

Docetaxel treatment in the elderly patient with hormone refractory prostate cancer

Victoria J Sinibaldi

Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins,
Baltimore, MA, USA

Abstract: Docetaxel is an anti-microtubular agent in the family of the taxanes, now FDA approved as first line chemotherapy for the treatment of hormone refractory metastatic prostate cancer. Recent data from two large randomized Phase III trials showed a survival advantage in hormone refractory prostate cancer patients treated with docetaxel. This discovery changed the perceptions about utilization of chemotherapy for this devastating disease and introduced a new paradigm/standard of care treatment for this patient population. The management of elderly patients with metastatic prostate cancer is an important issue because according to data from the Surveillance, Epidemiology, and End Results (SEER) program, the American Cancer Society, and the United Nations, the incidence of prostate cancer in elderly men is expected to increase since people are living longer. In this paper we will review the results of trials evaluating docetaxel in hormone refractory prostate cancer and the implications of these trials as they relate to diagnosis and management of this disease in the elderly man.

Keywords: docetaxel, hormone refractory prostate cancer, elderly patient

Introduction

Prostate cancer is a major health issue which continues to rank as the number one most common malignancy among American men, with an estimated incidence of 218,890 new cases expected to occur in 2007 (American Cancer Society 2007). More than 65% of all prostate cancers will be diagnosed in men 65 years of age and older, with 9% being 70 years of age or older (Jemal et al 2007).

Unfortunately, 22% of men diagnosed with prostate cancer will initially present with metastatic disease. Additionally, between the ages of 60 and 69, there is a 7% probability (1 in every 14) of men diagnosed with local or regional prostate cancer who will have disease that progresses to a metastatic state. In men 70 years of age and older there exists a 13.83% probability (1 in every 7) of developing metastatic disease (Jemal et al 2007). Hormonal therapy (ie, surgical or chemical castration) is the mainstay of treatment for patients with metastatic disease. While the initial response is quite favorable in most men (with improvement in pain, shrinkage of soft tissue metastases, and decreases in prostate specific antigen) the median duration of response has been in the range of only 18–24 months.

Historically, very few avenues of treatment were available for hormone refractory prostate cancer. Chemotherapy offered marginal response rates and was quite toxic (Eisenberger et al 1988). In the 1990s, studies evaluating mitoxantrone plus prednisone demonstrated improvement in pain when compared with best supportive care. FDA approval of this treatment regimen for patients with hormone refractory prostate cancer was for the first time based on palliative functional outcomes (Tannock et al 1996; Kantoff et al 1999).

In the continued search for treatments for hormone refractory prostate cancer, anti-microtubular agents were studied. Estramustine phosphate (a nitrogen mustard

Correspondence: Victoria J Sinibaldi
Sidney Kimmel Comprehensive Cancer
Center at Johns Hopkins, 550 North
Broadway, Suite #304, Baltimore,
MA 21205, USA
Tel +1 410 614 3209
Fax +1 410 614 7273
Email sinibvi@jhmi.edu

derivative of estradiol-17 beta phosphate) was the first of these agents. It is believed to combine hormonal effects with microtubular inhibition through microtubule associated proteins and has alkylating activity (Hudes et al 1992). This agent received FDA approval based on a response rate of 20%, however, its associated side effects, particularly severe nausea, vomiting and thromboembolic complications resulted in much reluctance in its use. In fact, Fossa and colleagues (Fossa et al 1990) reported that all aspects of quality of life deteriorated during its use. Although estramustine phosphate as a single agent showed limited activity, combination treatment with docetaxel revealed possible synergistic effects. Several studies demonstrated superior response rates with the combination treatment as evidenced by decline in prostate specific antigen and decrease in soft tissue metastases; however, no significant improvement in survival (Petrylak et al 1999; Savarese et al 1999; Sinibaldi et al 2002; Petrylak et al 2004).

