Case Study Series

Clinical Advances in Hematology & Oncology

Cases in the Management of Prostate Cancer: The Addition of Darolutamide to Androgen Deprivation Therapy and Docetaxel in a 55-Year-Old Man With Metastatic Hormone-Sensitive Prostate Cancer



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Case 3 of a 3-Part Series

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The Addition of Darolutamide to Androgen Deprivation Therapy and Docetaxel in a 55-Year-Old Man With Metastatic Hormone-Sensitive Prostate Cancer

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Patient Case

In November 2021, a 55-year-old man presented to his primary care physician reporting difficulties with urination. The patient was otherwise in good health. He worked as a software engineer and a financial investor.

During this office visit, the primary care physician prescribed treatment with tamsulosin and ordered blood work, including testing for prostate-specific antigen (PSA) levels. The results of the blood work were normal, except for an elevated PSA of 43.21 ng/mL (Table 1). It is important to note that this PSA test was the patient's first one. For years, his primary care physician had advised him that PSA screening was not needed according to recommendations from the US Preventive Services Task Force.¹ Based on the elevated PSA level, the patient was referred to a urologist.

The urologist performed a prostate needle biopsy, which revealed a prostate adenocarcinoma. Pathology findings included cT1c stage and Gleason grade 9 (G4+5=9) in all 12 biopsy cores sampled. The tumor was high risk according to criteria from the National Comprehensive Cancer Network (NCCN).² The urologist referred the patient for computed tomography (CT) and a bone scan. Both imaging studies were negative. However, based on the patient's PSA level and Gleason score, the urologist was highly suspicious of metastatic spread that was not readily identifiable with conventional imaging. The urologist consulted with a medical oncologist, who recommended that the patient undergo a prostate-specific membrane antigen (PSMA) positron emission tomography scan. At the time, the PSMA agent had been recently approved by the US Food and Drug Administration, and thus was not widely available. Therefore, the patient was not able to undergo the PSMA scan until early January.

The PSMA scan showed metastatic spread, with significant lymph node disease in the abdomen, pelvis, and upper chest/mediastinal area. Impressions from the PSMA scan included high heterogeneous uptake throughout the prostate gland, avid retroperitoneal and bilateral pelvic lymph nodes, and avid posterior mediastinal lymph nodes, which suggested nodal metastases. Osseous metastasis was suspected based on a mild focal uptake in an area of subtle sclerosis at the right iliac. Magnetic resonance imaging (MRI) confirmed these findings.

The patient was diagnosed with metastatic hormonesensitive prostate cancer. He expressed a desire for aggressive treatment. The oncologist recommended androgen deprivation therapy (ADT) plus chemotherapy.

The patient began treatment with relugolix in mid-January 2022. Docetaxel was initiated 2 weeks later, with 6 cycles planned. Within the first month, the patient's PSA level markedly decreased to 6.93 ng/mL. Shortly thereafter, findings from the ARASENS study were presented. This phase 3 trial demonstrated that the addition of darolutamide to the standard-of-care regimen used in this case improved overall survival.^{3,4} Per a recommendation from

On the Cover

Immunofluorescence micrograph of prostate cancer cells. The large cell nuclei, which contain DNA (dark blue), are typical of the rapid cell division that occurs in cancer. Proteins in the cytoplasm are green. One cell with red cytoplasm (above center) is undergoing mitotic cell division. The centrioles (yellow) and spindle fibers (light blue) needed for division can be seen.

Credit: Nancy Kedersha / Science Source

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Tal	ble	1.	Key	Points	of t	he Case
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Presentation and Work-Up: November 2021				
PSA Level	November 1, 2021: 43.21 ng/mL November 8, 2021: 48.80 ng/mL			
Biopsy Findings	November 10, 2021: Prostate adenocarcinoma Stage cT1c Gleason grade 9 (4+5) in 12/12 cores			
Imaging Findings	November 15, 2021: CT scan (negative) November 16, 2021: Bone scan (negative) January 7, 2022: PSMA (metastatic disease)			
Treatment: January 2022 to Present				
First-Line Treatment	January 14, 2022: initiated relugolix once daily January 28, 2022: initiated docetaxel every 3 weeks for 6 cycles March 1, 2022: initiated darolutamide twice daily			
PSA Level	January 5, 2022: 55 ng/mL February 2, 2022: 6.93 ng/mL March 11, 2022: 1.93 ng/mL May 2, 2022: 0.45 ng/mL			
Imaging Findings	January 12, 2022: MRI scan (metastatic disease) April 26, 2022: MRI scan (improvement relative to January 2022 scan)			

