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Current Perspective

Shifting paradigms in prostate cancer; docetaxel plus low-dose prednisone – finally an effective chemotherapy

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Abstract

Until now, the use of systemic chemotherapy for advanced androgen-independent prostate cancer has had very little to offer to patients. However, in 2004, two large randomised trials investigating docetaxel *vs.* mitoxantrone have both demonstrated survival improvements, and, in one of the trails, improvements in important secondary clinical outcome measures such as pain relief and quality of life measurements. In this current perspective, these two trials are summarised and discussed. It is concluded that, docetaxel every 3 weeks plus low-dose prednisone can be considered standard treatment for patients with androgen-independent disease.

Keywords: Prostate cancer; Androgen-independent; Docetaxel; Prednisone; Chemotherapy

1. Introduction

Prostate cancer is the most common cancer among men and is the second leading cause of death from cancer in males [1]. Androgen ablation therapy remains the mainstay of treatment in men with advanced disease. Eventually all patients will develop progressive disease, despite continued androgen suppression. Once progression occurs, prognosis is dismal. Patients who have been treated with combined androgen blockade may elicit a brief fall in prostate specific antigen (PSA) levels upon withdrawal of anti-androgen therapy, termed ''anti-androgen withdrawal syndrome''. However, objective responses to subsequent hormonal manipulations are infrequent and once anti-androgen therapy and withdrawal have been implemented, the median survival is 6–12 months, depending on the presence of symptoms and the patients' performance status [2–4].

2. Chemotherapy in androgen-independent (hormone-refractory) prostate cancer

Until recently, no cytotoxic agent had been able to consistently change the natural history of metastatic prostate cancer. A review by Yagoda and Petrylak [5] of 26 studies conducted in the late 1980s, involving single agent chemotherapy, demonstrated a disappointingly low overall response rate of 8.7% (95% Confidence Interval (CI), 6.4–9.0%), without a trend towards improvement in survival. Based upon this apparent lack of activity of chemotherapy, as well as the common perception that this patient population, is in general, too fragile to receive such treatment, patients with androgen-independent prostate cancer have not been routinely treated with chemotherapy. As the trials in the 1980s only enrolled patients with bidimensionally measurable disease, which in the setting of prostate cancer usually reflects extensive disease and correspondingly impaired performance status, these patients had little chance to benefit from any type of chemotherapy.

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In 1990, PSA was introduced as a surrogate endpoint in phase II studies by investigators from Memorial Sloan Kettering Cancer Center and this was rapidly adopted by others. Shortly thereafter, Canadian investigators introduced palliative measurement criteria, utilising pain, analgesic consumption and quality of life criteria to evaluate response to treatment. The endpoint migration resulting from using these surrogate measures have changed the characteristics of patients who are treated in clinical trials, including patients fulfilling the criteria of androgen-independent prostate cancer, but having less extensive disease and fewer disease-related symptoms [6,7].

3. Results of the mitoxantrone studies in the 1990s

In 1996, Tannock and collegues [8] reported on a randomised phase III study, involving 161 patients with androgen-independent disease, who were randomised to receive mitoxantrone 12 mg/m^2 every 3 weeks plus low-dose prednisone, or prednisone alone. Patients were required to complete pain- and health-related quality of life questionnaires at baseline. Patients were examined at intervals of 3 weeks when they were asked to repeat the questionnaires relating to their pain and quality of life. Pain relief was the primary endpoint of response in this study, defined as a 2-point reduction in the pain intensity scale of the Mc Gill–Melzak pain questionnaire, to be maintained on two consecutive evaluations at least 3 weeks apart and without an increase in analgesic consumption. This primary criterium of palliative response was met in 23 of the 80 patients (29%) on mitoxantrone plus prednisone, compared with 10 of 81 patients (12%) on prednisone alone, $P = 0.01$. The response duration was longer for treatment with mitoxantrone plus prednisone than for prednisone alone, median 43 *vs.* 18 weeks, $P < 0.001$. In addition, if both primary and secondary criteria of response (a decrease of $\geqslant 50\%$ in analgesic score without an increase in pain) were included to quantify the palliative benefit from treatment, this was achieved in more patients randomised to the chemotherapy arm, 30 of 80 (38%), than in patients on the control arm, 17 of 81 (21%), $P = 0.025$. However, there was no indication that chemotherapy had an impact on survival. The median survival was 12 months in both arms, $P = 0.27$ (log-rank). Based upon these study results, the Food and Drug Administration (FDA) granted approval of mitoxantrone plus prednisone as palliative chemotherapy in patients with androgen-independent prostate cancer.

