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ORIGINAL REPORT

Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer: Updated Survival in the TAX 327 Study

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ABSTRACT

Purpose
The TAX 327 study compared docetaxel administered every 3 weeks (D3), weekly docetaxel (D1), and mitoxantrone (M), each with prednisone (P), in 1,006 men with metastatic hormone-resistant prostate cancer (HRPC). The original analysis, undertaken in August 2003 when 557 deaths had occurred, showed significantly better survival and response rates for pain, prostate-specific antigen (PSA), and quality of life for D3P when compared with MP. Here, we report an updated analysis of survival.

Methods
Investigators were asked to provide the date of death or last follow-up for all participants who were alive in August 2003.

Results
By March 2007, data on 310 additional deaths were obtained (total = 867 deaths). The survival benefit of D3P compared with MP has persisted with extended follow-up ($P = .004$). Median survival time was 19.2 months (95% CI, 17.5 to 21.3 months) in the D3P arm, 17.8 months (95% CI, 16.2 to 19.2 months) in the D1P arm, and 16.3 months (95% CI, 14.3 to 17.9 months) in the MP arm. More patients survived ≥ 3 years in the D3P and D1P arms (18.6% and 16.6%, respectively) compared with the MP arm (13.5%). Similar trends in survival between treatment arms were seen for men greater than and less than 65 years of age, for those with and without pain at baseline, and for those with baseline PSA greater than and less than the median value of 115 ng/mL.

Conclusion
The present analysis confirms that survival of men with metastatic HRPC is significantly longer after treatment with D3P than with MP. Consistent results are observed across subgroups of patients.

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INTRODUCTION

Men with advanced prostate cancer are usually treated with androgen ablation therapies. Most men respond initially to hormonal treatment, but their disease evolves and becomes resistant to further hormonal therapy. Metastases, particularly to bone and lymph nodes, are frequent in men with hormone-refractory prostate cancer (HRPC). Men with HRPC frequently have pain and other symptoms leading to impairment of quality of life (QOL).

Prostate cancer was considered resistant to chemotherapy until the mid-1990s, when mitoxantrone with prednisone (MP) was shown in a Canadian study to have a role in the palliative treatment of metastatic HRPC.[1] Men with HRPC experienced an improvement in pain and QOL if treated with MP compared with prednisone alone. No survival benefit was detected in trials comparing mitoxantrone plus corticosteroids with corticosteroids alone, although the studies were not powered to detect small differences in survival.[1,2]

In 2004, reports of the TAX 327 and Southwest Oncology Group 99-16 studies showed significant survival benefit when docetaxel-based treatment was compared with mitoxantrone for men with metastatic HRPC.[3,4] The TAX 327 study randomly assigned 1,006 men with metastatic HRPC to receive docetaxel 75 mg/m^2 administered every 3 weeks (D3P), docetaxel 30 mg/m^2 administered weekly for 5 of 6 weeks (D1P), or mitoxantrone 12 mg/m^2 every 3 weeks (MP), each with prednisone 5 mg twice daily. The study showed significantly longer survival for the D3P arm compared with MP,

although significant differences were not found for the D1P arm. The D3P arm also showed better palliation, with a higher probability of pain and QOL response (and prostate-specific antigen [PSA] response) compared with MP. At the time of the initial analysis in August 2003, 557 of 1,006 participants in the trial had died.[3] Here, we report an updated survival analysis of the TAX 327 study. We also provide results for patient subgroups that were defined according to baseline characteristics.

METHODS

Details of eligibility and exclusion criteria are provided in the initial report.[3] In brief, men with metastatic prostate cancer were eligible if there was clinical or radiologic evidence of progressive disease or three increasing values of serum PSA, despite primary androgen deprivation. No previous therapy with cytotoxic agents except estramustine was permitted. Patients were required not to have other major medical conditions and were stratified by presence or absence of significant baseline pain and by Karnofsky performance status (KPS; required to be $\geq 70\%$).