Within the past decade, many Phase II trials have been conducted to compare docetaxel based regimens with mitoxantrone plus prednisone in an attempt to demonstrate improvement with respect to standard of care. In 2004, two large randomized Phase III studies showed a survival advantage in men receiving docetaxel based regimens (Retrylak et al 2004; Tannock et al 2004) without increased toxicity in the elderly. As a result, more men with prostate cancer who are elderly are being treated with docetaxel. This paper reviews the results of trials evaluating docetaxel-based regimens, characterizing the incidence and management issues in elderly men being treated for hormone refractory metastatic prostate cancer.

Defining the treatment needs of the elderly patient

Prostate cancer has a disproportionately higher incidence in elderly men. Albeit, the definition of "elderly" is arbitrary since aging is a very individualized process. For the purposes of this paper, we will refer to men 60 years of age and older as "elderly". In elderly men with prostate cancer, treatment must often be tailored to the individual patient, as age-related physical changes such as confounding medical problems from co-morbid diseases, and cognitive deficits may affect and complicate management (Balducci and Beghe 2001).

Attitudes of physicians to chemotherapy in the elderly patient

Since elderly men have historically had a shorter life expectancy, chemotherapy treatment in elderly men has been quite controversial. Additionally, it is at this elderly age when they are less able to withstand disease and treatment related

morbidity. The impact of relative benefit from therapy versus potential risks (side effects) associated with therapy has been an issue. Effective treatment is one that results in longevity, improved quality of life, and decreases anxiety over the uncertainties of living with cancer. Treatment goals would be to reduce pain, improve fatigue, and strengthen social relationships with family and friends. Until recently, only two chemotherapeutic agents were available. Estramustine phosphate at best offered only a 20% response rate. Palliation could be achieved only with mitoxantrone plus prednisone (Tannock et al 1996; Kantoff et al 1999).

Evidence supporting the use of docetaxel in elderly patients with prostate cancer

Docetaxel is now US FDA approved, in combination with prednisone for the first line treatment of patients with metastatic hormone refractory prostate cancer. Docetaxel is a semi-synthetic taxane, microtubular inhibitor. It causes disruption of the microtubular network in cells that is necessary for mitotic and cellular functions. Docetaxel binds to free tubulin and allows for binding of tubulin into stable tubules, inhibiting their disassembly. Prevention of disassembly of the microtubules results in the inhibition of mitosis and cell growth (Kaus et al 2003, Taxotere Prescribing Information [package insert] 2006) Not only is docetaxel an effective microtubule stabilizer, it also is highly effective at Bcl-2 inactivation. Bcl-2 is an anti-apoptotic protein necessary for cell growth. Disruption of the Bcl-2 cell survival signal results in cell death (Haldar et al 1997; Stein 1999; Kaus et al 2003).

The approval of docetaxel was based upon data from two large randomized Phase III trials (ie, TAX-327 and SWOG 9916) both showing significant improvement in overall survival compared with the previously referenced standard treatment (ie, mitoxantrone plus prednisone) (Petrylak et al 2004; Tannock et al 2004).

TAX-327

In the TAX-327 study, Tannock and colleagues (Tannock et al 2004) evaluated 1006 men with metastatic hormone refractory prostate cancer randomly assigned to 1 of 3 treatment arms: docetaxel 75 mg/m² iv every 21 days plus prednisone 5 mg orally twice daily up to 10 cycles; docetaxel 30 mg/m² iv weekly 5 of every 6 weeks plus prednisone 5 mg orally twice daily, up to 5 cycles; or mitoxantrone 12 mg/m² iv every 21 days plus prednisone 5 mg orally twice daily, up to 10 cycles. Pre-medication with dexamethasone 8 mg orally was given at 12 hours, 3 hours, and 1 hour prior to docetaxel

