ADIS DRUG PROFILE

Drugs 2005; 65 (16): 2287-2294
0012-6667/05/0016-2287/$39.95/0

Docetaxel

In Hormone-Refractory Metastatic Prostate Cancer

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Contents

Abstract

▲ The taxoid analogue docetaxel is a potent inhibitor of microtubular depolymerisation and, in hormone-refractory metastatic prostate cancer, it also counters the effects of the anti-apoptotic protein Bcl-2.

▲ Overall survival was significantly increased in patients with hormone-refractory metastatic prostate cancer receiving intravenous docetaxel every 3 weeks plus oral prednisone or estramustine, compared with patients receiving intravenous mitoxantrone every 3 weeks plus prednisone in two large phase III trials (TAX 327 and SWOG [Southwest Oncology Group] 9916).

▲ In the TAX 327 study, patients receiving docetaxel 75 mg/m^2 every 3 weeks plus prednisone had a median overall survival duration of 18.9 months; in the SWOG 9916 study, median overall survival duration was 17.5 months with docetaxel 60 mg/m^2 every 3 weeks plus estramustine 280mg three times daily on days 1–5. The median overall survival duration for the control arm of mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone was 16–17 months.

▲ Compared with mitoxantrone plus prednisone, docetaxel plus prednisone improved prostate specific antigen response rate, pain and health-related quality of life, and docetaxel plus estramustine increased progression-free survival.

▲ Adverse events were more common with docetaxel- than mitoxantrone-based treatment regimens, but most events associated with docetaxel were mild-to-moderate in severity.

Features and properties of docetaxel (Taxotere®)	
Featured indication	
The treatment of hormone-refractory metastatic prostate cancer	
Mechanism of action	
Inhibits microtubular depolymerisation, leading to mitotic arrest in cells, and counters the effects of the anti-apoptotic protein Bcl-2 in prostate cancer cells	
Dosage and administration (in combination with oral prednisone)	
Usual dosage	75 mg/m^2
Route of administration	Intravenous
Frequency	Once every 3wk
Pharmacokinetic profile (single dose of docetaxel 70–115 mg/m^2 administered intravenously over 1–2h as monotherapy in adult patients with cancer; mean values)	
Volume of distribution at steady state	113L
Total body clearance	21 L/h/m^2
Elimination half-life	11.1h
Most frequent adverse events in clinical trials (in combination with prednisone)	
Alopecia, fatigue, diarrhoea, grade 3/4 neutropenia, sensory neuropathy, nail changes, stomatitis	

Prostate cancer is not only the most common cancer found in men, but is also one of the most common causes of cancer deaths in males, second only to cancer of the lung and bronchus.[1] Most men presenting with metastatic prostate cancer have an initial response to hormonal ablation that lasts approximately 12–24 months.[2] Nevertheless, all will eventually develop hormone-refractory disease,[3] which has a median survival of 6–12 months.[3,4] In the late 1990s, the combination of mitoxantrone plus prednisone or hydrocortisone demonstrated disease palliation and an improved health-related quality of life (HR-QOL) compared with hormone therapy alone in patients with hormone-refractory metastatic prostate cancer[5,6] and, thus, became the reference regimen for this condition.[4] Nevertheless, neither this nor other combination regimens or various monotherapies improved survival duration in these patients.[3]

Docetaxel (Taxotere®)[1], a semisynthetic taxoid analogue, is an antineoplastic agent with marked antitumour activity both as a single agent and in combination regimens in advanced prostate cancer in preclinical[7] and phase II clinical studies.[8] Consequently, the potential for docetaxel-containing regimens in hormone-refractory metastatic prostate cancer has been investigated further in two recent phase III comparisons with mitoxantrone plus prednisone,[2,9] the results of which are the primary focus of the profile.

1. Pharmacodynamic Profile

The pharmacodynamic properties of docetaxel have been reviewed previously,[10] as have the properties specific to its action in prostate cancer.[7,11,12] This section summarises the pharmacodynamic properties of docetaxel that are relevant to its use in patients with hormone-refractory metastatic prostate cancer.

