therapy.
   c. Both a and b.
   d. Neither a or b.

9. Which of the following is true concerning sipuleucel-T administration?:
   a. It is contraindicated with visceral metastasis.
   b. The PSA level must be greater than 10.0 ng/mL before use.
   c. Premedication with acetaminophen and diphenhydramine will limit adverse reactions.
   d. It is given subcutaneously weekly for a total of three weeks.

10. What is the process for preparing sipuleucel-T?
   a. Sipuleucel-T is an autologous immunotherapy that relies on ex-vivo stimulation of dendritic cells by the patients autologous prostate cancer cells.
   b. Removal and concentration of dendritic cells with re-infusion of the cells along with GMCSF.
   c. Stimulation of the patient with IV GMCSF and PAP antigens with collection of dendritic cells. The cells are concentrated and then reinfused.
   d. Removal of dendritic cells from a patient and reinfusion after processing and expansion with GMCSF and PAP constructs.

POST-TEST FOR CME

11. Abiraterone has been shown to:
    a. Statistically improve OS in men with non- metastatic CRPC before chemotherapy.
    b. Statistically improve OS in men with metastatic CRPC after chemotherapy.
    c. Improve radiographic progression free survival in in patients with lung and liver metastases prior to chemotherapy.
    d. Improve time to CRPC in patients with biochemical recurrent prostate cancer.

12. Side effects related to the mechanism of action of abiraterone include:
    a. Decreased cortisol due to adrenal inhibition of CYP17A.
    b. Decreased DHEA-S due to adrenal inhibition of CYP17A.
    c. Increased cortisol due to feed back effects of ACTH.
    d. Decreased aldosterone due to feed back effects of ACTH

13. Patients with prostate cancer experienced a survival benefit of 4.8 months treated with enzalutamide compared to placebo in the AFFIRM trial. These data reflect which patient population?
    a. Men with mCRPC who have disease progression but were docetaxel naïve.
    b. Men with mCRPC who had disease progression following sipuleucel-T or abiraterone and prednisone.
    c. Men with mCRPC who have disease progression following docetaxel.
    d. Men with CRPC with either biochemical or radiographic disease progression who are docetaxel naïve and asymptomatic.

14. The rates of adverse events in the AFFIRM study were similar between the groups, despite a significantly longer exposure to enzalutamide and reporting time in the enzalutamide cohort compared to placebo. Concerning toxicities which were specific to enzalutamide in this study included which of the following?
    a. Significant QT prolongation.
    b. Seizure.
    c. Hepatotoxicity.
    d. Metabolic syndrome.

15. What was the improvement in median overall survival for patients receiving radium 223 on the randomized phase III ALSYMPCA trial?
    a. 1.0 months.
    b. 3.1 months.
    c. 3.6 months.
    d. 4.6 months.

16. The predominant form of decay of radium 223 is in the form of:
    a. Alpha particle.
    b. Beta particle.
    c. Gamma ray.
    d. Photon particles.

17. Choose the correct statement concerning cabazitaxel.
    a. It is as effective as docetaxel as first line chemotherapy in CRPC.
    b. Should be used with prophylactic growth factor support as second line therapy in CRPC.
    c. Has a 1 month improvement in survival when compared to mitoxantrone/prednisone.
    d. Is approved by the FDA as first line cytotoxic therapy for CRPC.

18. The use of denosumab (120 mg subcutaneously monthly) or zoledronic acid (4 mg IV monthly) should be discussed in one of these patients only.
    a. Hormone naïve symptomatic metastatic patient starting degarelix.
    b. Non metastatic castration resistant patient with PSA doubling time of 6 months.
    c. Non metastatic patient receiving leuprolide and presenting with an osteoporotic fracture. T score on DXA scan = -4.1.
    d. Asymptomatic metastatic castration resistant patient with increased activity on Tc99m bone scan.

19. Which of the following best describes the clinical benefit and toxicity of radium 223:
    a. Appropriate for all patients with castration resistant metastatic prostate cancer following docetaxel, its use associated with moderate myelosuppression.
    b. Delays time to symptomatic skeletal events, major side effect is hand-foot syndrome.
    c. Appropriate for patients with castration resistant metastatic prostate cancer with visceral metastases, minimal side effect profile.
    d. Appropriate for patients with castration resistant metastatic prostate cancer with symptomatic bone metastases, no known visceral mets, mild to moderate GI toxicity.

20. Which of the following statements are true:
    a. Primary testosterone suppression via medical or surgical castration is required for optimal use of abiraterone + prednisone.
    b. Sipuleucel-T improves overall survival and delays time to symptomatic skeletal events.
    c. Enzalutamide is a first generation lyase inhibitor.
    d. Abiraterone + prednisone improves survival of patients with castration resistant non-metastatic prostate cancer.

Notes