Cabazitaxel Improves Progression-Free and Overall Survival in Metastatic Prostate Cancer After Progression on Abiraterone or Enzalutamide

De Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med. 2019;381:2506-2518.

Study Overview

Objective. To evaluate the efficacy of cabazitaxel compared to androgen-signaling–targeted inhibitors (ASTIs) in patients with metastatic castration-resistant prostate cancer who have received docetaxel and have progressed within 12 months of treatment with either abiraterone or enzalutamide.

Design. The CARD trial was an international, randomized, open-label phase 3 trial conducted across 13 European countries.

Setting and participants. Eligible patients were 18 years of age or older; had metastatic castration-resistant prostate cancer previously treated with docetaxel; and had disease progression during 12 months of treatment with abiraterone or enzalutamide. All patients had histologically proven prostate cancer, castrate levels of serum testosterone, and disease progression, defined by at least 2 new bone lesions or rising prostate-specific antigen (PSA) level. A total of 255 patients underwent randomization between November 2015 and November 2018, with 129 assigned to receive cabazitaxel and 126 patients assigned to receive an ASTI, 58 of whom received abiraterone and 66 of whom received enzalutamide. Patients who had received an ASTI in the setting of castrate-sensitive metastatic prostate cancer were included.

Intervention. Patients were randomized in a 1:1 fashion to receive either cabazitaxel or abiraterone or enzalutamide. Patients receiving cabazitaxel 25 mg/m^2 intravenously every 3 weeks also received oral prednisone daily and primary prophylactic granulocyte-colony stimulating factor. Patients assigned to receive an ASTI received abiraterone 1000 mg orally daily with prednisone 5 mg twice daily or enzalutamide 160 mg daily. Patients in the ASTI group who had progressed on abiraterone were assigned to enzalutamide, and alternatively, those on enzalutamide were assigned to abiraterone. Patients were treated until 1 of the following occurred: imaging-based disease progression, unacceptable toxicity, or advancing to an alternative therapy.

Main outcome measures. The primary endpoint was imaging-based progression-free survival, which was defined as the time from randomization until objective tumor progression, progression of bone lesions, or death. The secondary endpoints were overall survival, progression-free survival, PSA response, tumor and pain responses, a new symptomatic skeletal event, and safety.

Results. The median follow-up was 9.2 months. Imaging-based disease progression or death from any cause occurred in 95 (73.6%) participants in the cabazitaxel group, as compared to 101 (80.2%) who were assigned to receive an ASTI. The median imaging-based progression-free survival was 8.0 months in the cabazitaxel group and 3.7 months in the abiraterone/enzalutamide group. The median duration of treatment was longer in those receiving cabazitaxel (22 vs 12.5 weeks). The primary reason for treatment discontinuation was disease progression (in 43.7% of patients receiving cabazitaxel and 71% receiving an ASTI) or an adverse event (19.8% and 8.9%, respectively).

The trial's secondary endpoints demonstrated improved outcomes in the cabazitaxel group compared to the abiraterone/enzalutamide group. There were 70 deaths (54.2%) in the cabazitaxel group and 83 (65.9%) in the ASTI group. Both the median overall survival (13.6 months in the cabazitaxel group and 11 months in the ASTI group) and the median progression-free survival (4.4 months

and 2.7 months, respectively) were improved in those who received cabazitaxel. There was a 50% or greater reduction in the PSA level from baseline in 35.7% of the cabazitaxel group and 13.5% of the ASTI group.

Regarding the safety of the agents, the incidence of adverse events was similar in each group (38.9% in the cabazitaxel group and 38.7% in the ASTI group). Treatment discontinuation occurred more frequently in the cabazitaxel group (19.8%) compared to the ASTI group (8.9%). Adverse events of grade 3 or higher occurred more frequently with cabazitaxel; these were asthenia (4% vs 2.4%), diarrhea (3.2% vs 0), peripheral neuropathy (3.2% vs 0 patients), and febrile neutropenia (3.2% vs 0 patients).

Conclusion. Patients who had disease progression within 12 months on an ASTI and had previously been treated for metastatic castration-resistant prostate cancer with docetaxel had longer imaging-based progression-free survival and overall survival when treated with cabazitaxel compared to those treated with an alternative ASTI. Other clinical outcomes, including overall survival and progression-free survival, were also improved in the cabazitaxel group.

Commentary

Four ASTIs are approved for therapy in men with advanced prostate cancer. The next line of therapy following progression on an ASTI, whether to consider second-line androgen targeted inhibitors or proceed to taxane-based chemotherapy, has been unclear. The current CARD trial sought to answer this question and provides evidence that cabazitaxel is the next line of therapy for these patients. The trial's primary endpoint, imaging-based disease progression, was reported in 73.6% of those who received cabazitaxel and in 80.2% of those who received abiraterone or enzalutamide. Patients treated with cabazitaxel had a longer imaging-based progression-free survival (8.0 months vs 3.7 months) and a longer duration of treatment (22 vs 12.5 weeks).

Because there is clinical evidence of cross-resistance between different ASTIs, the value of sequential therapy has been unclear. Emergence of androgen-receptor splice variant 7 (AR-V7) mutational status in circulating tumor cells is associated with poor outcomes with secondary androgen-signaling inhibitor therapy, and may be an indicator of resistance to subsequent androgen-signaling inhibitors.[1,2] In the PROPHECY trial, the response rates to subsequent androgen targeted therapy in patients with AR-V7 mutations ranged from 30% to 40%.[3] Understanding how AR-V7 mutational status may impact such outcomes will certainly help define whether a subgroup exists in whom use of second-line androgen signaling inhibitors may be considered.

The patients enrolled in the current study appear to represent a subgroup of patients with biologically aggressive disease or with inherent resistance to ASTIs. The patients included in this study progressed within 1 year of androgen targeted therapy, which is representative of a more aggressive population of patients who may be hormone insensitive and derive more benefit from chemotherapy. Initial androgen deprivation therapy was given for 13.7 and 12.6 months to the cabazitaxel and enzalutamide/abiraterone arms, respectively, prior to developing castrate-resistant prostate cancer. Patients enrolled in this study also previously received docetaxel, deselecting those who are taxane-resistant and therefore may be less likely to respond to additional taxane-based therapy. Detection of AR-V7 splice variant expression in circulating tumor cells, consideration of biomarker data, and sensitivity to taxanes may help guide decisions regarding the use of sequential androgen-targeted agents; however, there has been no clear data to guide such an approach. It is also important to consider that, because this is a European study, the approved dose given in this trial was 25 mg/m^2. The PROSELICA trial previously demonstrated noninferiority of 20 mg/m^2 compared with 25 mg/m^2, with fewer adverse events, which is the dose now utilized in the United States.[4]

The adverse events of grade 3 or greater occurring in the cabazitaxel group should be discussed with patients, including fatigue, diarrhea, peripheral neuropathy, and febrile neutropenia.

The data from the CARD trial provide guidance regarding therapy sequencing in those with advanced prostate cancer after progression on first-line androgen targeted inhibitors and docetaxel; however, further work is needed to understand the universal application of this data in this cohort.

Applications in Clinical Practice

Patients with metastatic castration-resistant prostate cancer who have received docetaxel and progressed on an androgen-signaling inhibitor within 12 months should be considered for cabazitaxel over an alternative androgen-signaling inhibitor. This decision should be based on several factors, including AR-V7 mutational status, duration of androgen deprivation therapy, and hormone and taxane sensitivity in the past. Future studies are likely to incorporate genomic biomarkers rather than clinical criteria alone to make treatment decisions.

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