for those receiving the every-21-day dosing; dexamethasone 8 mg orally was given just prior drug administration for those receiving the weekly docetaxel dosing. Anti-emetics were given according to each individual practice. The study was designed to detect a 33% difference in survival between the docetaxel-based regimens compared with the mitoxantrone regimen. The study was not adequately powered to compare directly the two docetaxel regimens with each other. The patient population included approximately 45% men with symptomatic bone pain, with 90% having bone metastases. A quarter also had soft tissue metastases. Median prostate specific antigen at baseline ranged from 108 to 123 ng/mL. All patients had received at least one prior hormonal treatment. The reported median survival was 18.9 months in the group receiving docetaxel on the every-21-day schedule, 17.4 months in the group receiving weekly docetaxel and 16.5 months in the mitoxantrone group. The hazard ratio of death in the group that received docetaxel every 21 days compared with those who received mitoxantrone was 0.76 (95% confidence interval [CI] 0.62–0.94, $p = 0.009$). In the group receiving weekly docetaxel, the hazard ratio was 0.91 (95% CI 0.75–1.11, $p = 0.36$). The every-21-day administration of docetaxel was associated with a survival benefit but the weekly schedule was not. While a 2-month difference in median survival may not seem like very much, the hazard ratio of 20% is a better functional outcome of overall survival benefit over time. This survival benefit is similar to the results reported in studies of chemotherapy for other solid tumors, such as breast and lung cancer, which suggests that prostate cancer has the same favorable chemo-sensitivity. Improvement in pain was achieved in 35%, 31%, and 22% of patients receiving docetaxel every 21 days, docetaxel weekly, and mitoxantrone every 21 days respectively. Toxicity in the every-21-day docetaxel was primarily myelosuppression. Weekly docetaxel was tolerated with minimal myelosuppression in patients age 65 years and older, including those with poor performance status (Balducci et al 2000). Although the efficacy was better with the every-21-day schedule, treatment with weekly docetaxel is an option for elderly men diagnosed with hormone refractory prostate cancer. Quality of life as measured by the Functional Assessment of Cancer Therapy-Prostate tool was similar in the docetaxel arms, both of which produced better scores compared with the group that received the mitoxantrone plus prednisone arm.

SWOG 9916

In the SWOG 9916 study, Petrylak and colleagues (Tannock et al 2004) evaluated 634 men with hormone refractory

prostate cancer with 21 cycles of either estramustine phosphate 280 mg 3 times a day orally, days 1–5, plus docetaxel 60–70 mg intravenously day 2 plus dexamethasone 60 mg orally in 3 divided doses prior to each docetaxel infusion. The comparative arm included mitoxantrone 12–14 mg/m² intravenously every 21 days plus prednisone 5 mg orally twice a day. This study was designed to detect a 33% difference in survival. Patient characteristics included 36% of men with symptomatic bone pain and median prostate specific antigen at baseline ranging between 84 and 90 ng/mL. Ninety percent of patients enrolled had bone metastases and a quarter of the patients also had soft tissue metastases. The median overall survival was 17.5 months for the group of patients receiving the estramustine phosphate plus docetaxel compared with 15.6 months for the group of patients that received the mitoxantrone plus prednisone. This was clinically significant with the p value equal to 0.02. Prostate specific antigen declines were greater in the group receiving estramustine phosphate plus docetaxel group compared to the mitoxantrone plus prednisone (50% vs 27%, $p < 0.001$). This is important to note because decline in prostate specific antigen has been correlated with improved survival in men with hormone refractory prostate cancer. The median time to progression for the two groups was 6.3 months and 3.2 months respectively. This is a 27% improvement favoring the estramustine phosphate plus docetaxel arm ($p < 0.001$). The safety and tolerability of each treatment arm was also evaluated. Grade 3 and 4 toxicity was more common in the group that received estramustine phosphate plus docetaxel and included neutropenia, nausea, vomiting and cardiovascular events, largely attributable to the estramustine phosphate. For the group that received the mitoxantrone plus prednisone, higher rates of gastrointestinal events (particularly diarrhea and vomiting), higher rates of hematologic events, and higher rates of peripheral vascular and cardiovascular toxicity (particularly deep vein thrombosis and myocardial infarction) were seen. Overall, the benefits resulting from the estramustine phosphate plus docetaxel treatment came at the cost of higher toxicity. There was no increase in treatment related deaths, nor was there an increase rate of discontinuation of treatment between the two arms. Similar quality of life outcomes were also reported for the two groups.