CT, computed tomography; MRI, magnetic resonance imaging; PSA, prostatespecific antigen.

his oncologist, the patient began treatment with darolutamide in March 2022. To manage urinary retention, the patient began self-catheterization in April 2022.

The patient developed a few side effects that are common with ADT, including loss of libido and hot flashes. Overall, however, he feels well. He maintains a rigorous exercise program and follows a healthy diet. Follow-up testing confirmed that he has good cardiovascular health.

The patient's PSA levels ultimately became undetectable. A follow-up MRI performed in April 2022 showed improvements relative to the first MRI performed in January 2022. At an upcoming visit, the patient and oncologist will discuss options for treatment of the primary tumor (radiation or cryotherapy).

Clinical Implications

This patient case illustrates important contemporary issues in the management of prostate cancer. The case describes integration of next-generation PSMA imaging with conventional imaging, including CT and bone scans. The NCCN guidelines now state that it is possible to rely on PSMA imaging when metastasis is suspected in high-risk patients with apparent localized disease.² This new imaging technique can help precisely locate the disease, which can allow the correct diagnosis. Ultimately, the incorporation of PSMA imaging will impact many clinical decisions. It is important to remember that the current therapies were approved based on the use of conventional imaging techniques.

Cancer is a collection of genetic changes. The longer the tumor is allowed to grow, the more genetic heterogeneity it accumulates, and the less responsive it becomes to treatment. Earlier treatment will lead to better outcomes. This principle holds true for metastatic prostate cancer. Identification of metastatic disease as early as possible will allow initiation of aggressive treatment that will likely improve outcomes.

Rationale for Therapeutic Decisions

The type of scenario seen in this case is all too common when treating patients with prostate cancer. The patient's PSA level and Gleason score indicate the presence of metastasis, but conventional imaging does not show it. For patients such as this, the standard-of-care first-line treatment is ADT with the addition of either docetaxel or an androgen receptor (AR) pathway inhibitor. This standard of care is based on data from phase 3 trials. Overall survival was improved among patients treated with docetaxel plus ADT compared with ADT alone.⁵⁻⁸ Clinical benefit was also seen with the addition of an AR pathway inhibitor (abiraterone acetate, enzalutamide, or apalutamide) to ADT compared with ADT alone.⁹⁻¹²

Based on the benefits observed with the addition of docetaxel or an AR pathway inhibitor to ADT, the triple combination of an AR pathway inhibitor added to docetaxel and ADT was explored. However, conflicting results were reported. The first phase 3 trial exploring this triple combination was ENZAMET, which failed to show a benefit in overall survival with the addition of enzalutamide to docetaxel and ADT.¹² In contrast, recent publications of the PEACE-1 trial and the ARASENS trial each reported a significant benefit in overall survival with the addition of apalutamide or darolutamide, respectively.^{4,13}

ARASENS: Darolutamide Plus ADT and Docetaxel

ARASENS was an international, randomized, doubleblind, placebo-controlled phase 3 trial. Patients were enrolled between November 2016 and June 2018 from across 23 countries. This study evaluated the addition of the AR pathway inhibitor darolutamide to the standardof-care treatment of docetaxel plus ADT in men with metastatic, hormone-sensitive prostate cancer.⁴

The trial enrolled adult patients with prostate cancer



Figure 1. Overall survival in the full analysis set in the phase 3 ARASENS trial, which evaluated the addition of darolutamide to androgen deprivation therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer. NE, not estimable. Adapted from Smith MR et al. *N Engl J Med.* 2022;386(12):1132-1142.⁴

that was confirmed as metastatic based on bone scans, CT, or MRI. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. They were candidates for ADT and docetaxel per the investigator. The study excluded several types of patients from enrollment: those with regional lymph-node involvement only (N1, below the aortic bifurcation); those who had received ADT more than 12 weeks before randomization; those who had received second-generation androgenreceptor pathway inhibitors, chemotherapy, or immunotherapy before randomization; and those treated with radiotherapy within 2 weeks before randomization.⁴

