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INVITED OPINION

Prostate Cancer

Therapy decisions for the symptomatic patient with metastatic castration-resistant prostate cancer

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Metastatic prostate cancer continues to kill approximately 30,000 men per year. Since 2010, five new therapeutic agents have been Food and Drug Administration (FDA) approved to treat metastatic castration-resistant prostate cancer (mCRPC). With the increasing number of therapies available to clinicians, the most effective sequence in which to implement these treatments remains unknown. The presence or absence of symptoms (i.e., bony pain, visceral crisis) is a key parameter that informs the decision-making process regarding therapy. Treatment algorithms based on: 1) asymptomatic/minimal symptoms, 2) moderate symptoms or chemotherapy ineligible or 3) symptomatic disease need to be developed.

Prostate cancer is the most common epithelial malignancy in men. In 2013, >230 000 new cases of prostate cancer were diagnosed while the number of deaths remained below 30 000 largely due to emerging new therapies to treat metastatic disease.[1] Since 2010, five new therapeutic agents were FDA approved and internationally used to treat mCRPC as well as an additional bone targeted therapy for the prevention of skeletal related events (SREs) (**Table 1**). With the increasing number of therapies available to clinicians, the most effective sequence in which to implement these treatments remains unknown. The purpose of this article is to summarize the clinical treatment paradigm for symptomatic, mCRPC in 2015 (**Figure 1**).

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The presence or absence of symptoms (i.e., bony pain, visceral crisis) is a key parameter that informs the decision-making process regarding therapy. In this opinion piece, we discuss treatment algorithms based on: (1) asymptomatic/minimal symptoms, (2) moderate symptoms or chemotherapy ineligible with significant symptoms or (3) symptomatic disease. Although we discuss each separately, there is a continuum between categories as symptoms develop and the disease progresses.

ASYMPTOMATIC, MINIMAL SYMPTOMS

In 2010, the FDA approved Sipuleucel-T for the treatment of asymptomatic or minimally symptomatic mCRPC. Sipuleucel-T is an autologous dendritic cell (DC) vaccine consisting of patient DCs primed with a GM-CSF- prostatic acid phosphatase (PAP) fusion protein prior to reinfusion. The goal of this immunotherapy is to utilize a T cell response to the PAP presented by the mature DC against the cancer.[2] In a phase III study, Sipuleucel-T improved overall survival 4.1 months when compared to placebo.[3] Interestingly, there was no difference in time to disease progression and PSA response – therefore, it is not possible to measure how it might be working. This vaccine is available both in the pre- and post-docetaxel setting.

MODERATE SYMPTOMS OR CHEMOTHERAPY INELIGIBLE WITH SIGNIFICANT SYMPTOMS

For mCRPC patients with moderate symptoms, progression on Sipuleucel-T or are chemotherapy ineligible, the next-generation of hormonal therapy is available. Abiraterone acetate is an irreversible inhibitor of cytochrome P450 isoform-17 (CYP17), which is a key enzyme catalyzing the synthesis of androgens in both the adrenal glands and testes. The precursor agent of abiraterone acetate is ketoconazole, which inhibited multiple cytochrome P450 enzymes. Although ketoconazole treatment decreased PSA levels, the difficulty in dosing and side effect profile made it difficult to tolerate.[4] Abiraterone acetate was FDA approved in 2011 in the postchemotherapy setting based on a phase III trial showing an increase in overall survival, 14.8 months, compared to 10.9 months in the placebo-prednisone control.[5] In 2013, abiraterone acetate showed a trend toward overall survival in the predocetaxel setting leading to its FDA approval for chemotherapy-naïve patients.[6] The final analysis of COU-AA-302 was relased in 2015, which showed a statistically significant 4.4 month increase in the median overall survival with abiraterone acetate before chemotherapy.[7] Further analysis of the COU-AA-301 trial showed that abiraterone acetate significantly improved pain symptoms and decreased SRE in the postchemotherapy setting.[8] Clinicians have extrapolated this result to the prechemotherapy setting and are using abiraterone acetate as an alternative to upfront chemotherapy with moderate symptoms or in patients who are ineligible for chemotherapy. In the prechemotherapy trial, abiraterone acetate did significantly delay the use of opioids for cancer pain in a secondary endpoint.