Parallel to the above study, the Cancer and Leukemia Group B (CALGB) conducted a study to compare mitoxantrone 14 mg/m^2 every 3 weeks plus hydrocortisone *vs.* hydrocortisone alone [9]. No symptomatic disease was required for study entry. The study was designed to detect an increase in the survival duration in the chemotherapy arm, with a target accrual set at 232 patients to test for an increase in survival by 50%. Although there were more patients obtaining a greater than 50% PSA reduction in the mitoxantrone plus hydrocortisone arm and a small, but statistically significant, difference with respect to time to disease progression (a secondary endpoint) favouring the chemotherapy arm, again there was no difference in survival between the treatment arms. The median duration of survival was 12.3 months on mitoxantrone plus hydrocortisone, *vs.* 12.6 months on hydrocortisone alone.

Based upon the results of these two trials, many patients in the United States (US) and Canada have received mitoxantrone plus low-dose corticosteroids as a standard palliative therapeutic option. In Europe, however, in view of the modest effects and the lack of a survival benefit, many physicians were reluctant to adopt mitoxantrone plus corticosteroids as standard therapy. More importantly, though, the mitoxantrone study results prompted renewed interest in chemotherapy trials in advanced prostate cancer.

4. 'Proof-of-concept' trials using the taxanes

Shortly following the reports of the randomised mitoxantrone studies, 'proof-of-concept' studies were initiated to test the feasibility and therapeutic potential of the taxanes, paclitaxel and docetaxel [6,7]. In view of the assumed reduced side-effects, particularly reduced myelotoxicity and fatigue by administering taxanes weekly, several studies explored weekly schedules. Estramustine, a fusion product of nitrogen mustard linked to oestradiol-17β-phosphate, has limited cytotoxic effects when given as a single agent [6]. The recent recognition that its mechanism of activity primarily involves the inhibition of microtubule function and mitosis and that it can act synergistically with taxanes in preclinical models, led to clinical studies to investigate the therapeutic potential of the combined use of the taxanes plus estramustine [10–16].

Summarising the results from these 'proof-of-concept' studies, both taxanes yielded PSA responses in approximately 50% of patients [17,18]. Docetaxel was more extensively tested and provided more consistent results, either in 3-weekly regimens (docetaxel at 75 mg/m^2) or weekly (most frequent regimen 30 mg/m^2 for 5 or 6 weeks). Moreover, for the first time using single agent chemotherapy in this disease entity, objective responses were noted in one third of patients for whom response could be evaluated.

The combined regimens of a taxane plus estramustine appeared to result in even higher PSA response rates,

with approximately two-thirds of patients fulfilling the criteria of a PSA response, defined as a reduction of at least 50% and measured on two occasions, at least 4 weeks apart [6,7]. The initial studies using combined paclitaxel or docetaxel plus estramustine were hampered by notable cardiovascular toxicity, mostly deep venous thrombosis and pulmonary thromboembolism. In an attempt to modify the dose and the duration of the estramustine administration, as well as the prophylactic use of anticoagulant therapy, this toxicity appeared to be at least partially alleviated [15].

In addition to the frequent PSA responses, and pain relief and objective responses, the most interesting observations from these 'proof-of-concept' studies were median survival figures that well exceeded the 12 months survival obtained in the mitoxantrone studies. Moreover, it was recognised that these figures could not simply be explained by patient selection alone. The outliers in these favourable survival data were studies using the combined approach of paclitaxel plus estramustine (median survival 17 months) and docetaxel plus estramustine (median survival 24 months) [12,15]. These survival data prompted the initiation of two large randomised phase III studies, that were both designed to test for a survival improvement.

5. International phase III study of docetaxel plus prednisone or mitoxantrone plus prednisone, TAX 327 study

The TAX 327 study was built on the primary hypothesis that treatment with docetaxel plus low-dose prednisone would improve overall survival compared with that obtained by mitoxantrone plus prednisone [19]. Docetaxel was administered either every 3 weeks at a dose of 75 mg/m^2 (Arm A), or weekly at a dose of 30 mg/m^2 (5 of 6 weeks, Arm B), both for a maximum of 30 weeks. Arm C comprised of mitoxantrone at a dose of 12 mg/m^2 every 3 weeks, also for a maximum of 30 weeks. Patients in all three arms received additionally 5 mg of prednisone orally twice daily. Hence, the dose intensity of docetaxel in the two docetaxel-containing study arms was equivalent, 25 mg/m^2 per week, and the duration of treatment, and the prednisone regimens were identical in the three study arms. Key eligibility criteria included documented metastatic disease, disease progression during hormonal therapy and receiving androgen-deprivation therapy as maintenance therapy. Pain, analgesic intake, and quality of life were assessed at baseline. Pain was assessed by means of the present pain intensity (PPI) scale from the McGill–Melzack questionnaire. Patients recorded their daily PPI score and analgesic use in a diary. The quality of life was assessed with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. Patients were stratified by pain and analgesic consumption and by baseline Karnofsky performance status.

