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

Dr. Robert Dreicer received honoraria from Millenium, Bayer and Medivation. □

References

1. Berthold D, Pond G, Roessner M, de Wit R, Eisenberger M, Tannock I. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clin Cancer Res* 2008;14(9):2763-2767.
2. Mostaghel E, Montgomery B, Nelson P. Castration-resistant prostate cancer: targeting androgen metabolic pathways in recurrent disease. *Urol Oncol* 2009;27(3):251-257.
3. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364(21):1995-2005.
4. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367(13):1187-1197.
5. Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363(5):411-422.
6. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369(3):213-223.
7. de Bono J, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial *Lancet* 2010;376(9747):1147-1154.
8. Antonarakis ES, Eisenberger MA. Expanding treatment options for metastatic prostate cancer. *N Engl J Med* 2011;364(21): 2055-2058.

9. Ryan CJ, Smith MR, de Bono JS et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013;368(2):138-148.
10. Garcia J, Dreicer R. Immunotherapy in castration-resistant prostate cancer: integrating sipuleucel-T into our current treatment paradigm. *Oncology (Williston Park)* 2011;25(3):242-249.
11. Schellhammer PF, Chodak G, Whitmore JB, Sims R, Frohlich MW, Kantoff PW. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the immunotherapy for prostate adenocarcinoma treatment (IMPACT) trial. *Urology* 2013;81(6):1297-1302.
12. Small E, Lance R, Redfern C et al. A randomized phase II trial of sipuleucel-T with concurrent or sequential abiraterone acetate plus prednisone in metastatic castrate-resistant prostate cancer. *J Clin Oncol* 2013;31:abstr 5047.
13. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol* 2013;24(7):1802-1807.
14. Schrader A, Boegemann M, Ohlmann C et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur Urol* 2014;65(1):30-36.
15. Loriot Y, Bianchini D, Ileana E et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol* 2013;24(7):1807-1812.
16. Tannock I, de Wit R, Berry W et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351(15):1502-1512.
17. Agency for Health Care Policy and Research. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostatic cancer. Evidence Report/Technology Assessment, no. 4:73.
18. Harris V, Lloyd K, Forsey S, Rogers P, Roche M, Parker C. A population-based study of prostate cancer chemotherapy. *Clin Oncol (R Coll Radiol)* 2011;23(10):706-708.
19. Lee RJ, Saylor PJ, Dror Michaelson M et al. A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. *Clin Cancer Res* 2013;19(11):3088-3094.
20. Slovin SF, Higano CS, Hamid O et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. *Ann Oncol* 2013;24(7):1813-1821.
21. Saad F, Hotte S, North S et al. Randomized phase II trial of custirsen (OGX-011) in combination with docetaxel or mitoxantrone as second-line therapy in patients with metastatic castrate-resistant prostate cancer progressing after first-line docetaxel: CUOG trial P-06c. *Clin Cancer Res* 2011;17(17):5765-5773.