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Cabazitaxel

Filling one of the gaps in the treatment of prostate cancer

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Prostate cancer is the second most frequently diagnosed cancer in men and the fifth most common cancer overall. Globally, more than 900,000 new cases of prostate cancer will be diagnosed in 2010 and more than 260,000 will, unfortunately, die from the disease. In the US, an estimated 217,000 new cases of prostate cancer and 32,000 deaths are expected this year.[1] Definitive therapy (surgery or radiation) is highly effective, but if the tumor escapes the gland, treatment options are limited. For this population of patients, androgen suppression is the cornerstone of initial therapy.[2] Furthermore, progression to castration resistant prostate cancer (CRPC) is inevitable. The current front-line treatment for patients with CRPC is the chemotherapeutic agent docetaxel (administered every 3 weeks). Until now, it is the only agent that has been shown to prolong survival in CRPC.[3] The approval trial for docetaxel found a median overall survival of 19.2 months for patients receiving docetaxel plus prednisone compared to 16.3 months for patients receiving mitoxantrone plus prednisone ($p = 0.0094$).[3] Mitoxantrone plus prednisone is often utilized for its palliative benefits, but two randomized trials failed to demonstrate a survival advantage.[4,5]

In an effort to prolong survival in patients with metastatic CRPC, various novel combination regimens involving docetaxel with anti-angiogenic agents, chemotherapies and targeted agents have been evaluated, none of which have proven in phase 3 studies to extend survival.[6-8] Furthermore, two monotherapy agents (ixabepilone[9] and satraplatin[10]) failed to produce a statistical survival benefit in patients with CRPC. Subsequently, once a patient progresses on docetaxel, proven treatment options are nonexistent. Thus, the publication by de Bono and colleagues in the October 3, 2010 issue of Lancet demonstrating a survival benefit for the cabazitaxel plus prednisone treatment arm for patients with metastatic CRPC whose disease has progressed after docetaxel-based therapy is of clear significance for these patients.[11]

Cabazitaxel is a tubulin-binding taxane (a partially synthesized derivative of 10-deacetylbaccatin III, the major natural taxoid derived from Pacific yew tree), which showed activity in docetaxel-resistant cancer cell lines.[12] It was selected for clinical development primarily due to poor affinity for the ATP-dependent drug efflux pump P-glycoprotein (P-gp; also known as ABCB1).[13] A phase I clinical trial using an every 3 week schedule observed objective responses in two patients with CRPC; one of whom was refractory to docetaxel.[14] Based on these data, de Bono et al. conducted an open-labeled, multi-center, multinational, randomized phase 3 trial in men ($n = 755$) with CRPC comparing cabazitaxel (25 mg/m^2 q3wks) plus prednisone (10 mg/day) with mitoxantrone (12 mg/m^2 q3wks) plus prednisone (10 mg/day).[11] All of the patients had received androgen suppression and had progressive disease (androgen suppression was continued). Furthermore, all of the patients had previously progressed during or after treatment with a docetaxel-containing regimen. Cabazitaxel resulted in a 2.4 months improvement in overall survival and median progression free survival of

2.8 months in the cabazitaxel group versus 1.4 months in the mitoxantrone treatment group.

Cabazitaxel resulted in more allergic-type reactions, which required prophylaxis treatment. The combination of cabazitaxel plus prednisone resulted in a significant increase in grade 3 or higher adverse events neutropenia; 82% for cabazitaxel compared with 58% for mitoxantrone and diarrhea (6% vs. <1%, respectively). The cabazitaxel treatment group had a 4.9% increase in treatment-related mortality. One unfortunate study design flaw was the variation in investigator treatment of febrile neutropenia, which may have contributed to the excess mortality. Prior to using cabazitaxel, a treatment plan needs to be initiated to manage febrile neutropenia (this should include colony-stimulating factors, patient education, pre-selected antibiotic regimens and support measures in place).

Cabazitaxel provides an important addition to our treatment armamentarium for treating metastatic CRPC in the post-docetaxel setting.[15] The one question left unanswered by the trial above is the definition of docetaxel resistance. It is clear cabazitaxel is active in this disease, but would some of these patients have responded to a re-challenge of docetaxel? In addition, will the combination of cabazitaxel with prednisone result in more activity than docetaxel/prednisone when combined with novel agents? However, cabazitaxel is primarily metabolized via cytochrome P450 3A4 and 3A5 and thus one should be careful of drug interactions in designing combination studies.

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