The study was designed to detect with 90% power a Hazard Ratio (HR) of 0.75 for death in the docetaxel groups compared with the mitoxantrone group, with a two-sided type I error of 0.05 and with the data analysed according to the intention-to-treat. The sample size was established as 1002 patients, and analysis was planned after 535 deaths had occurred. To adjust for multiple comparisons, a P-value of 0.04 was set to indicate statistical significance for the combined docetaxel groups compared with the mitoxantrone group, while a P-value of 0.0175 was set for the comparison of each docetaxel group with the mitoxantrone group.

A total of 1006 patients were randomised from March 2000 to June 2002. The baseline characteristics of the patients, including prior treatment, median PSA at study entry, histopathology and sites of disease, were well balanced among the three treatment groups. The median age of the patients was 68 years. Approximately 45% of the patients had pain at entry.

Overall survival (the primary end point) was superior for the docetaxel groups compared with mitoxantrone-treated patients. When the two docetaxel groups were combined and compared with the mitoxantrone group, the HR for death was 0.83 (95% CI, 0.70–0.99), $P = 0.04$. The reduction in the risk of death was greatest in the group receiving docetaxel every 3 weeks, HR 0.74 (95% CI, 0.62–0.94), $P = 0.009$. There was a trend in reduction in the risk of death also on docetaxel weekly (HR 0.91), but this was not statistically significant. The median duration of survival was 18.9 months in the group given docetaxel every 3 weeks, 17.4 months on weekly docetaxel, and 16.5 months on mitoxantrone. Adjustment for potential imbalances in prognostic factors by full stratified and backward Cox proportional hazard models gave identical results, (HRs of 0.74 and 0.75, respectively), for the comparison of docetaxel every 3 weeks *vs.* mitoxantrone.

A pain response, defined as a two-point reduction in the PPI score, or a 50% or greater reduction in the analgesic score for at least 3 weeks, was obtained more frequently in patients on docetaxel every 3 weeks than among those treated with mitoxantrone, 35% *vs.* 22%, respectively, $P = 0.01$. The percentage of patients who obtained a pain response on weekly docetaxel was 31% and did not differ significantly from that of the mitoxantrone group. The rates of PSA response were significantly higher in both docetaxel groups compared with mitoxantrone; docetaxel every 3 weeks, 45%, weekly docetaxel, 48%, mitoxantrone, 32%, $P < 0.001$, for both comparisons. An objective tumour response was noted in 12% of patients on docetaxel every 3 weeks, 8% on weekly docetaxel and 7% on mitoxantrone. The slightly higher response rate on docetaxel every 3 weeks com-

pared with mitoxantrone did not reach statistical significance.

As expected, grade 3 and 4 neutropenia was encountered more frequently in the group receiving docetaxel every 3 weeks (32%), compared with those receiving weekly docetaxel (2%), or mitoxantrone (22%). However, clinical sequelae in terms of febrile neutropenia were infrequent (3% for those on docetaxel every 3 weeks and 2% on mitoxantrone). Two patients died from sepsis during treatment, one in the docetaxel group and one in the mitoxantrone group. Grade 3 or 4 non-haematological toxicity was uncommon in all three treatment arms. Adverse events that led to the discontinuation of treatment included fatigue, musculoskeletal or nail changes, sensory neuropathy and infection in the docetaxel groups and cardiac dysfunction in the mitoxantrone group. There was no trend towards a lower frequency with weekly docetaxel than with docetaxel administered every 3 weeks. Of note, anorexia, change in taste, tearing and epitaxis were more frequent in the patients on weekly docetaxel. The serious adverse event rates on docetaxel every 3 weeks, weekly docetaxel, and mitoxantrone were 26%, 29%, and 20%, respectively. Eleven percent fewer patients completed protocol treatment on weekly docetaxel, compared with those given docetaxel every 3 weeks.