Physical examination and radiologic investigations, including computed tomography and bone scanning, were performed at baseline, along with blood tests, including serum PSA. Pain was self-reported using the Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire.[5] Participants kept a pain diary, and the daily analgesic intake was summed to give an Analgesic Score (AS) by assigning 4 points for a standard dose of narcotic analgesics and 1 point for a standard dose of non-narcotic analgesics; patients were regarded as having substantial pain if the baseline PPI was ≥ 2 or AS ≥ 10. QOL was assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire.[6] The maximum score is 156 points, indicating excellent QOL. Minimally symptomatic patients were defined by a near normal level of QOL (FACT-P score > 128), minimal pain (PPI < 2), and low analgesic consumption (AS < 10). Treatment was planned for up to 10 cycles of 3 weeks for the D3P arm and up to five cycles of 6 weeks for the D1P arm. Patients were evaluated for pain, QOL, and serum PSA every 3 weeks. They were observed until progression of disease, severe adverse event, or withdrawal of consent. Investigators were required to observe patients until death.

The present update of survival has been undertaken by contacting investigators and requesting the last date of follow-up or date of death of their patients. Ethics board approval was reactivated in centers where the approval for the TAX 327 study had expired.

Overall survival was analyzed using the Kaplan-Meier method, and comparisons between treatment arms were performed using the log-rank test; the D1P and D3P arms were compared individually with the MP arm. Exploratory subgroup analyses were also performed for patients separated on the basis of age, PSA at baseline, presence or absence of visceral disease, KPS, and levels of pain and QOL at baseline. For continuous outcomes (eg, age, PSA, and FACT-P), patients were grouped by the median value. All randomly assigned patients were included in the analysis of survival, and all randomly assigned patients with available baseline data were included in the subgroup analyses. All statistical tests were two-sided.

RESULTS

Overall Survival

The study included 1,006 patients from 24 countries, and the initial survival analysis was performed in August 2003 when 557 deaths had occurred. By March 2007, 310 additional deaths were recorded, resulting in a total of 867 deaths; 111 patients have been lost to follow-up, and 28 patients were alive with a last follow-up date within the previous year. Updated survival curves are shown in Figure 1, and details are listed in Table 1. The median survival time was 19.2 months in the D3P arm, 17.8 months in the D1P arm, and 16.3 months in the MP arm. When compared with the previous analysis, the difference in median survival between the D3P and MP arms has increased slightly to 2.9 months, the hazard ratio (HR) has changed minimally, and the *P* value is slightly stronger ($P = .004$). The difference in survival between the D1P and MP arms remains nonsignificant ($P = .09$). The percentages of patients who survived for more than 3 years in the D3P, D1P, and MP arms were 18.6%, 16.8%, and 13.5%, respectively (Table 1).

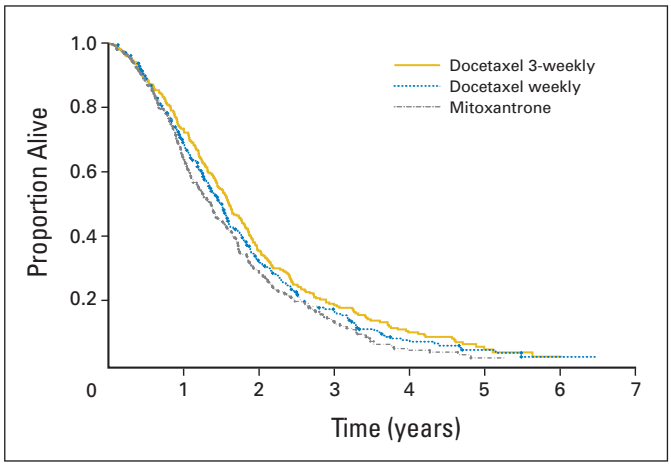

Fig 1. Overall survival data from March 2007, with 867 deaths among 1,006 randomly assigned patients.

Subgroup Analyses

Median survival times and 95% CIs for the defined subgroups as a function of treatment arm are shown as a Forrest plot in Figure 2.

