Treating Patients with Metastatic Castration Resistant Prostate Cancer: A Comprehensive Review of Available Therapies

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Purpose: The availability of newly approved treatment options for metastatic castration resistant prostate cancer is not matched with conclusive data on optimal sequencing strategies and resistance patterns. A comprehensive review of efficacy and safety data for new agents and current knowledge regarding treatment sequencing would enable treating physicians to make rational drug selections in patients with metastatic castration resistant prostate cancer.

Materials and Methods: We searched MEDLINE® and relevant congresses for data on cabazitaxel, docetaxel, ^{223}radium dichloride, abiraterone, enzalutamide and sipuleucel-T, focusing on sequencing strategies, resistance mechanisms and biomarkers of response.

Results: Abiraterone and enzalutamide target the androgen axis with different mechanisms of action. Abiraterone blocks cytochrome P450 17, inhibiting androgen synthesis, whereas enzalutamide inhibits androgen receptor, reducing nuclear translocation of the androgen receptor complex and subsequent DNA binding. Both agents provide improved overall survival in patients with metastatic castration resistant prostate cancer who received prior docetaxel treatment and in those who are chemotherapy naïve. Cabazitaxel provides improved overall survival in patients with metastatic castration resistant prostate cancer with prior docetaxel therapy. Sipuleucel-T provides improved overall survival in asymptomatic patients and ^{223}radium provides improved overall survival in chemotherapy naïve and chemotherapy treated patients with symptomatic bone metastases. Selecting the correct treatment with metastatic castration resistant prostate cancer is complex as no head-to-head trials have been done and comparison between existing trials is difficult due to differences in

Abbreviations and Acronyms

ADT = androgen deprivation therapy

AE = adverse event

AR = androgen receptor

AR-V = AR splice variant

COU-AA-302 = Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients with mCRPC

CTC = circulating tumor cell

CYP17 = cytochrome P450 17

FDA = Food and Drug Administration

mCRPC = metastatic castration resistant prostate cancer

OS = overall survival

PFS = progression-free survival

PREVAIL = Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients with Progressive Metastatic Prostate Cancer

PSA = prostate-specific antigen

QoL = quality of life

rPFS = radiographic progression-free survival

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study populations and a lack of validated biomarkers. Factors to consider include prior therapy, symptom burden, metastasis type, performance status, comorbidities, adverse event profiles and patient preference. Another consideration is treatment sequence since some agents affect responses to subsequent choices. For example, resistance to abiraterone or enzalutamide may result in limited responses to subsequent androgen targeted agents. Identifying factors predictive of resistance is an area of ongoing research with androgen receptor variants representing a good candidate. Prognostic factors for survival are also likely to be useful and are currently being studied.

Conclusions: New therapies for metastatic castration resistant prostate cancer have brought new challenges with regard to treatment selection and sequencing. While hormonal agents provide good therapeutic responses, resistance may be intrinsic without prior drug exposure. Identifying predictors of response and relevant biomarkers will allow therapies to be more precisely tailored to individual patient profiles.

Key Words: prostatic neoplasms, neoplasm metastasis, castration, drug therapy, androgen antagonists

FOR many years the mainstay of treatment for mCRPC was docetaxel. Since 2010, several treatments have shown a survival benefit in patients with mCRPC in phase 3 trials, leading to regulatory approval and subsequent inclusion in treatment guidelines (table 1).[1]

Despite the numerous treatment options for mCRPC the impact on survival is less than optimal and there are limited data to provide guidance regarding how to optimally sequence approved treatments for individual patients. Recently results from several studies of mCRPC began to identify clinical factors that predict benefit from androgen axis targeted and other therapies, which might help inform treatment decisions for individual patients. This article provides an overview of phase 3 trial data for androgen axis targeting agents in mCRPC as well as perspectives on other recently approved mCRPC agents, a review of studies attempting to assess the impact of resistance to androgen axis targeting agents and emerging data on prognostic factors and biomarkers in patients with mCRPC.