- Taxanes are potent inhibitors of microtubular depolymerisation,[13,14] which leads to mitotic arrest in the G2M phase of the cell cycle.[11] Taxanes also induce antineoplastic activity in prostate cancer cell lines by countering the effects of the anti-apoptotic protein Bcl-2,[15] which is overexpressed in prostate cancer cells in response to androgen withdrawal.[16] In both of these mechanisms, docetaxel has demonstrated greater potency than its parent drug, paclitaxel.[13,14,17]
- Docetaxel-induced apoptosis was shown to occur via a different pathway in androgen-responsive (LNCaP) and androgen-independent (PC-3) prostate cancer cell lines.[18]
- Preclinical studies of prostate cancer cell lines demonstrated enhanced antitumour activity when docetaxel was combined with a number of anticancer agents, including estramustine[19,20] (see section 3 for discussion of the clinical trial evaluating this combination), a metabolite of capecitabine (5′-deoxy-5-fluorouridine [5′-DFUR]),[21] pegylated interferon-α-2b,[22] an angiogenesis inhibitor TNP-470[23] and a demethylating agent 5-aza-2′-deoxycytidine (5-AZA-CdR).[24]
- The combination of docetaxel plus oblimersen sodium, an antisense oligonucleotide to the Bcl-2 messenger RNA, demonstrated encouraging antitumour activity in a phase I study of patients with hormone-refractory metastatic prostate cancer[25] (see section 3 for phase II study results).

2. Pharmacokinetic Profile

This section summarises the pharmacokinetic data for docetaxel from phase I studies in adult patients with cancer that are found in the manufacturer's prescribing information.[26]

- Intravenous docetaxel 70–115 mg/m^2 administered over 1–2 hours demonstrated linear kinetics with a terminal elimination half life of 11.1 hours.[26] The mean total body clearance was 21 L/h/m^2 and mean steady-state volume of distribution was 113L. Elimination is mainly via the faeces. Docetaxel was about 94% protein bound in *in vitro* studies.[26]
- The pharmacokinetics of docetaxel were not affected by the age or gender of the patient, and pretreatment with dexamethasone did not alter the total body clearance of docetaxel.[26]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

- In 40 patients with hormone-refractory metastatic prostate cancer, systemic clearance of docetaxel from plasma when the drug was coadministered with prednisone was similar to that observed when docetaxel was given alone.[26]
- *In vitro* studies have shown that docetaxel is metabolised via the cytochrome P450 (CYP3A4) isoenzyme and docetaxel metabolism can be inhibited when it is coadministered with CYP3A4 inhibitors, such as ketoconazole.[26] Studies in patients with hormone-refractory metastatic prostate cancer have demonstrated that combined treatment with docetaxel plus ketoconazole[27] or ritonavir,[28] two CYP3A4 inhibitors, may enhance antitumour activity.

3. Therapeutic Efficacy

Phase III Studies

The efficacy of docetaxel in hormone-refractory metastatic prostate cancer has been established in two pivotal phase III trials, the TAX 327[9] and the SWOG (Southwest Oncology Group) 9916 studies.[2] Both were randomised, nonblind, multicentre studies, and both have been fully published.

Eligible patients in each study had confirmed adenocarcinoma of the prostate with evidence of metastatic disease, despite androgen-ablative therapy and cessation of antiandrogen treatment.[2,9] Criteria for progressive disease were based on physical examination or imaging studies (where the disease was measurable, progression of a bidimensionally measurable lesion) or an increase in serum prostate-specific antigen (PSA) levels based on at least two consecutive samples obtained at least a week apart. At the time of enrolment, at least 4 weeks had to have passed since receiving antiandrogen therapy or radiotherapy.[2,9] The median age in both studies was similar (≈69 years) with a range of 36–92 years.[2,9] The median duration of follow-up was 32[2] and 21[9] months.