Using a predefined stringent criterium of at least 16 points improvement in the FACT-P score compared with baseline, on two measurements obtained at least three weeks apart, a quality-of-life response was significantly more frequently obtained in the patients treated with docetaxel, 22% in the group given docetaxel every 3 weeks and 23% in the group on weekly docetaxel, as compared with 13% for those on mitoxantrone ($P = 0.009$ and 0.005 for the two comparisons, respectively). The greatest benefits in the docetaxel groups were in the subscale representing disease-specific concerns, including weight loss, appetite, pain, physical comfort, and bowel and genitourinary functions.

Secondary analyses were conducted to evaluate the survival benefit in selected patient subgroups. HRs for overall survival for docetaxel every 3 weeks *vs.* mitoxantrone every 3 weeks showed similar benefit for all subgroups tested, including age (<65 years, $\geqslant$65 years, $\geqslant$75 years), pain *vs.* no pain, and Karnofsky performance score $\leqslant$70 *vs.* $\geqslant$80 [20].

Of all patients entered onto the study, 15% had been enrolled based on PSA progression as the first evidence of metastatic disease progression. An exploratory analysis in this subset of patients showed that in the combined docetaxel subgroups ($N = 98$), the median survival was 23.7 months, in the subgroup receiving docetaxel every 3 weeks ($N = 48$) it was 24.1 months, and in the mitoxantrone group ($N = 50$) it was 20.8 months [20]. The HR for docetaxel every 3 weeks *vs.* mitoxantrone was 0.67 (95% CI 0.36–1.25). Although the *posthoc* nature of this analysis, as well as the modest sample size of the subset of patients and hence wide boundaries of the CIs does not allow firm conclusions to be drawn, the 33% reduction in the risk of death with use of docetaxel every 3 weeks in this subgroup of patients with asymptomatic PSA progression, compared with a 24% reduction in the overall patient population receiving docetaxel every 3 weeks, may warrant the further investigation of docetaxel in earlier disease stages.

6. Docetaxel and estramustine compared with mitoxantrone and prednisone, Southwest Oncology Group Study 99–16

Southwest Oncology Group Study (SWOG) 99–16 was built on the prejudice that the combination of docetaxel plus estramustine had the greatest therapeutical potential and was the comparator against mitoxantrone plus low-dose prednisone [21]. Like in the TAX 327 trial, this study was primarily designed to test for survival improvements and was planned to accrue 620 patients to detect an improvement of 33% in median survival in the group given docetaxel plus estramustine. Of 674 eligible patients (770 were randomised, 96 patients were found to be ineligible), 338 were assigned to receive 280 mg estramustine three times daily on days 1–5 plus docetaxel 60 mg/m^2 on day 2, and 336 had received mitoxantrone 12 mg/m^2 on day 1 plus 5 mg of prednisone twice daily, each given in 21-day cycles. Following the observation of increased cardiovascular toxicity (particularly deep venous thrombosis and pulmonary embolism) in patients given the docetaxel plus estramustine regimen, a protocol amendment was made halfway through the study to allow the inclusion of daily warfarin and aspirin in the group assigned to receive estramustine.

The patient characteristics were well balanced and very similar to those of the patients enrolled in the TAX 327 study. In SWOG 99–16 one third of the patients had pain, and 19% were enrolled based upon PSA progression alone. Also, in this study the median overall survival was superior in the group receiving docetaxel than in the group receiving mitoxantrone and prednisone, 17.5 *vs.* 15.6 months, respectively, $P = 0.02$. The corresponding HR for death was 0.80 (95% CI, 0.67–0.97). The median time to progression was 6.3 months on docetaxel plus estramustine and this was 3.2 months on mitoxantrone and prednisone, $P < 0.001$. PSA responses were obtained in 50% and 27% of patients, respectively, $P < 0.001$. There was no difference in pain relief, as reported by the patients.

The incorporation of estramustine in the docetaxel regimen was characterised by increased toxicity; grade 3–4 nausea and vomiting, (19% *vs.* 6%), grade 3–4 cardiovascular events (mostly deep venous thrombosis

and pulmonary embolism, 13% *vs.* 6%) and all grade 3–4 toxicities together (54% *vs.* 34%), were more frequently observed among patients receiving docetaxel and estramustine compared with those receiving mitoxantrone and prednisone, all comparisons $P < 0.001$. There was no indication that the incidence of cardiovascular toxicity was reduced after the initiation of the protocol amendment of prophylactic anticoagulant therapy in the group receiving estramustine.

7. Discussion

The results of these two phase III studies show that both the combination of docetaxel and low-dose prednisone and docetaxel every 3 weeks plus estramustine every 3 weeks result in superior survival compared with the standard treatment of mitoxantrone plus prednisone. The docetaxel regimens significantly improved overall survival, which was the primary endpoint in both trials, by 2.5 and 2 months, respectively. The corresponding HRs for a reduction in the risk of death were 0.74 (95% CI 0.62–0.94) and 0.80 (95% CI 0.67–0.97), respectively.