METASTATIC CASTRATION RESISTANT PROSTATE CANCER TREATMENT EVOLUTION

The benefits of recently approved treatments for mCRPC have been shown in 7 randomized phase 3 trials (table 2).

Trials of Androgen Axis Targeting Agents

After Chemotherapy. Abiraterone and enzalutamide target the androgen axis. Abiraterone inhibits androgen synthesis by the adrenal glands and testes, and within the prostate tumor by blocking CYP17, a critical enzyme in testosterone synthesis.[2] In contrast, enzalutamide targets AR, including intracellular signaling functions.[3]

The efficacy of abiraterone and enzalutamide in mCRPC was proved initially in men who had received prior docetaxel chemotherapy. In the abiraterone trial 1,195 patients received prednisone 5 mg twice daily in combination with oral abiraterone 1,000 mg once daily or placebo.[2,4] In the enzalutamide trial 1,199 patients received oral enzalutamide 160 mg daily or placebo.[3] After 20.2 months of median followup in the abiraterone trial OS was longer for abiraterone/prednisone vs placebo/prednisone (median 15.8 vs 11.2 months, $p < 0.001$).[4] In the enzalutamide trial, which was reported with shorter followup (median 14.4 months), OS was also longer for enzalutamide vs placebo (median 18.4 vs 13.6 months, $p < 0.001$).[3] For both agents superiority vs the control arm was demonstrated for other end points, including standard assessments (PSA response rate, tumor response, time to PSA progression and rPFS) as well as other end points (time to skeletal events, pain palliation and health related QoL).[2–6]

AEs that were more frequent for abiraterone/prednisone vs placebo/prednisone included urinary tract infection in 12% vs 7% of patients ($p = 0.02$), fluid retention/edema in 31% vs 22% ($p = 0.04$) and hypokalemia in 17% vs 8% ($p < 0.001$) with the latter 2 AEs attributable to mineralocorticoid excess resulting from CYP17 blockade.[2] AEs that appeared more frequent for enzalutamide vs placebo treatment included fatigue in 34% vs 29% of cases, diarrhea in 21% vs 18%, hot flashes in 20% vs 10%, musculoskeletal pain in 14% vs 10%, headache in 12% vs 6%, hypertension in 7% vs 3% and seizures in 0.6% vs 0%.[3]

Overall each trial provided confirmation that mCRPC remains in part an androgen driven disease

Table 1. *FDA approved anticancer treatments for mCRPC, excluding treatments specifically for bone metastases*

Treatment	Mechanism	Indication	Dose	Initial FDA mCRPC Approval Date
Docetaxel (Taxotere®)*	Taxane chemotherapy (microtubule inhibitor)	mCRPC	75 mg/m^2 Intravenously every 3 weeks	5/04
Sipuleucel-T (Provenge®)	Autologous cellular immunotherapy	Asymptomatic or minimally symptomatic mCRPC	250 ml Infusion containing 50 million or greater autologous activated CD54+ cells, every 2 weeks, 3 doses	4/10
Cabazitaxel (Jevtana®)*	Taxane chemotherapy (microtubule inhibitor)	mCRPC with previous docetaxel treatment	25 mg/m^2 Intravenously every 3 weeks	6/10
Abiraterone acetate (Zytiga®)*	CYP17 (androgen synthesis) inhibitor	mCRPC	1000 mg Orally once daily	4/11
Enzalutamide (Xtandi®)	AR inhibitor	mCRPC	160 mg Orally once daily	9/12
^{223}Radium dichloride (Xofigo®)	α Particle emitting radiopharmaceutical	mCRPC with symptomatic bone metastases + no known visceral metastatic disease	50 kBq (1.35 μCi)/kg body wt intravenously every 4 weeks, 6 doses	5/13

* Combination agent oral prednisone 10 mg daily.

even after progression on chemotherapy and that androgen blockade through different mechanisms can lead to improved patient outcomes.[2,3]