In the TAX 327 study, patients (n = 1006) were randomised to receive intravenous docetaxel 75 mg/m^2 every 3 weeks, intravenous docetaxel 30 mg/m^2 once weekly for 5 of 6 weeks or intravenous mitoxantrone 12 mg/m^2 every 3 weeks; all patients also received oral prednisone 5mg twice daily every day. The inclusion of a weekly docetaxel arm was based on the assumption that toxicity would be reduced in this elderly patient population.[9] In the SWOG 9916 study, eligible patients (n = 674) received one of two treatment regimens, each given every 21 days: intravenous docetaxel 60 mg/m^2 on day 2 plus oral estramustine 280mg three times daily on days 1–5, or intravenous mitoxantrone 12 mg/m^2 on day 1 plus oral prednisone 5mg twice daily every day.[2] The addition of estramustine was on the basis of its synergistic activity with docetaxel *in vitro* (section 1).[2] In both studies, patients receiving docetaxel were premedicated with dexamethasone.[2,9] During the SWOG 9916 study, the treatment protocol for patients receiving estramustine was amended to include prophylactic anticoagulation with warfarin 2 mg/day plus aspirin (acetylsalicylic acid) 325 mg/day to reduce the risk of estramustine-associated vascular risks.[2]

Patients were excluded from either study if prior radiotherapy was to ≥25%[9] or ≥30%[2] of the bone marrow. In the TAX 327 study,[9] patients were also excluded if they had received prior treatment with cytotoxic agents, apart from estramustine, whereas in the SWOG 9916 study, patients were excluded if they had received chemotherapy with estramustine, taxanes, anthracyclines or mitoxantrone, or more than one previous systemic therapy.[2]

Both studies were designed to primarily assess whether docetaxel could improve overall survival compared with standard mitoxantrone therapy.[2,9] Secondary efficacy criteria included progression-free survival duration,[2] objective response rates,[2,9] reduction in PSA levels,[2,9] reduction in pain[9] and improvements in HR-QOL.[9]

Serum PSA was measured every 3 weeks and a response was generally defined as a reduction from baseline levels of ≥50% that was maintained for at least 3 weeks.[2,9] Pain was assessed using the Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire[9] in which scores range from 1 to 5, with higher scores indicating more severe pain.[29] A 2-point reduction in the PPI score, with-

out an increase in analgesic consumption, was considered a pain response, as was a reduction in analgesic use without an increase in the PPI score (both maintained for ≥2 weeks).[9] HR-QOL was assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire; in this tool, scores range from 0 to 156, with higher scores indicating a better HR-QOL. A 16-point increase from baseline on two occasions at least 2 weeks apart was considered to be an HR-QOL response.[9]

- In the two pivotal phase III studies, overall median survival was significantly increased in patients receiving docetaxel every 3 weeks plus prednisone[9] or estramustine[2] compared with those receiving mitoxantrone plus prednisone in intent-to-treat analyses. Kaplan-Meier estimates of survival are shown in figure 1.

- In the TAX 327 study,[9] the median duration of survival in the group receiving docetaxel 75 mg/m^2 every 3 weeks plus prednisone 5mg twice daily was 18.9 months compared with 16.5 months in patients receiving mitoxantrone 12 mg/m^2 every 3 weeks plus the same dosage of prednisone ($p = 0.009$). The corresponding hazard ratio for death was 0.76 (95% CI 0.62, 0.94).

- The difference in survival duration between patients receiving docetaxel 30 mg/m^2 once weekly plus prednisone and patients receiving mitoxantrone every 3 weeks plus prednisone was not significant (17.4 vs 16.5 months).[9]

- In the SWOG 9916 study, the median duration of survival in the group receiving docetaxel 60 mg/m^2 every 3 weeks plus estramustine 280mg three times daily on days 1–5 was 17.5 months compared with 15.6 months in the group receiving mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone 5mg twice daily ($p = 0.02$), with a hazard ratio for death of 0.80 (95% CI 0.67, 0.97).[2]

- Progression-free survival was significantly increased in patients receiving docetaxel plus estramustine compared with those receiving mitoxantrone plus prednisone (6.3 vs 3.2 months; $p < 0.001$).[2] In this same study, the difference in response rates was not significant between treatment groups, with a partial response in measurable disease observed in 17% versus 11% of patients.[2]