All patients in the trial were treated with ADT (administered as a luteinizing hormone-releasing hormone agonist or antagonist) or had undergone an orchiectomy within 12 weeks before randomization. Within 6 weeks after randomization, all patients additionally received 6 cycles of docetaxel (75 mg/m² every 21 days), with prednisone or prednisolone administered at the investigator's discretion. Per the study protocol, oral dexamethasone (8 mg given at 12 hours, 3 hours, and 1 hour before the docetaxel infusion) was recommended as premedication to prevent docetaxel-related hypersensitivity reactions and fluid retention.⁴

A total of 1306 patients were randomly assigned to receive additional treatment with either darolutamide (600 mg twice daily) or matched placebo. Darolutamide or placebo were continued until symptomatic disease progression, change in antineoplastic therapy, unacceptable toxicity, patient or physician decision, nonadherence, or death.

At randomization, stratification factors included the

metastasis stage (nonregional lymph node metastases only [M1a] vs bone metastases with or without lymph node metastases [M1b] vs visceral metastases with or without lymph node or bone metastases [M1c]) and alkaline phosphatase level (below vs at or above the upper limit of normal). Patients were assessed every 12 weeks. They underwent contrast-enhanced chest, abdomen, and pelvic CT or MRI and bone scanning at baseline, within 30 days after the last cycle of docetaxel, and yearly thereafter during the study.⁴

The patients' baseline characteristics were well-balanced between the darolutamide and placebo arms. The median age was 67 years in both groups (range, 41 to 89), with 36.5% of patients younger than 65 years and 46.6% of patients ages 65 to 74 years. Most patients were white (51.9%) or Asian (36.4%), and were from the Asia-Pacific region (36.2%) or North America (18.7%). Most patients (71.1%) had an ECOG performance status of 0, and 78.2% had a Gleason score of 8 or higher. At screening, 79.5% of patients had bone metastases (stage M1b), and 17.5% had visceral metastases (stage M1c). The median serum PSA level was 30.3 ng/mL in the darolutamide arm and 24.2 ng/mL in the placebo arm.⁴

Data cutoff for the primary analysis took place on October 25, 2021. The median duration of treatment was 41 months in the darolutamide arm vs 16.7 months in the placebo arm. The proportion of patients still receiving the assigned treatment was 45.9% in the darolutamide arm vs 19.1% in the placebo arm. A similar proportion of patients in both treatment arms successfully completed 6 cycles of docetaxel (87.6% in the darolutamide arm and 85.5% in the placebo arm).⁴

The primary endpoint of the ARASENS study was overall survival. The median follow-up was 43.7 months in the darolutamide arm and 42.4 months in the placebo arm. The median overall survival was not estimable in the darolutamide arm vs 48.9 months in the placebo arm (Figure 1).⁴ This difference resulted in a 32.5% reduced risk of death among patients receiving darolutamide (hazard ratio [HR], 0.68; 95% CI, 0.57-0.80; P<.001). The significant benefit in overall survival was observed even though 75.6% of patients in the placebo arm went on to receive subsequent life-prolonging systemic therapies (including different AR pathway inhibitors). The 4-year rate of overall survival was 62.7% (95% CI, 58.7-66.7) with darolutamide vs 50.4% (95% CI, 46.3-54.6) with placebo. The benefit in overall survival associated with darolutamide was observed across most patient subgroups.⁴

A statistically significant benefit with darolutamide was also reached in several secondary endpoints of the ARASENS study. For example, the median time to castration-resistant prostate cancer was not reached with darolutamide compared with 19.1 months with placebo (HR, 0.36; 95% CI, 0.30-0.42; P<.001). The median time to pain progression was not reached with darolutamide vs 27.5 months with placebo (HR, 0.79; 95% CI, 0.66-0.95; P=.01). The median symptomatic skeletal event-free survival was 51.2 months with darolutamide vs 39.7 months with placebo (HR, 0.61; 95% CI, 0.52-0.72; P<.001). The median time to first symptomatic skeletal event was also significantly longer with darolutamide, although this endpoint was not reached in both treatment arms (HR, 0.71; 95% CI, 0.54-0.94; P=.02). The median time to initiation of subsequent systemic antineoplastic therapy was not reached with darolutamide vs 25.3 months with placebo (HR, 0.39; 95% CI, 0.33-0.46; P<.001).