Enzalutamide is an androgen receptor antagonist that prevents its translocation to the nucleus and is a more potent inhibitor than bicalutamide. Like abiraterone acetate, enzalutamide is FDA approved in both the pre- and postchemotherapy setting. The AFFIRM trial showed a median overall survival of 18.4 months in the enzalutamide treatment arm versus 13.6 months in the placebo group.[9] Recently, the PREVAIL trial, which looked at enzalutamide versus placebo in chemotherapy-naïve patients, was stopped early when an interim analysis showed a significant reduction in the risk of death

Table 1: Sentinel trials for metastatic castration-resistant prostate cancer therapies

Trial	*Year*	*Treatment*	*Outcome*	*Reference*
IMPACT	2010	Sipileucel-T versus placebo	OS: 25.8 versus 21.7 months	3
COU-AA-301	2011	Abiraterone versus placebo; postdocetaxel	OS: 14.8 versus 10.9 months	5
COU-AA-302	2015	Abiraterone versus placebo; predocetaxel	OS: 34.7 versus 30.3 months	7
AFFIRM	2012	Enzalutamide versus placebo; postdocetaxel	OS: 18.4 versus 13.6 months	9
PREVAIL	2014	Enzalutamide versus placebo; predocetaxel	OS: 32.4 versus 30.2 months	10
ALSYMPCA	2013	Radium-223 versus placebo	OS: 14.0 versus 11.2 months	11
TAX327	2004	Docetaxel q3 weeks versus mitoxantrone	OS: 18.9 versus 16.5 months	12
TROPIC	2010	Cabazitaxel versus mitoxantrone; postdocetaxel	OS: 15.1 versus 12.7 months	13

Over the past decade, several phase III trials have shown an increase in OS. These trials have increased the number of available therapies to clinicians. Additional research is on-going to determine the most effective sequence for these new treatments. OS: median overall survival; NR: not reached

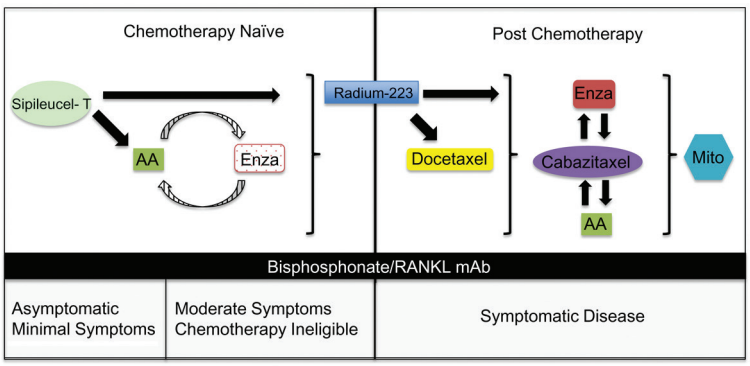

Figure 1: Treatment algorithm for metastatic castration-resistant prostate cancer (mCRPC). The therapy for mCRPC is complex with multiple options depending on patient characteristics and symptoms. Sipileucel-T is for asymptomatic patients only. Abiteratone acetate (AA) was recently approved in the chemotherapy-naïve setting and also has a role in more advanced patients. Enzalutamide (Enza) can precede or follow treatment with abiraterone acetate. Radium-223 is available in both pre- and post-chemotherapy patients with symptomatic, bone only metastatic disease. Cabazitaxel is a second-line chemotherapeutic followed by third-line therapy, mitoxantrone (Mito). Bisphosphonates and denosumab have been shown to decrease skeletal related events in patients with metastatic prostate cancer.

in the enzalutamide arm.[10] The most effective sequence of abiraterone acetate and enzalutamide use is currently being debated and will need further clarification.

Currently, chemotherapy is the standard, next-line therapy after progression on abiraterone acetate and enzalutamide. For patients with symptomatic bony disease who are not chemotherapy candidates and have no visceral disease, radium-223 is a potential therapeutic option. Radium-223 is an alpha-emitting radioisotope, which acts as calcium mimic. The compound is readily taken up in the bone, particularly in areas of osseous metastases. Alpha emitters have a shorter range of tissue penetration, which minimizes myelosuppression and has higher energy transfer compared to beta emitters. The ALSYMPCA trial was a randomized phase III trial looking at the effect of radium-223 with standard of care versus placebo with standard of care in patients previously exposed to docetaxel or unfit for docetaxel. Radium-223 increased overall survival to 14 months versus 11.2 months in the placebo group.[11] This agent is typically administered with the assistance of radiation oncology or nuclear medicine.