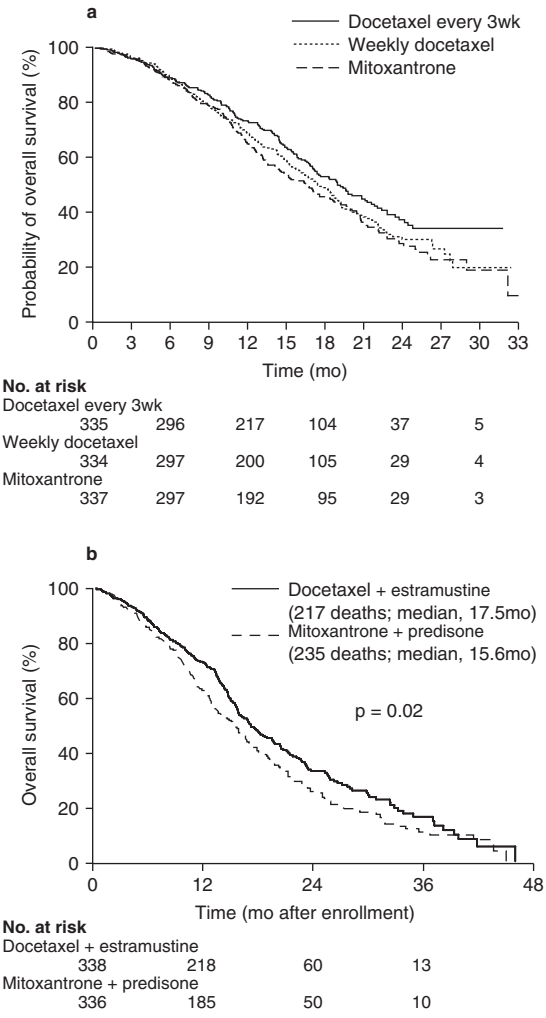

Fig. 1. Kaplan-Meier estimates of the overall survival of men with hormone-refractory metastatic prostate cancer receiving docetaxel or mitoxantrone. Results are from two large, randomised, nonblind, multicentre, phase III studies in which (**a**) patients (n = 1006) were randomised to intravenous (IV) docetaxel 75 mg/m^2 every 3 weeks, IV docetaxel 30 mg/m^2 once weekly for 5 of every 6 weeks or IV mitoxantrone 12 mg/m^2 every 3 weeks; all patients also received oral prednisone 5mg twice daily[9] and (**b**) patients (n = 674) received IV docetaxel 60 mg/m^2 on day 2 plus oral estramustine 280mg 3 times daily on days 1–5, or IV mitoxantrone 12 mg/m^2 on day 1 plus oral prednisone 5mg twice daily[2] (reproduced from Tannock et al.[9] and Petrylak et al.[2] Copyright © 2005 Massachusetts Medical Society. All rights reserved. Adapted with permission 2005).

- In both phase III studies, rates of PSA response were significantly higher in patients receiving docetaxel every 3 weeks plus prednisone (45% vs 32%) or once-weekly docetaxel plus prednisone (48% vs 32%)[9] or docetaxel plus estramustine (50% vs 27% of patients)[2] than in patients receiving mitoxantrone plus prednisone ($p < 0.001$ for all comparisons).
- Pain was reduced more frequently in patients receiving docetaxel 75 mg/m^2 every 3 weeks plus prednisone than in those receiving mitoxantrone plus prednisone (35% vs 22%; $p = 0.01$).[9] The percentage of patients experiencing a reduction of pain was not significantly different between the once-weekly docetaxel and mitoxantrone groups (31% vs 22%).[9]
- HR-QOL, assessed in 815 patients, was improved in significantly more patients receiving docetaxel every 3 weeks (22% of patients) or once weekly (23%) plus prednisone than in patients receiving mitoxantrone (13%) plus prednisone (both $p < 0.01$).[9]

Phase II Studies

As a result of the efficacy shown in these two phase III studies,[2,9] docetaxel is being evaluated in combination with a number of novel agents in patients with hormone-refractory metastatic prostate cancer.[30-34] Results of promising combinations evaluated in phase II studies are summarised using PSA response criteria as described previously.