Table 1. Survival of Men Treated With D3P, D1P, or MP: Initial and Updated Data

Data	D3P (n = 335)	D1P (n = 334)	MP (n = 337)
Original data, 2003			
Patients who died			
No.	166	190	201
%	50	57	60
Survival time, months			
Median	18.9	17.4	16.5
Range	17.0-21.2	15.7-19.0	14.4-18.6
Hazard ratio	0.76	0.91	
95% CI	0.62 to 0.94	0.75 to 1.11	
P	.009	.36	
Updated data, 2006-2007			
Patients who died			
No.	285	285	297
%	85.1	85.3	88.1
Survival time, months			
Median	19.2	17.8	16.3
Range	17.5-21.3	16.2-19.2	14.3-17.9
Hazard ratio	0.79	0.87	
95% CI	0.67 to 0.93	0.74 to 1.02	
P	.004	.086	
Survival > 3 years			
3-year survival rate, %	18.6	16.8	13.5

Abbreviations: D3P, docetaxel administered every 3 weeks plus prednisone; D1P, weekly docetaxel plus prednisone; MP, mitoxantrone plus prednisone.

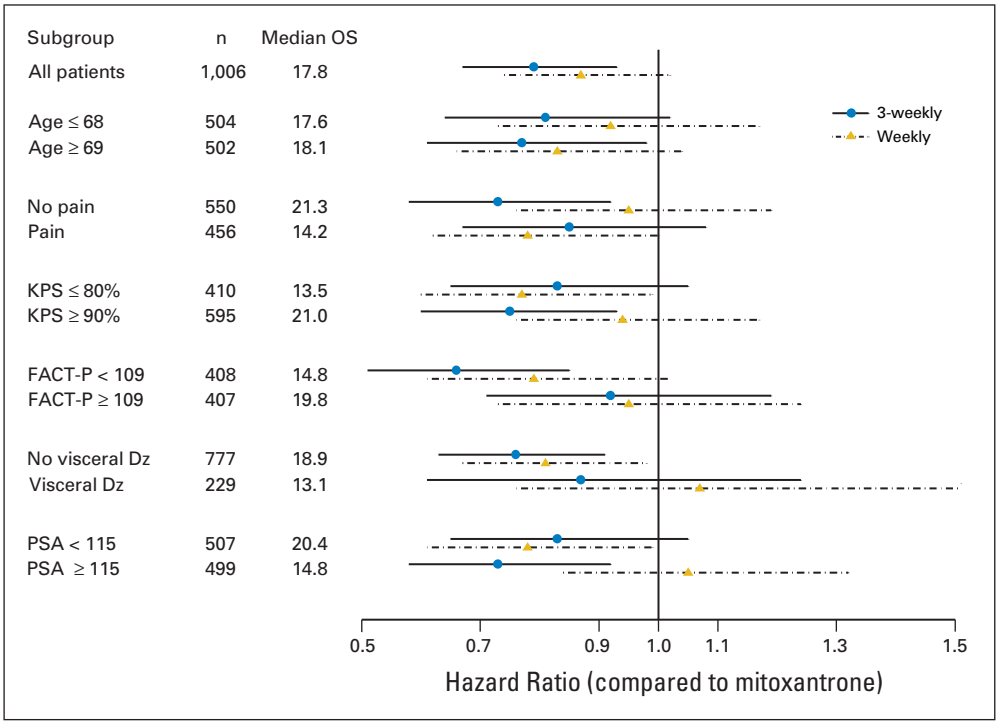

Fig 2. Survival among various subgroups treated on the TAX 327 trial. At left are the subgroups defined in this exploratory analysis, the number of patients in each subgroup, and their median survival time in months, independent of treatment. At right is a Forrest plot showing the median hazard ratios and their 95% CIs for survival on the docetaxel arms compared with the mitoxantrone arm. OS, overall survival; KPS, Karnofsky performance status; FACT-P, Functional Assessment of Cancer Therapy–Prostate; Dz, disease; PSA, prostate-specific antigen.

