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RESEARCH HIGHLIGHT

Cabazitaxel: a new drug for metastatic prostate cancer

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In Western countries, prostate cancer is the most common malignancy in men and ranks third in mortality. In 2010, an estimated 217 730 new cases are anticipated in the United States, and about 32 050 men are expected to die from the disease.[1] Until 2004, numerous clinical trials in men with metastatic castration-resistant prostate cancer (mCRPC) failed to demonstrate any significant change in overall survival. The only option for symptomatic patients at that time was mitoxantrone, a type II topoisomerase inhibitor that disrupts DNA synthesis and repair in cells, approved due to its beneficial effect on quality of life. Docetaxel with prednisone was the first chemotherapy regimen to demonstrate an improvement in overall survival in this patient population (18.9 months versus 16.5 months; hazard ratio (HR)=0.76; P=0.009) relative to mitoxantrone and prednisone.[2] This regimen was approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of mCRPC.

It would be another 6 years, however, before any agent demonstrated a survival benefit in patients who progressed on docetaxel.[3] Cabazitaxel is a second-generation semisynthetic taxane that inhibits microtubule depolymerization, leading to cell cycle arrest and cell death.[4] Unlike other taxane compounds, cabazitaxel appears to penetrate the blood–brain barrier and is a poor substrate for the multidrug-resistant P-glycoprotein efflux pump that is a possible mechanism for taxane resistance.[5,6]

A company-sponsored phase III clinical trial of cabazitaxel versus mitoxantrone (TROPIC) was conducted in 28 countries in 755 patients with mCRPC previously treated with docetaxel. Eligible patients were at least 18 years of age (median: 68 years), had an ECOG performance status of 0–2, and had pathologically proven prostate cancer with documented disease progression during or after treatment with a cumulative dose of docetaxel >225 mg m^{-2}. The median dose of docetaxel received pre-study was 576.6 mg m^{-2} in the cabazitaxel group and 529.2 mg m^{-2} in the mitoxantrone group. Patients with measurable disease were required to have documented disease progression by RECIST criteria, while patients with non-measurable disease were required to have rising serum prostate-specific antigen (PSA) concentrations or the appearance of at least one new radiographically demonstrable lesion. In addition, all patients were castrated by orchiectomy, luteinizing hormone–releasing hormone agonists, or both, and underwent antiandrogen withdrawal after biochemical recurrence for at least 4 weeks (6 weeks for bicalutamide). Patients were randomized to receive prednisone 10 mg per day with mitoxantrone 12 mg m^{-2} or cabazitaxel 25 mg m^{-2}. Patients in both arms of the trial appeared to be well balanced in terms of baseline characteristics and treatment histories. At the end of the trial, all significant measures of antitumor activity favored cabazitaxel. Tumor response rates by RECIST criteria were 14.4% for the cabazitaxel group versus 4.4% for the mitoxantrone group (P=0.0005). Median progression-free survival was 2.8 months with cabazitaxel and 1.4 months with mitoxantrone. Time to progression was also significantly longer with cabazitaxel (8.8 months versus 5.4 months; P<0.0001). PSA declines of at least 50% were seen in 39.2% of patients in the cabazitaxel group and 17.8% of patients in the mitoxantrone group (P=0.0002).[7] Most importantly, median overall survival was 15.1 months with cabazitaxel versus 12.7 months with mitoxantrone (HR=0.72; P<0.0001).

On the basis of guidelines recommending 12 weeks of treatment before adjustment of therapy for mCRPC, an amendment was made to the trial protocol after 59 patients had been enrolled to exclude patients previously receiving a cumulative dose of docetaxel <225 mg m^{-2}. Subgroup intention-to-treat analysis of overall survival consistently favored cabazitaxel in all subgroups, with no significant correlation between total previous dose of docetaxel and treatment response. Median time from last docetaxel dose to disease progression was similar in both groups (0.8 months for cabazitaxel versus 0.7 months for mitoxantrone). Time interval since last dose of docetaxel also did not correlate with treatment response.