- In a randomised, phase II trial, patients received intravenous docetaxel 30 mg/m^2 once weekly for 3 of every 4 weeks as monotherapy (n = 25) or in combination with thalidomide 200mg orally each day (n = 50).[30] A PSA response was achieved in 53% of patients receiving combined therapy compared with 37% in those receiving docetaxel alone (difference not statistically significant).[30]
- In phase II noncomparative studies, PSA responses were observed in 81% of 37 patients receiving intravenous docetaxel 36 mg/m^2 once weekly (on day 2) plus oral calcitriol 0.5 μg/kg once weekly (day 1) for 6 of every 8 weeks[33] and in 68% of 34 patients receiving a 21-day cycle of intravenous docetaxel 70 mg/m^2 (day 2) plus oral estramustine 240mg three times daily (days 1–5) plus intravenous carboplatin (dose required to achieve an area under the concentration-time curve of 5 mg/mL/min) [day 2].[31]
- Intravenous docetaxel 75 mg/m^2 (on day 6) plus intravenous oblimersen sodium 7 mg/kg (days 1–8) administered every 3 weeks achieved PSA responses in 14 of 27 (52%) patients, and the median survival was 19.8 months.[32] The mean oblimersen steady-state concentration was found to be an important determinant of antitumour activity.[32]
- The combination of intravenous docetaxel 60 mg/m^2 (on day 1) plus intravenous vinorelbine 15 mg/m^2 (days 1 and 8) administered in 21-day cycles achieved a PSA response in 7 of 19 (37%) chemotherapy-naive patients and 6 of 21 (29%) patients who had received prior chemotherapy for their hormone-refractory metastatic prostate cancer.[34]

4. Tolerability

- Patients receiving docetaxel plus prednisone[9] or estramustine[2] had a higher incidence of adverse events than patients receiving mitoxantrone plus prednisone in the two phase III studies discussed in section 3. However, most adverse events associated with docetaxel treatment were not severe.[2,9] The increased incidence of nausea, thromboembolism and cardiovascular events that is characteristic of estramustine[2] may have contributed to the docetaxel plus estramustine adverse events profile seen in the SWOG 9916 study.
- Adverse events occurring in ≥10% of patients receiving docetaxel every 3 weeks and significantly more often than with mitoxantrone in the TAX 327 study are shown in figure 2.[9]
- At least one serious adverse event was reported by 26% and 29% of patients receiving docetaxel every 3 weeks or once weekly in the TAX 327 study compared with 20% of those receiving mitoxantrone.[9] Withdrawal of treatment due to an adverse event occurred in 11%, 16% and 10% of patients, respectively.[9] There was no evidence that once-weekly administration of docetaxel was associated with less toxicity than docetaxel every 3 weeks.[9]