There was no significant difference between the darolutamide and placebo arms in the median time to worsening of disease-related physical symptoms (19.3 months and 19.4 months, respectively). The median time to initiation of opioid treatment for at least 7 consecutive days was not reached in both arms, and this endpoint was not tested hierarchically for significance.⁴

The toxicity profile reflected the use of docetaxel in both arms. The addition of darolutamide did not significantly alter the incidence of any grade, grade 3 to 5, or serious adverse events. The most common adverse events occurred more frequently during the period of docetaxel administration. Among these, neutropenia was the most common grade 3/4 adverse event, reported in 33.7% of the darolutamide arm and 34.2% of the placebo arm.⁴

Several adverse events of special interest in patients receiving AR pathway inhibitors were monitored in the ARASENS trial. The incidences of fatigue, falls, fractures, mental impairment, cardiovascular events, vasodilation and flushing, and diabetes mellitus and hyperglycemia were similar between the darolutamide and placebo arms. The incidence of rash was higher with darolutamide vs placebo (16.6% vs 13.5%, respectively), as was hypertension (13.7% vs 9.2%, respectively).⁴

During the study, deaths occurred in 4.1% of the darolutamide arm and 4.0% of the placebo arm. An adverse event led to treatment discontinuation in 13.5% of patients in the darolutamide arm and 10.6% of patients in the placebo arm.⁴

PEACE-1: Abiraterone Acetate Plus ADT and Docetaxel

The PEACE-1 trial was an open-label, randomized, activecontrolled phase 3 study with a 2×2 factorial design.¹² The trial evaluated the efficacy and safety of abiraterone acetate plus prednisone, with or without radiotherapy, added to the standard-of-care therapy of docetaxel plus ADT in men with metastatic, hormone-sensitive prostate cancer. Patients were enrolled between November 2013 and December 2018 from 7 European countries. During this time, the standard-of-care treatment for patients with metastatic hormone-sensitive prostate cancer evolved, leading to 2 major protocol amendments. The first (in 2015) was to allow for the combined use of docetaxel with ADT. The second (in 2017) made docetaxel mandatory for the remainder of patients enrolled in the trial, based on data showing that ADT plus abiraterone acetate improved overall survival vs ADT alone. This change permitted the trial to evaluate the addition of abiraterone acetate to ADT plus docetaxel.13

The study permitted enrollment of adult patients with prostate cancer confirmed to be metastatic by bone scan, CT, or MRI. Patients had to have adenocarcinoma; those with pure small-cell carcinoma were not eligible for enrollment. The patients had an ECOG performance status of 0, 1, or 2 (if based on bone pain). Metastatic prostate cancer had to be considered de novo. Patients who had received a definitive local therapy to treat their prostate cancer were not eligible for enrollment. The trial limited enrollment to patients who had received ADT for 3 months or less before randomization.¹³

Patients were randomly assigned to 1 of 4 treatment arms: standard of care (docetaxel [75 mg/m² for six 3-week cycles] plus ADT), standard of care plus radiotherapy (74 Gy in 37 fractions administered throughout 7 to 8 weeks, starting between 3 and 8 weeks after completion of docetaxel), standard of care plus abiraterone acetate (1000 mg once daily) and prednisone (5 mg twice daily), and standard of care plus radiotherapy and abiraterone acetate. All patients received continuous ADT, administered either as a gonadotropin-releasing hormone agonist or antagonist, or bilateral orchiectomy. Abiraterone acetate and prednisone were continued until disease progression, withdrawal of consent, unacceptable toxicity, or death. Randomization was stratified by study site, ECOG performance status (0 vs 1 or 2), type of ADT (gonadotropinreleasing hormone agonist vs antagonist vs bilateral orchiectomy), planned administration of docetaxel (yes vs no), and disease extent or burden based on metastatic status (lymph node metastases only [M1a] vs bone metastases with or without lymph node metastases [M1b] vs visceral metastases [M1c]).¹³

The trial randomly assigned 1172 patients to treatment. The treatment arms were pooled into 2 groups for analysis: 583 patients treated with the standard of care plus abiraterone acetate (with or without radiotherapy), and 589 patients treated with the standard of care without abiraterone acetate (with or without radiotherapy). In each group, half of the patients were assigned to receive radiotherapy.

