CHEMOTHERAPY

Improved survival in second-line advanced prostate cancer treated with cabazitaxel

New data on cabazitaxel have led to FDA approval for its use in second-line treatment of metastatic castration-resistant prostate cancer. The TROPIC trial, led by Johann de Bono, compared the treatment outcomes of cabazitaxel and mitoxantrone in patients with progressive disease and found that cabazitaxel conferred a 30% reduction in the risk of death and increased median overall survival by 2.4 months.

Docetaxel in combination with prednisone is standard first-line chemotherapy in patients with hormone-refractory, castration-resistant metastatic prostate cancer. However, therapeutic options are limited for patients who have disease progression after docetaxel-based chemotherapy. In this setting, mitoxantrone is often used to treat disease and alleviate symptoms, such as pain, and to improve patients' quality of life. Nevertheless, no treatments have been able to prolong survival in this population.

Cabazitaxel, a novel microtubule inhibitor, has demonstrated antitumor activity in phase I and II clinical trials in patients with docetaxel-refractory solid tumors—including metastatic castration-resistant prostate cancer. In light of these findings, de Bono and colleagues compared the safety and efficacy of prednisone-based regimens combined with either mitoxantrone or cabazitaxel. The investigators carried out a randomized phase III trial enrolling 755 patients (from 146 centers in 26 countries) with castration-resistant prostate cancer who had disease progression after treatment with docetaxel.

Between 2 January 2007 and 23 October 2008, patients participating in the TROPIC trial received 10 mg of oral prednisone daily and either 12 mg/m² mitoxantrone intravenously over 15–30 mins (*n* = 377) or 25 mg/m² cabazitaxel intravenously over 1 h (*n* = 378) every 3 weeks. The cabazitaxel dose was selected to limit the

primary treatment-related toxic effect of neutropenia, according to data from phase I and II studies. Treatment was continued for a maximum of 10 cycles (to minimize the risk of cardiac toxic effects associated with mitoxantrone).

Overall survival was the primary end point. Time to progression was also measured as indicated by either prostate-specific antigen progression, pain progression, tumor progression, or death. In addition, the amount of pain the patients experienced and the incidence of treatment-related side effects were monitored. Median follow up for both treatment groups combined was 12.8 months.

At the cutoff for final analysis (25 September 2009), 234 deaths were recorded in the cabazitaxel group and 279 deaths in the mitoxantrone group. The median overall survival was 15.1 months in patients treated with cabazitaxel compared with 12.7 months in patients treated with mitoxantrone. This result corresponds to a 30% reduction in relative risk of death for patients receiving cabazitaxel. The median progression-free survival was also superior in the cabazitaxel group (2.8 months versus 1.4 months in the mitoxantrone group).

Significant improvements in prostate-specific antigen response and tumor response were recorded in the cabazitaxel group. However, there was no significant difference in pain experienced by patients or time-to-pain progression between the two treatment groups.

Patients in the cabazitaxel group received a median of six treatment cycles compared with four cycles in the mitoxantrone group. The main reason for treatment discontinuation in both groups was disease progression.

The most common severe (grade 3 or higher) adverse event observed was neutropenia, which was more frequent in patients treated with cabazitaxel than

those treated with mitoxantrone. Indeed, the most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences.

The researchers suggest that patients treated with cabazitaxel should be monitored for adverse effects. Moreover, strategies such as prophylactic treatment with granulocyte colony-stimulating factor or modifying the cabazitaxel dose could be used to manage these toxic effects.

Nevertheless, the most significant finding is the overall survival benefit in patients with castration-resistant prostate cancer who had disease progression after treatment with docetaxel. Cabazitaxel is the first agent to achieve such an outcome in this patient population.

“We believe that cabazitaxel should now be standard therapy,” de Bono comments. He adds “combinations with abiraterone and trials of cabazitaxel versus docetaxel in the first-line setting are now warranted.”

Lisa Richards

Original article de Bono, J. S. *et al.* Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 376, 1147–1154 (2010)