In Chemotherapy Naïve Patients. The clinical benefits of abiraterone and enzalutamide have also been shown in trials of men with asymptomatic or minimally symptomatic, chemotherapy naïve mCRPC. In the COU-AA-302 abiraterone trial 1,088 patients received oral abiraterone 1,000 mg daily plus prednisone 5 mg twice daily or placebo plus prednisone.[7,8] In the PREVAIL enzalutamide trial 1,717 patients received oral enzalutamide 160 mg daily or placebo.[9] In both trials co-primary end points were OS and rPFS. Notably the trials differed in inclusion criteria with visceral metastases permitted in the enzalutamide trial but not in the abiraterone trial.[7–9] After a median 49.4-month followup abiraterone/prednisone vs placebo/prednisone resulted in longer median OS (34.7 vs 30.3 months, $p = 0.0027$), representing a 20% risk reduction.[10] With enzalutamide rPFS data were reported after 12-month followup and showed superiority for enzalutamide vs placebo (median not reached vs 3.9 months, $p < 0.001$) with an 81% risk reduction. OS findings from PREVAIL, analyzed at a median followup of 26 months, also showed superiority for enzalutamide vs placebo (median not reached vs 31.0 months, $p < 0.001$) with a 27% risk reduction.[9] In an earlier interim analysis median OS had been estimated as 32.4 months for enzalutamide vs 30.2 months for placebo. Notably a survival advantage for enzalutamide vs placebo was observed in patients with visceral disease. Abiraterone and enzalutamide showed benefits vs placebo in other end points, including higher rates of PSA response and tumor response, longer time to PSA progression or initiation of chemotherapy and delayed deterioration of patient reported QoL/functional status. The trials differed in other secondary/exploratory end points reported. Abiraterone delayed several pain related end points and enzalutamide delayed skeletal related events.[7–9]

In COU-AA-302 AEs that appeared more frequent for abiraterone plus prednisone vs placebo plus prednisone included fatigue in 40% vs 35% of patients, arthralgia in 29% vs 24%, peripheral edema in 26% vs 21%, hot flush in 23% vs 18%, diarrhea in 23% vs 18%, hypertension in 22% vs 14% and liver enzyme increases (grade 3/4 alanine aminotransferase or aspartate aminotransferase increase) in 3% to 6% vs 1%.[8] In PREVAIL AEs that appeared to be more frequent for enzalutamide vs placebo included fatigue in 36% vs 26% of patients, back pain in 27% vs 22%, constipation in 22% vs 17%, hot flush in 18% vs 8%, hypertension in 13% vs 4% (grade 3/4 in 7% vs 2%), asthenia in 13% vs 8% and falls in 12% vs 5%.[9]

Overall these trials demonstrated that androgen axis targeted agents can also provide clinical benefits to men with asymptomatic or minimally symptomatic mCRPC who have not received chemotherapy.

Recent Trials of Nonhormonal Agents in Metastatic Castration Resistant Prostate Cancer

Other randomized phase 3 trials have shown that other nondocetaxel agents could extend survival or provide benefit in patients with mCRPC (table 2).

Sipuleucel-T is a therapeutic cancer vaccine prepared by extracting peripheral blood mononuclear cells from the individual patient via leukapheresis. The cells are shipped to a manufacturing facility, where antigen presenting cells are cultured ex vivo with PA2024 recombinant fusion protein (prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor). After approximately 40 hours the cells are washed, resuspended and shipped back to the clinic provided