The baseline characteristics were well-balanced between the groups. The median age was 66 to 67 years, and ranged from 37 to 94 years. The ECOG performance status was 0 in 70.3% of patients. The patients had M1a (8.4%), M1b (80.8%), or M1c (10.8%) disease. The metastatic burden was high in 56.9% of patients. Most patients (74.2%) had a Gleason score of 8 to 10. The median serum PSA level was 14 ng/mL in the abiraterone acetate group and 11 ng/mL in the control group.¹³

The PEACE-1 study had 2 co–primary endpoints: radiographic progression-free survival (evaluated by either CT, MRI, or bone scan) and overall survival. After a median follow-up of 3.53 years in the overall population, the median radiographic progression-free survival was 4.46 years in the abiraterone acetate group vs 2.22 years in the control group. Treatment with abiraterone acetate reduced the relative risk of radiographic progression or death by 46% (adjusted HR, 0.54; 99.9% CI, 0.41-0.71; P<.0001).¹³

For the overall survival analyses, the median followup periods were 4.41 years for the overall population and 3.81 years for the population receiving ADT plus docetaxel. The median overall survival in the abiraterone acetate group was 5.72 years, compared with 4.72 years in the control group. Treatment with abiraterone acetate led to an 18% reduction in the risk of death from any cause (adjusted HR, 0.82; 95.1% CI, 0.69-0.98; *P*=.030).¹³

In the overall population, the benefit with abiraterone acetate on radiographic progression-free survival was observed across several of the predefined patient subgroups. Exceptions included patients who had bilateral orchiectomy and those who did not receive docetaxel based on the investigator's decision. The impact of abiraterone acetate on overall survival was particularly pronounced in patients with a high volume of metastatic burden.¹³

Based on the evolution of the standard-of-care regimen throughout the study period, the population of 710 patients whose standard of care consisted of docetaxel plus ADT were analyzed separately. The addition of abiraterone acetate to the standard of care showed a statistically significant benefit in the overall population. Therefore, the group of patients who had received only docetaxel plus ADT (with or without abiraterone acetate) underwent assessment for both co-primary endpoints. In this population, the median radiographic progression-free survival was 4.46 years with the addition of abiraterone acetate compared with 2.03 years without the addition of abiraterone acetate. Abiraterone acetate reduced the relative risk of radiographic progression or death by 50% (adjusted HR, 0.50; 99.9% CI, 0.34-0.71; P<.0001). The median overall survival was also significantly improved in this population of patients (from 4.43 years to not reached, respectively) with a concordant reduction in the relative risk of death from any cause by 25% (adjusted HR, 0.75; 95.1% CI, 0.59-0.95; P=.017).¹³

The degree of metastatic burden seemed to affect both co-primary endpoints in the population of patients who had received only docetaxel plus ADT as the standard of care. In patients with low metastatic burden, the addition of abiraterone acetate to the standard of care reduced the relative risk of radiographic progression or death by 42%. This risk was reduced by 53% in patients with high metastatic burden. The addition of abiraterone acetate was associated with a 28% reduction in the relative risk of death from any cause in patients with a high metastatic burden. The data were not mature in patients with low metastatic burden, and therefore no conclusive response in overall survival could be determined for this group.¹³

Several secondary endpoints were assessed in the PEACE-1 study. Among the 710 patients whose standard of care consisted of docetaxel plus ADT, the addition of abiraterone acetate was associated with longer median survival free of castration-resistant prostate cancer (3.21 vs 1.45 years; HR, 0.38; 95% CI, 0.31-0.47; P<.0001). The median prostate cancer–specific survival was also improved in patients who received abiraterone acetate vs those who did not in the ADT-plus-docetaxel arm (not reached vs 4.72 years; HR, 0.69; 95% CI, 0.53-0.90; P=.0062).¹³