SYMPTOMATIC DISEASE

Chemotherapy is the treatment of choice for patients with symptomatic bony or visceral disease and for patients who have progressed on prior therapies (i.e. abiraterone acetate, enzalutamide). In 2004, the TAX327 trial showed that docetaxel given every 3 weeks had increased overall survival when compared with mitoxantrone (18.9 *vs* 16.4 months) and became the standard first-line chemotherapy for mCRPC patients.[12] The treatment decision for the second-line therapy after docetaxel remains controversial with no clear standard of care.

Cabazitaxel is a semi-synthetic taxane that shares a similar mechanism of action to docetaxel. In the phase III trial, TROPIC, cabazitaxel increased overall survival compared to mitoxantrone in the postdocetaxel setting (15.1 *vs* 12.7 months).[13] Mitoxantrone is a topoisomerase II inhibitor, which was FDA approved in combination with prednisone in 1996 for an increased palliation benefit when compared to prednisone alone.[14] Due to side effects and lack of survival benefit, mitoxantrone is most often used as a third-line chemotherapeutic in patients with an appropriate performance status.

Given the number of agents approved in the postdocetaxel setting, including abiraterone acetate and enzalutamide, there is a need for additional prospective studies to define the most effective sequence of these therapies. There is retrospective evidence to suggest that cabazitaxel before abiraterone acetate may be the preferred order after progression on docetaxel, but a prospective study would be necessary to clarify.[15] In addition, the increasing use of abiraterone acetate in prechemotherapy patients and recent approval of enzalutamide in this setting will likely narrow down the list of potential treatments after docetaxel. Molecular targeted therapies, next-generation antiandrogens, and immunotherapies are currently in the research pipeline and may further expand the list of treatment options both in the chemotherapy-naïve patient and postdocetaxel.

BONE TARGETED THERAPIES

Strontium-89 and samarium-153 are beta emitters, which were FDA approved in the 1990's for management of symptomatic bone pain from metastatic disease. Both agents showed an improvement in bone pain but did not increase overall survival.[16,17] The favorable side effect profile and improved overall survival benefit of radium-223 makes it an attractive alternative to strontium-89 and samarium-153.[18]

Bisphosphonates, such as zoledronic acid, are commonly used in the treatment of metastatic disease. These agents are used to slow the development of osteopenia/osteoporosis while on hormonal therapy, prevent against SREs, and treat hypercalcemia of malignancy.

Use of zoledronic acid in mCRPC significantly decreased the time-to-first SRE as well as the total number of SREs.[19] Denosumab is human, monoclonal antibody against RANK ligand, which is a mediator of bone resorption. A phase III trial showed denosumab to be noninferior to zoledronic acid in preventing SRE.[20] A secondary analysis showed superiority favoring the use of denosumab. Both bisphosphonates and RANK ligand targeted antibodies effectively complement the treatment of metastatic prostate cancer and continue to be widely used.

The treatment of symptomatic, castration-resistant prostate cancer has seen several advances in therapy over the past decade. With multiple clinical trials ongoing, the use of existing treatments and implementation of new drugs will surely evolve in the coming years.

EDITORIAL (BY DR JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

During a urologic oncology conference hosted by my institution, my colleague Paul Corn, MD in medical oncology was asked to present some cases on the emerging topic of how to rationally sequence and/or combine novel therapies for castrate-resistant prostate cancer. Compared with a decade ago, we can now offer such patients a lot more than morphine, spot radiation, and eventual hospice care. All approved agents in the class have been studied and approved for the FDA in a single drug versus placebo type of setting, with some important distinctions as to whether the study was pre- or post-chemotherapy. Although the survival and many secondary endpoints are improved with these agents, curative results are generally not observed, and one wonders whether or not this field will go the route of multi-agent protocols as with many chemotherapy regimens. Dr. Corn came up with an eye-opening set of mathematical observations:

a. There are 6 new therapies possible: docetaxel, cabazitaxel, abiraterone, enzalutamide, sipuleucel-T, and radium-223
b. There are 720 possible sequences
c. There are 15 unique combinations using two agents at a time
d. There is little chance for randomized phase III evidence to sort all of this out!

The solutions to this dilemma may be in the further study of mechanisms and predictive biomarkers. Excellent examples of the "future" here can be found in Logothetis *et al*.'s model of the Spiral Model of Progression[21] and the recently reported AR variant receptor model that correlates with drug resistance.[22] In this issue, Dr. Pienta's team present the available evidence and use patient symptom assessment as a baseline measurement to guide practical therapy choices.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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