Unfortunately, cabazitaxel toxicity was significant in this post-docetaxel mCRPC population. In the cabazitaxel group, 18% of patients discontinued treatment because of adverse events (mostly neutropenia and renal failure), compared with 8% in the control group. Grade ⩾3 neutropenia was seen in 81.7% of patients receiving cabazitaxel compared to 58% of patients receiving mitoxantrone. The most common (⩾5%) grades 3–4 adverse reactions were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue and asthenia. Deaths due to causes other than disease progression within 30 days of last dose of study drug were reported in 18 (5%) cabazitaxel-treated patients compared to only 3 (>1%) mitoxantrone-treated patients. The most common fatal adverse reactions in cabazitaxel patients were infections (n=5) and renal failure (n=4).[7] Interestingly, the designated dose of cabazitaxel in this trial was higher than the starting dose of this agent (20 mg m^{-2}) in breast cancer clinical trials that enrolled younger patients.[8] Managing the toxicity of cabazitaxel and optimizing patient selection will be critical as this agent becomes more widely used.

Cabazitaxel was granted fast-track designation by the FDA in November 2009. The new drug application submission was completed in March 2010 and was granted priority review in April 2010. Approval by the FDA occurred less than 3 months later, based on the results of the TROPIC study.

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In the same year, two other agents attracted the attention of oncologists when both led to significant increases in overall survival in patients with mCRPC. One of them was sipuleucel-T, a patient-specific therapeutic cancer vaccine, derived from the patient's own immune cells that targets prostate alkaline phosphatase. In a phase III randomized trial of 512 patients, those treated with sipuleucel-T survived 25.8 months versus 21.7 months compared to placebo (HR=0.78; P=0.03),[9] leading to FDA approval in April 2010. Another investigational agent, abiraterone acetate (in combination with prednisone), has demonstrated a significant improvement in overall survival in men with mCRPC post-docetaxel compared to patients treated with prednisone/prednisolone. Treatment with abiraterone acetate resulted in a 35% reduction in the risk of death (HR=0.65; P<0.0001) and a 36% increase in median survival (14.8 months versus 10.9 months) compared with placebo. These findings were presented in October 2010 at the European Society for Medical Oncology Congress. FDA approval is anticipated.

Patients with prostate cancer now face a more promising future. Cabazitaxel is the first approved chemotherapy drug to show a survival benefit in patients with disease progression following standard chemotherapy. Abiraterone has shown significant improvement in overall survival in the post-docetaxel setting, but many anticipate that, along with sipuleucel-T, its optimal use may eventually be in the prechemotherapy setting. Another agent, MDV3100, an androgen receptor antagonist, is currently being tested in a phase III study in patients post-docetaxel. Promising phase I/II study results have recently been published.[10]

Cabazitaxel, however, fills an unmet medical need and is clearly needed. Patient selection remains the critical question. In particular, what is the optimal interval between prior docetaxel treatment and cabazitaxel. If patients never respond to docetaxel and in fact rapidly progress on treatment, is cabizataxel ideal? Additionally, studies must determine whether longer treatment with docetaxel (as per PSA Working Group II criteria recommending no treatment stoppage for PSA changes) will have an effect on cabazitaxel activity. Perhaps one should even consider looking at cabazitaxel as a front-line agent. Finally, for this patient population, toxicity may be a significant factor in decisions regarding the use of cabazitaxel. In a group of men with a median survival of only 15 months this rate of toxic deaths, grade 4 neutropenia and gastrointestinal toxicity may 'not be worth it' to many. Lower doses may be used in some patients, but it is unclear how this would affect the drug's efficacy.

With three new drugs, 2010 year appears to be a landmark year for prostate cancer treatment. The improvement in survival demonstrated by cabazitaxel gives us an important new weapon to treat men with mCRPC post docetaxel. Patient selection and the timing of the use of this agent as well as abiraterone and sipuleucel-T are very important questions as we attempt to make real progress in this disease.

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