Table 2. *Baseline characteristics and findings of recent mCRPC phase 3 trials*

	Pre-chemotherapy Trials			Post-Docetaxel Trials			Bone Metastatic, Nonvisceral
	IMPACT*[,11]	COU-AA-302*[,7,8]	PREVAIL[9]	TROPIC[12]	COU-AA-301†[,2,4]	AFFIRM‡[,3,43]	ALSYMPCA[13]
Arm:							
Experimental (No. pts)	Sipuleucel-T (341)	Abiraterone/prednisone (546)	Enzalutamide (872)	Cabazitaxel/prednisone (378)	Abiraterone/prednisone (797)	Enzalutamide (800)	^{223}Radium + best supportive care (614)
Control	Placebo	Prednisone	Placebo	Mitoxantrone/prednisone	Prednisone	Placebo	Placebo + best supportive care
				Baseline characteristics			
Age:							
Median age	72	71	72	68	69	69	71
% 75 or Greater	Not reported	34	36	18	28	25	28
% Performance score:							
0—1	100	100	100	93	90	91	87
2 or Greater	0	0	0	7	10	9	13
% Metastases:							
Bone	93	83	85	80	89	92	100
Visceral	0	0	11	25	32	27	0
% Prior docetaxel	16	0	0	100	100	100	57
Median baseline PSA (ng/ml)	51.7	42.0	54.1	143.9	128.8	107.7	146
				Results			
Median mos survival (improvement over comparator arm)	OS 25.8 (4.1), time to objective progression 3.7 (0.1)	OS 35.3 (5.2), rPFS 16.5 (8.3)	Interim OS 32.4 (2.2), median rPFS not reached vs 3.9 in comparator arm (1-yr rPFS 65% for 51% improvement)	OS 15.1 (2.4), PFS 2.8 (1.4)	OS 15.8 (4.6), rPFS 5.6 (2.0)	OS 18.4 (4.8), rPFS 8.3 (5.4)	OS 14.9 (3.6), for PFS, rPFS + time to objective progression no imaging on trial
% Most frequent AEs:							
Any grade hematological + nonhematological (25% or greater)	Chills (54), fatigue (39), back pain (34), pyrexia (29), nausea (28)	Fatigue (40), back pain (33), arthralgia (29), fluid retention (29), peripheral edema (26)	Fatigue (36), back pain (27)	Anemia (97),§ leukopenia (96),§ neutropenia (94),§ thrombocytopenia (47),§ diarrhea (47), fatigue (37), nausea (34)	Fatigue (47), fluid retention/edema (33), back pain (33), nausea (33), arthralgia (30), constipation (28), bone pain (27)	Fatigue (34), back pain (26)	Bone pain (50), diarrhea (25), anemia (31), nausea (36), fatigue (26)
Grade 3 or greater (5% or greater)	Not applicable	Cardiac disorders (7), alanine aminotransferase increased (6)	Hypertension (7)	Neutropenia (82),§ leukopenia (68),§ anemia (11),§ febrile neutropenia (8),§ diarrhea (6), fatigue (5), asthenia (5)	Fatigue (9), anemia (8), back pain (7), bone pain (6), arthralgia (5), cardiac disorders (5)	Fatigue (6), back pain (5)	Bone pain (21), anemia (13), thrombocytopenia (7)

* Trial excluded patients with liver metastases or ECOG (Eastern Cooperative Oncology Group) performance score 2 or greater.
† Abiraterone Acetate in Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy.
‡ Safety and Efficacy Study of MDV3100 in Patients with Castration-Resistant Prostate Cancer Who Have Been Previously Treated with Docetaxel-Based Chemotherapy.
§ Hematological data based on laboratory assessments.

that release specifications are met. Sipuleucel-T is then infused in a manner similar to any blood product. This procedure is repeated every 2 weeks for a total of 3 infusions.[11] In the phase 3 IMPACT (Provenge® [Sipuleucel-T] Active Cellular Immunotherapy Treatment of Metastatic Prostate Cancer After Failing Hormone Therapy) trial men with asymptomatic mCRPC, including approximately 20% who had received prior chemotherapy, were randomized to receive 3 infusions of sipuleucel-T or analogously prepared placebo containing only peripheral blood mononuclear cells.[11] Sipuleucel-T was associated with longer OS (median 25.8 vs 21.7 months, $p = 0.03$), although it had no effect on time to disease progression or PSA.[11] AEs associated with sipuleucel-T were mostly infusion related and transient. They occurred within 1 day after infusion and resolved 1 to 2 days later. More frequent AEs for sipuleucel-T vs placebo included chills in 54% vs 13% of patients, pyrexia in 29% vs 14%, headache in 16% vs 5%, pain in 13% vs 7%, myalgia in 10% vs 5%, flu-like illness in 10% vs 4%, hypertension in 7% vs 3% and hyperhidrosis in 5% vs 1%.