Other studies evaluating estramustine phosphate plus docetaxel

Kreis and Budman (1999), Savarese et al (1999), and Sinibaldi et al (2002) also evaluated the combination of

docetaxel plus estramustine. The median age of men was 62 for the Phase II trial reported by Kreis and Budman, but all other trials including the phase I trial reported by Kreis and Budman, reported a median age greater than 65 years of age. While significant prostate cancer specific antigen reductions were reported (82%, 69%, 45%) respectively, the combination was associated with an approximate 10% rate of thromboembolic complications. The thromboembolic complications were attributed to the estramustine. Based on this data and data from SWOG 9916, the future role of estramustine phosphate in this stage of disease is questionable.

Studies evaluating single-agent docetaxel

As a single agent, docetaxel has been extensively evaluated. Picus and colleagues (Picus et al 1999) evaluated an every-3-week schedule at a dose of 75 mg/m² given intravenously, with 46% achieving a prostate specific antigen decline of greater than 50%. Treatment was associated with grade 3 and grade 4 neutropenia in 46% of the patients. Other investigators (such as Berry et al 1999; Berry and Beer 2003; Beer et al 2003; Earhart 1999) evaluated a weekly schedule of docetaxel 36 mg/m² administered intravenously weekly times 6 weeks followed by a 2-week rest period. Prostate specific antigen declines were 41% and 47%, respectively. The grade 3 and grade 4 neutropenia was less than 10% for both studies. While none of the studies specifically compared the tolerance of docetaxel in elderly as opposed to young men, most of the patients who entered the studies were elderly, and reportedly had good tolerance.

Toxicities associated with docetaxel as reported in the TAX327 and other studies

Analyses of data from the TAX-327 showed no correlation between age and myelosuppression, the major dose-limiting toxicity of this therapy. Therefore, age should not be a contraindication for treatment with docetaxel. The TAX 327 trial did show that the every-21-day administration of docetaxel was associated with greater neutropenia compared with the weekly docetaxel schedule. The every-21-day docetaxel arm had patients with a median age of 68, range 42–92 years, with 20% of patients, equal or greater than 75 years of age. The weekly docetaxel schedule had patients with a median age of 69, range of 36–92 years, with 21% of patients \geq 75 years of age. The risk of neutropenia was more a potential toxicity, related to the schedule of docetaxel administration

as opposed to age of the population, with an incidence of 32% grade 3 and grade 4 neutropenia in the every-21-day docetaxel arm versus 2% incidence of grade 3 and grade 4 neutropenia in the weekly docetaxel arm. The incidence of febrile neutropenia, and its potential complication of death was seen in only 3% of the every-21-day docetaxel dosing schedule, but not at all in the weekly schedule. Prophylaxis with colony stimulating factor (GM-CSF), especially in men receiving the every-21-day docetaxel dosing schedule, should be considered in men greater than 65 years of age and is now listed in the National Comprehensive Cancer Network guidelines v.1 (2006). Docetaxel should be administered only when the absolute neutrophil count is \geq 1500 cells/mm³. In patients who experience febrile neutropenia, with absolute granulocyte counts of less than 500 cells/mm³ for greater than 1 week, severe skin reaction, or neurotoxicity, the dose of docetaxel should be decreased from 75 mg/m² to 60 mg/m², intravenously every 3 weeks. Treatment should be discontinued if the patient continues to experience any recurrent life threatening or persistent morbidity. In the TAX 327 study, the incidence of grade 3 and grade 4 thrombocytopenia occurred in only 1% of patients receiving the every 21-day docetaxel dosing arm and not at all in the weekly schedule. Berry and Beer (2003) reported on the grade 3 hematologic toxicity of a weekly docetaxel schedule in men below and above the age of 70 years finding no significant difference in incidence (95% CI). There was also no difference in overall hematologic and non-hematologic toxicity equal or greater than grade 2 in a comparison of pooled individual patient data from 2 Phase II studies of weekly docetaxel in androgen-dependent prostate cancer. The study also did not reveal significant differences in efficacy or toxicity in men aged over 70 years, compared with younger patients (Beer et al 2003).