Similar trends in survival between treatment arms were seen for patients greater than and less than the median age of 68 years. The HRs for younger and older patients were 0.81 and 0.77, respectively, for D3P compared with MP. Similar results were found when using a more extreme age cutoff of 75 years (HR = 0.80 for older patients).

In the TAX 327 study, the median serum PSA at baseline was 115 ng/mL. Among patients with lower and higher PSA levels at baseline, the HRs were 0.83 and 0.73, respectively, indicating similar benefits of D3P compared with MP for patients with a greater or lesser burden of disease.

The presence of visceral involvement is a known adverse prognostic factor for men with metastatic prostate cancer when compared with patients with only bone and/or nodal disease. In the present study, the 22% of patients with visceral disease died on average 6 months earlier than those without visceral metastases. The HR was 0.87 for the subgroup of men with visceral metastases when comparing D3P with MP.

Patients with a KPS ≥ 90% lived approximately 8 months longer than patients with a KPS ≤ 80%; however, the HRs for these groups were similar at 0.75 and 0.82, respectively, for D3P compared with MP.

There were 456 patients with substantial pain at baseline (defined by PPI ≥ 2 and/or AS ≥ 10), and survival time was shorter for those with pain. The HRs for patients without and with pain were 0.73 and 0.85, respectively, for D3P compared with MP.

Men with better or worse QOL, as indicated by their FACT-P score at baseline, had HRs of 0.92 and 0.66, respectively, when treated with D3P compared with MP. For minimally symptomatic patients (FACT-P score > 128, PPI < 2, and AS < 10), the trend for survival benefit was maintained for D3P compared with MP.

DISCUSSION

This updated survival analysis of the TAX 327 study is consistent with the previously reported results. The difference in median survival time for D3P compared with MP is now 2.9 months ($P = .004$, HR = 0.79). Treatment with D1P did not lead to a significant survival benefit compared with MP. Although differences in median survival are relatively small, they are accompanied by improvement in pain control and QOL and are clinically meaningful.

As expected, patients with visceral disease, pain, poorer performance status, and higher values of baseline PSA had shorter survival times. In general, the survival benefit for patients randomly assigned to the D3P arm compared with the MP arm was consistent across subgroups, adding support to the primary result. Therefore, the earlier mentioned factors are indicators of poor prognosis but not predictors of response.

As described previously, men treated with weekly docetaxel were more likely to experience early deterioration of QOL.[7] This result, either because of progression of disease or toxicity as a result of treatment, and the continuing evidence that this treatment does not lead to a significant improvement in survival compared with treatment with mitoxantrone indicate that the weekly docetaxel schedule should not be adopted, with the possible exception of patients who are at high risk of neutropenic fever.

In contrast to the earlier Canadian study[1] that evaluated mitoxantrone, the TAX 327 trial has included patients with and without symptoms. In general, the chances of prolonging survival with D3P seemed similar among patients with higher and lower disease burden as indicated by level of serum PSA, the presence or absence of substantial pain, and the QOL or performance score. This analysis does not address whether docetaxel should be used in patients with minimal symptoms or whether it is appropriate to defer treatment until more symptoms occur. However, considering the similar benefit among subgroups and the potential for QOL to deteriorate as a result of disease progression, it seems reasonable to offer treatment to patients with symptoms and to those who are likely to develop symptoms in the near future, based on the burden of disease and the PSA doubling

time. There is no established second-line therapy for men with HRPC who experience progression after docetaxel therapy, but several trials are evaluating new agents. The number of patients fit enough for second-line therapy is likely to increase if first-line therapy with docetaxel is initiated earlier in the course of disease, but potential benefits of early treatment must be counterbalanced by the potential toxicity of treatment. Also, future studies should evaluate the cost effectiveness of docetaxel and other new treatments for men with prostate cancer.

In conclusion, docetaxel administered every 3 weeks with prednisone remains the preferred treatment option for most patients with metastatic HRPC. The consistency of results among subgroups indicates rigorous data.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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