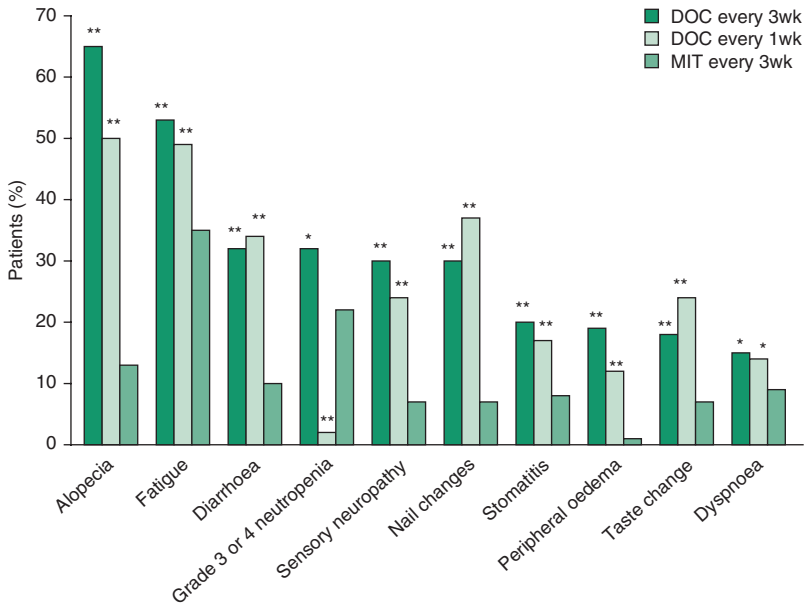

Fig. 2. Tolerability of docetaxel (DOC) compared with that of mitoxantrone (MIT) in hormone-refractory metastatic prostate cancer.[9] The percentage of adverse events reported in ≥10% of DOC recipients and occurring significantly more frequently than with MIT is shown. In the multicentre, nonblind TAX 327 study, men (n = 1006) with hormone-refractory metastatic prostate cancer were randomised to receive intravenous (IV) DOC 75 mg/m^2 every 3 weeks, IV DOC 30 mg/m^2 once weekly for 5 of every 6 weeks, or IV MIT 12 mg/m^2 every 3 weeks; all patients also received oral prednisone 5mg twice daily. * $p \leq 0.05$, ** $p \leq 0.0015$ vs MIT.

- In the SWOG 9916 study, adverse events led to treatment withdrawal in 16% of patients receiving docetaxel plus estramustine compared with 10% of patients receiving mitoxantrone plus prednisone.[2]
- Adverse events that were significantly more frequent with docetaxel/estramustine compared with mitoxantrone/prednisone in this trial included nausea and vomiting (20% vs 5%; $p < 0.001$), cardiovascular events (15% vs 7%; $p = 0.001$), neurological events (7% vs 2%; $p = 0.001$) and grade 3 or 4 neutropenic fever (5% vs 2%; $p = 0.01$).[2] The incidence of severe neutropenia did not differ significantly between treatment groups (16% vs 13%).[2]
- In the TAX 327 study, a major decrease in left ventricular ejection fraction of ≥10% from baseline to below the lower limit of normal was more frequent with mitoxantrone plus prednisone than with docetaxel administered every 3 weeks or once weekly plus prednisone (7% vs 1% and 2%; $p \leq 0.0015$ and $p \leq 0.05$).[9] However, grade 3–5 cardiac adverse events were more common with docetaxel plus estramustine than with mitoxantrone plus prednisone in the SWOG 9916 study (15% vs 7%; $p = 0.001$).[2]
- Toxicity profiles were manageable in the phase II studies discussed in section 3.[30-34] A prophylactic anticoagulant was added to reduce the risk of venous thrombosis in patients receiving docetaxel plus thalidomide,[30] and in patients receiving docetaxel plus vinorelbine, filgrastim was added to reduce the risk of neutropenia.[34]

5. Dosage and Administration

In men with hormone-refractory metastatic prostate cancer, the recommended dosage of docetaxel is 75 mg/m^2 as a 1-hour intravenous infusion once every 3 weeks in combination with oral prednisone 5mg twice daily every day.[26] For patients who experience severe adverse reactions, including febrile neutropenia, the docetaxel dosage should be reduced to 60 mg/m^2 every 3 weeks.

Before treatment with docetaxel, all patients should be premedicated with oral corticosteroids to

reduce the severity of hypersensitivity reactions and fluid retention. The manufacturer recommends oral dexamethasone at a reduced dose regimen of dexamethasone 8mg at 12 hours, 3 hours and 1 hour prior to the start of treatment, given the concomitant use of oral prednisone in the treatment regimen.[26]

6. Docetaxel: Current Status in Hormone-Refractory Metastatic Prostate Cancer

Docetaxel in combination with prednisone is approved for the treatment of hormone-refractory metastatic prostate cancer in the US[4] and EU.[35] Intravenous docetaxel administered every 3 weeks plus oral prednisone or oral estramustine demonstrated a significant survival advantage compared with the previous standard therapy, intravenous mitoxantrone plus oral prednisone, in men with this indication in two well designed phase III trials. The combination of docetaxel and prednisone has now become the recommended treatment for such patients.[4,36]

Acknowledgements

At the request of the journal, Sanofi-Aventis provided a non-binding review of this article.

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