In the patient population treated with docetaxel and ADT as the standard of care, the rate of grade 3 or higher adverse events was 63% among patients who received abiraterone acetate vs 52% in patients who did not receive abiraterone acetate. Fatal adverse events occurred in 7 abiraterone acetate–treated patients and in 3 patients who did not receive abiraterone acetate. In the population of patients treated with ADT without docetaxel, 66% of patients who received abiraterone acetate had at least one grade 3 or worse adverse event, and 4% had a fatal adverse

event. Among patients treated with ADT and docetaxel, the frequency of grade 3 or higher adverse events reported in at least 5% of patients was relatively similar between patients who did or did not receive abiraterone acetate. Grade 3 or higher events that were more common in the abiraterone acetate arm included hypertension (22% vs 13%) and hepatotoxicity (6% vs 1%).¹³

ENZAMET: Enzalutamide Plus ADT and Early Docetaxel

ENZAMET was a multinational, open-label, randomized phase 3 trial in men with metastatic hormone-sensitive prostate cancer.¹² The trial evaluated the addition of enzalutamide to first-line treatment with ADT with or without early docetaxel. The study enrolled patients with prostate cancer with metastases apparent on CT, bone scan, or both. The patients had an ECOG performance status of 0, 1, or 2. Prior adjuvant testosterone suppression for up to 2 years was permitted if the treatment had been completed at least 12 months before enrollment.¹²

The study randomly assigned 1125 men to receive enzalutamide (160 mg once daily) plus the standard of care or the standard of care alone. Initially, the standard of care consisted of ADT (a standard nonsteroidal antiandrogen, such as bicalutamide, nilutamide, or flutamide) administered with continuous testosterone suppression. After the enrollment of the first 88 patients, the early administration of docetaxel with testosterone suppression was permitted in a protocol update. The decision to add docetaxel was at the discretion of the patients and their physicians. When used, docetaxel was administered at a dose of 75 mg/m² every 3 weeks for up to 6 cycles (up to 2 cycles of docetaxel were permitted before randomization). In both treatment arms, therapy was continued until disease progression or unacceptable toxicity. Stratification factors included the volume of disease (high vs low), planned use of early docetaxel (yes vs no), planned use of bone antiresorptive therapy (yes vs no), score on the Adult Comorbidity Evaluation 27 questionnaire, and trial site. The primary endpoint was overall survival.

The median follow-up was 34 months. At 3 years, the rate of overall survival was 80% in the enzalutamide arm vs 72% in the standard-of-care arm (HR, 0.67; 95% CI, 0.52-0.86; *P*=.002). The secondary endpoint of time to clinical progression was also significantly prolonged with the addition of enzalutamide compared with the standard of care alone. The 3-year event-free survival was 68% vs 41%, respectively (HR, 0.40; 95% CI, 0.33-0.49; *P*<.001).¹²

The effect of concurrent docetaxel was assessed in a prespecified subgroup analysis. In this analysis, enzalutamide significantly improved the time to clinical progression among patients treated with docetaxel (HR, 0.48; 95% CI, 0.37-0.62). However, the addition of enzalutamide did not improve overall survival (HR, 0.90; 95% CI, 0.62-1.31).¹²

Among patients treated with docetaxel, grade 2 peripheral sensory neuropathy was reported in 9% of enzalutamide-treated patients vs 3% of those treated with the standard of care. In comparison, none of the enzalutamide-treated patients who did not receive early docetaxel developed grade 2 peripheral neuropathy.¹²

Disclosure

Dr Crawford is a member of the academic advisory board of Tolmar, and he has performed disease state consulting for Tolmar. He is a consultant, advisor, meeting participant, or lecturer for Bayer. He is a consultant or advisor for MDx, Genomic Health, Janssen, Dendreon, and Ferring. He has performed a scientific study or trial for the NIH and the University of Colorado Cancer Center. Dr Crawford's wife is a former employee of Dendreon.

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