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Docetaxel in Hormone-Refractory Metastatic Prostate Cancer

A Viewpoint by Ronald de Wit

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Prostate cancer is the most common cancer among men and is the second leading cause of cancer death in males. For decades, chemotherapy in patients who had become androgen independent (hormone-refractory prostate cancer) was considered minimally effective. In the 1990s it was recognised that the use of mitoxantrone plus low-dose prednisone improved pain in one-third of patients with symptomatic bone metastases, but median survival was not improved. Still, these results prompted proof-of-concept studies with docetaxel in every 3 weeks and once-weekly regimens, with or without the addition of estramustine.

The notable response rates observed in these studies, and in particular the promising survival figures, prompted two phase III studies investigating docetaxel versus mitoxantrone that were designed to test for survival improvement. The international TAX 327 study investigated docetaxel (either once every 3 weeks or once-weekly) plus prednisone versus mitoxantrone plus prednisone. The Southwest Oncology Group (SWOG) 9916 study was designed around the assumption that the combination of docetaxel plus estramustine had even greater potential; it was compared with mitoxantrone plus prednisone.

The results of these studies and the subsequent approval of docetaxel plus prednisone in hormone-refractory metastatic prostate cancer in the US and EU form the backbone of the accompanying Drug Profile. Both phase III studies showed that docetaxel once every 3 weeks, either with prednisone or with estramustine, results in superior survival compared with mitoxantrone plus prednisone. TAX 327 also demonstrated superior pain relief and improved health-related quality of life with docetaxel plus prednisone, which commenced during the actual chemotherapy.

In addition to these key findings, the studies provided other meaningful insights. Although TAX 327 was not powered to test between the every 3 weeks and the once-weekly docetaxel regimens, only the every 3 weeks regimen significantly improved survival compared to the mitoxantrone regimen. Moreover, docetaxel at the dose of 75 mg/m^2 once every 3 weeks was very well tolerated in this patient population and there was no indication that the once-weekly regimen had a better toxicity profile. Hence, there is no apparent role for the use of once-weekly docetaxel in hormone-refractory prostate cancer. SWOG 9916 also found superior survival with docetaxel, but the addition of estramustine increased gastrointestinal and cardiovascular toxicity considerably.

Although the data from TAX 327 and SWOG 9916 cannot be formally compared, the patient characteristics of the patients enrolled in the two studies and the median survival duration seen in the mitoxantrone control arms were strikingly similar. The apparent lack of improved efficacy with the docetaxel/estramustine combination versus the docetaxel every 3 weeks/prednisone regimen on the one hand, and the increased toxicity seen with the addition of estramustine on the other hand, provides little rationale for the further use of estramustine in the docetaxel regimen.

Docetaxel every 3 weeks plus low-dose prednisone can be considered the standard chemotherapy regimen in patients with hormone-refractory prostate cancer. It should also be regarded as the reference regimen when investigating the incorporation of new active agents into existing treatment regimens, as well as for investigating the potential role of docetaxel earlier in the course of the disease. Such patients may include those at high risk of recurrence at the time of radical prostatectomy, or at the time of first occurrence of relapse. Many such studies are already in progress and, hopefully, will lead to further therapeutic improvement in the near future. ▲