Cabazitaxel is a next generation taxane chemotherapy developed to overcome resistance to docetaxel treatment. In the TROPIC (XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer) trial men with mCRPC that had progressed after docetaxel treatment received intravenous cabazitaxel 25 mg/m^2 or mitoxantrone 12 mg/m^2 every 3 weeks for up to 10 cycles, each in combination with prednisone 10 mg daily.[12] Compared with mitoxantrone, cabazitaxel treatment resulted in longer median OS (15.1 vs 12.7 months) and PFS (2.8 vs 1.4 months, each $p < 0.0001$), significantly higher rates of PSA and tumor response, and longer time to PSA progression. AEs associated with cabazitaxel were characteristic of taxanes. The most frequent AEs were hematological, including grade 3 or greater neutropenia (82% of cases with cabazitaxel vs 58% with mitoxantrone) and leukopenia (68% vs 42%). Grade 3 or greater febrile neutropenia with cabazitaxel vs mitoxantrone developed in 8% vs 1% of cases. The most frequent nonhematological AEs of any grade for cabazitaxel vs mitoxantrone included gastrointestinal disturbances such as diarrhea in 47% vs 11% of patients, nausea in 34% vs 23% and vomiting in 23% vs 10%, fatigue in 37% vs 27% and peripheral neuropathy in 14% vs 3%.

More recently phase 3 data were reported for ^{223}radium, an α emitting radiopharmaceutical agent that accumulates preferentially in bone metastases. The ALSYMPCA (A Phase III Study of Radium-223 Dichloride in Patients with Symptomatic Hormone Refractory Prostate Cancer with Skeletal Metastases) trial in 921 men included those with castration resistant prostate cancer metastatic to bone (2 or more sites) with pain (evidenced by regular use of analgesic medication or external beam radiation therapy for cancer related bone pain within the previous 12 weeks) with no known visceral metastases.[13] Patients had received or were ineligible for/unable/unwilling to receive docetaxel. They were randomized to 6 cycles of intravenous ^{223}radium or placebo every 4 weeks, each in combination with best standard of care. This was the routine care provided at each center, such as local external beam radiation therapy or glucocorticoid, antiandrogen, ketoconazole or estrogen treatment. Chemotherapy, hemibody external radiotherapy and other systemic radionuclides were not permitted. The study was stopped after a positive interim analysis. OS was longer for ^{223}radium vs placebo (median 14.9 vs 11.3 months, $p < 0.001$) as was time to first symptomatic skeletal event and time to elevation in PSA or alkaline phosphatase. A higher proportion of patients treated with ^{223}radium had an improvement in QoL. Post hoc analyses showed that ^{223}radium reduced pain scores and opioid use compared with placebo.[14] Rates of AEs of all grades, or grade 3 or greater were lower in the ^{223}radium arm vs the placebo arm. Rates of grade 3 or greater hematological AEs included anemia in 13% vs 13% cases, thrombocytopenia in 7% vs 2% and neutropenia in 2% vs 1%. Of the frequent nonhematological AEs of all grades, only diarrhea in 25% vs 15% of patients, vomiting in 18% vs 14% and peripheral edema in 13% vs 10% seemed more frequent with ^{223}radium whereas bone pain (50% vs 62%) was less frequent and other AEs had similar rates.[13]

POTENTIAL LIMITATIONS IN APPLYING PHASE 3 TRIAL FINDINGS TO CONTEMPORARY CLINICAL PRACTICE

Exposure to docetaxel has been used as a convenient but artificial disease setting leading to compartmentalization of subsequently approved agents into pre-docetaxel and post-docetaxel roles. The dearth of active agents to use as comparators in clinical trials resulted in a low bar so that all nonchemotherapy trials tested new agents against placebo or placebo plus prednisone. Therefore, although several options are effective treatments for mCRPC, each treatment with a different toxicity profile, it is difficult to assess the comparative effectiveness of treatments when there is a paucity of head-to-head comparator trials. Currently there are no data to indicate whether one treatment is more effective than another. Cross-trial comparisons are hampered by variations in available treatments based on the era in which the trial was

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