The clearance of docetaxel is through hepatic metabolism. Caution should definitely be observed with administration in patients with hepatic dysfunction. Drug clearance is independent of renal function and appears to have no effect on nephrotoxicity. Clearance is independent of age (Earhart 1999; Taxotere Prescribing Information [package insert] 2006). Elderly patients may be more susceptible to mucositis, and diarrhea, but these adverse events were not statistically different in incidence based on dose schedule (Tannock et al 2004; Goker and Rodenhuis 2005). Prompt treatment to prevent dehydration and failure of vascular support should be considered when administering docetaxel. Advanced age and associated co-morbidities such as diabetes may increase risk of peripheral and central neuropathy. Dose reductions are advised for severe sensory neuropathy, which occurred

in 30% of the every-21-day docetaxel schedule and 24% of the weekly docetaxel schedule overall; but only 1.8% was grade 3 or grade 4 toxicity in the TAX-327 study (Tannock et al 2004). The TAX-327 study also reported nausea and vomiting in 42% of the patients receiving the every-21-day docetaxel schedule and 41% of the weekly docetaxel schedule; however, grade 3 and grade 4 nausea was only 2.7% in the every-21-day docetaxel arm. Therefore, anti-emetic prophylaxis should be individualized as per one's practice. Peripheral edema was seen in 19% in the every-21-day docetaxel schedule, and in 12% of the weekly docetaxel schedule (Tannock et al 2004). In order to potentially avoid reversible hypersensitivity reactions and fluid retention, pretreatment steroids are highly recommended. Occurrences of these symptoms are significantly decreased with pre-medication of dexamethasone prior to docetaxel infusions. Although cardiotoxicity is another risk in the elderly, routine use of protective measures is unnecessary. Fatigue, hair thinning, and skin rashes are often more common with the every-21-day schedule. Nail changes are more common with the weekly schedule than with the every-21-day schedule (37% vs 30%, respectively) (Tannock et al 2004). Grade 3 and grade 4 blockage of the lacrimal drainage apparatus causing excessive tearing occurred in 0.6% in the TAX 327 study, but Esmaeli and colleagues reported this as a more common occurrence with the weekly schedule (Esmaeli et al 2003). Excessive eye tearing should be monitored and prompt intervention is imperative.

Of the 333 patients treated with docetaxel plus prednisone every 3 weeks in the TAX 327 study, 63% (209 patients) were equal or greater than 65 years of age, and 20% (68 patients) were equal or greater than 75 years of age. Adverse events (all grades) that occurred at rates equal or greater than 10% in patients 65 years of age or older versus younger patients included: anemia (71% vs 59%), infection (37% vs 24%), nail changes (34% vs 23%), anorexia (21% vs 10%), and weight loss (15% vs 5%) (Haldar et al 1997).

Docetaxel as upfront therapy or second-line therapy

Docetaxel has shown efficacy when given up front or as second-line therapy. The optimal duration of therapy is not known. The TAX-327 study showed improved patient outcomes in the groups of patients that received docetaxel plus prednisone compared with the group that received mitoxantrone plus prednisone. Small pilot studies suggest that intermittent therapy is feasible and may reduce toxicity in a small subset of patients.

Conclusions

As our population ages, the number of elderly patients with prostate cancer is expected to increase. Studies have shown that elderly patients may benefit from chemotherapy to the same extent as younger patients. Age-related factors such as social, functional, and cognitive impairment may complicate management. The safety, efficacy, and convenience of therapy should be optimized. The decision to proceed with chemotherapy treatment relies upon a careful assessment of the patient's co-morbidities and functional status, and a thorough discussion of the risks and benefits of treatment. Mitoxantrone plus prednisone was previously accepted as standard chemotherapy for this stage of disease; however, docetaxel-based regimens have been shown to both palliate symptoms and prolong survival in hormone refractory prostate cancer. Docetaxel is now universally accepted as the best available chemotherapy for prostate cancer progressing on hormonal therapy.

Disclosures

Victoria J. Sinibaldi is a member of the Advisory Board and Speaker's Bureau for Sanofi-Aventis Pharmaceuticals.

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