Any potential conservative remark on the magnitude of the survival gain does not hold against the important additional finding of significantly superior pain relief and quality of life during docetaxel chemotherapy in the TAX 327 study. Moreover, the 2.5 and 2 months difference in absolute survival should be examined taking into consideration that in both trials a third to 50% of the patients receiving mitoxantrone either crossed over to docetaxel, or received at least one other antineoplastic therapy after having had no response on their assigned treatment.

Further, docetaxel 75 mg/m^2 every 3 weeks plus low-dose prednisone was remarkably well tolerated, with only 3% neutropenic complications and, again, the important finding of improved quality of life that was already seen during the course of the chemotherapy. The increased improvement in quality of life in patients receiving docetaxel may indicate that the benefit from the better antitumour efficacy by docetaxel nullifies the toxicity resulting from the chemotherapy administration. These important findings should end our present conservative approaches with regard to using chemotherapy in patients with androgen-independent prostate cancer. This conservatism may have been valid in 2004, but no longer holds true in 2005.

The TAX 327 study also examined out whether any therapeutical benefit remained for the weekly administration of docetaxel, which was assumed to be less toxic compared with the conventional 3 week schedule. However, the weekly regimen did not provide the survival improvement as was obtained with docetaxel every 3 weeks. Moreover, weekly docetaxel administration did not result in fewer clinical side-effects. On the contrary, the weekly regimen gave more gastrointestinal side-effects, tearing and epistaxis, and 11% fewer patients completed the weekly regimen compared with those given docetaxel every 3 weeks. Although grade 3 or 4 neutropenia was observed more frequently in patients on docetaxel every 3 weeks, the low incidence of neutropenic fever (3%) demonstrates that the 75 mg/m^2 dose every 3 weeks is well tolerated and its administration at the out-patient clinic is considerably more convenient for patients than the weekly regimen. The SWOG 99–16 study had similar results to TAX 327 in terms of a statistically significant survival improvement and also a significantly longer median time to progression. With the reservation that palliative measures were less punctually collected than in the TAX 327 study, self-reported pain relief did not appear differ between the two groups. The addition of estramustine to the docetaxel regimen clearly increased toxicity compared with the standard regimen. Patients on docetaxel and estramustine had significantly more gastro-intestinal and cardiovascular (mostly deep venous thrombosis and pulmonary thromboembolism) toxicities. In view of this increased toxicity profile on the one hand and the apparent lack of improved effectiveness compared with the similar survival benefit that was obtained with docetaxel every 3 weeks plus prednisone in the TAX 327 study on the other, there appears no further role for the use of estramustine as an add-on to docetaxel.

The finding that docetaxel in the TAX 327 study was not only superior in terms of reaching the primary endpoint, survival improvement, but also resulted in better pain relief and quality of life improvements has established docetaxel every 3 weeks plus low-dose prednisone as a new standard treatment and as a reference guide for future drug development in patients with advanced prostate cancer. Moreover, secondary analysis of survival in different subgroups has shown this survival benefit for all of the patient categories examined. The suggestion of an increased survival benefit in patients who entered the trial because of PSA progression as first evidence of metastatic disease progression, presumably reflecting a lower disease volume, warrants further investigation with docetaxel-based chemotherapy in earlier stages of advanced prostate cancer, or even in the adjuvant setting in high-risk patients at the time of radical prostatectomy.

8. Conclusions

These two independent randomised studies have demonstrated that docetaxel-based chemotherapy improves the overall survival of patients with androgen-independent prostate cancer, compared with standard chemotherapy of mitoxantrone plus low-dose prednisone.

Docetaxel every 3 weeks plus low-dose prednisone gave the best efficacy results in terms of survival improvement, pain responses and PSA responses, as well as a favourable toxicity profile, that resulted in a better quality of life improvement that was already seen during the course of the chemotherapy. The use of estramustine in combination with docetaxel was found to increase toxicity and did not appear to result in better efficacy compared with the regimen of docetaxel alone. Secondary analyses of data from TAX 327 patients given docetaxel every 3 weeks compared with those treated with mitoxantrone showed that the survival benefit was obtained in all of the patient categories investigated and was independent of age, presence or absence of pain and performance status.

Docetaxel every 3 weeks plus low-dose prednisone can be considered new standard treatment for patients with androgen-independent prostate cancer.

Conflict of interest statement

None declared.

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