Recent docetaxel studies establish a new standard of care in hormone refractory prostate cancer

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Introduction: *Treatment of hormone refractory prostate cancer (HRPC) has generally aimed at increasing symptom free survival in asymptomatic patients and improving quality of life in symptomatic patients. However, recent randomized studies might be shifting the paradigm towards achieving an improved overall survival.*
Methods: *Two large randomized controlled studies were conducted using mitoxantrone plus prednisone as a control arm compared to docetaxel-based regimens.*
Results: *In the TAX 327 trial, 3-weekly docetaxel plus prednisone proved significantly superior to mitoxantrone plus prednisone (an established reference regimen) in extending survival, reducing levels of prostate specific antigen (PSA), controlling pain and improving quality of life. The Southwest Oncology Group's study (protocol 99-16) randomized patients to either docetaxel plus estramustine or mitoxantrone plus prednisone. Compared with the mitoxantrone regimen, docetaxel plus estramustine significantly extended median overall survival and time to progression. Men treated with the docetaxel regimen were also more likely to have a PSA response. In this study, the two regimens were similarly effective in relieving pain.*
Conclusion: *These studies have an important impact on the management strategy of hormone refractory prostate cancer. Docetaxel is the first agent shown significantly to extend survival in HRPC. Although this proven benefit must be balanced against toxicity, docetaxel should now be considered the standard of care for most patients that fail first-line or more hormonal manipulations. Drug combinations which may further extend survival and improve quality of life are actively being pursued, as is the possibility of using docetaxel in the adjuvant setting.*

Key Words: urology, docetaxel, hormone refractory prostate cancer

Introduction

In hormone refractory prostate cancer (HRPC), the aims of treatment are to extend the period asymptomatic patients remain free of symptoms, to improve quality of life in those who do have symptoms and, if possible, to improve survival. To this end, many drugs have been investigated, alone and in combination.[1-6]

As single agents, cyclophosphamide, doxorubicin, estramustine, fluorouracil and cisplatin have modest activity. This is more marked when estramustine is combined with vinblastine or etoposide and, more recently, with taxanes. Other combinations assessed include mitoxantrone plus prednisone, and a triple agent regimen of ketoconazole plus doxorubicin plus hydrocortisone.

Randomized controlled trials of single agent and combination chemotherapy have tended to show a response in prostate specific antigen (PSA), subjective benefit and longer time to progression. However, until publication of the two studies reviewed below, no treatment for androgen-refractory prostate cancer had been shown significantly to extend survival.[5,6]

Recent randomized controlled trials

Our understanding of how best to treat hormone refractory prostate cancer has been changed by the findings of two large randomized controlled trials. Both were conducted in patients who had been androgen deprived. Both had survival as their primary endpoint; and both compared docetaxel-based regimens against mitoxantrone plus prednisone, an established reference treatment for HRPC.[3,7,8] The full results of these trials have recently been reported

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in the New England Journal of Medicine.[5,6]

TAX 327[5]

In the multinational phase III study TAX 327, 1006 men with progressing metastatic HRPC were randomized to one of three treatment arms: mitoxantrone 12 mg/m^2 q 3 weeks; docetaxel 30 mg/m^2 weekly for 5 of every 6 weeks; or docetaxel 75 mg/m^2 q 3 weeks. In all three arms patients received prednisone 5 mg bid; and, in all three arms, the intended duration of treatment was 30 weeks. The two docetaxel regimens were chosen to have similar dose intensity and were similarly active in phase II studies. Patients treated with docetaxel received dexamethasone premedication.

Patients were stratified at baseline by presence or absence of pain: a score of 2 or greater on the Present Pain Intensity (PPI) scale or a mean analgesic score (AS) of at least 10 versus a PPI score of less than 2 or an AS of less than 10. They were also stratified by baseline Karnofsky Performance Status (KPS 70% or less versus 80% or greater).

The three treatment arms were well balanced for age (median 68 or 69 years across the groups), Gleason score, prior treatment, performance status, presence of bone or visceral metastases, serum PSA, evidence of progression at entry and median follow-up.

There were 201 deaths among patients assigned to mitoxantrone, compared with 166 among patients assigned to docetaxel q 3 weeks (hazard ratio 0.76). The hazard ratio in the weekly docetaxel group was 0.91 (190 deaths).

Compared with patients receiving the mitoxantrone regimen, those treated with docetaxel q 3 weeks had a significantly longer median survival (18.9 versus 16.5 months, p=0.009). They were also significantly more likely to experience a 50% or greater reduction in PSA level, a predefined reduction in pain, and improved quality of life. More detailed data are given in Figure 1 and Table 1. The 17.4 month median survival with weekly docetaxel was intermediate between that among patients treated with mitoxantrone and that of patients receiving 3-weekly docetaxel.

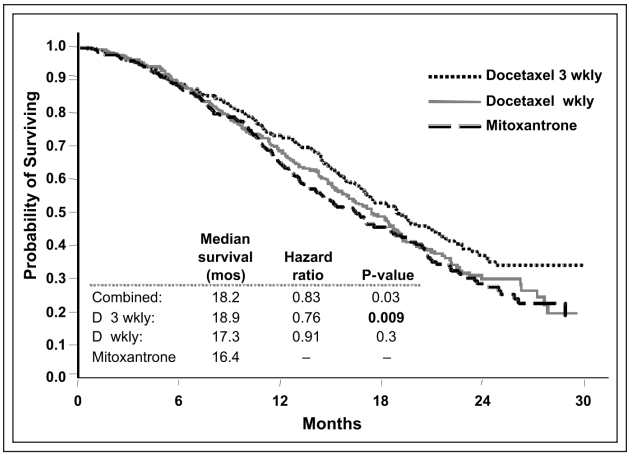

Figure 1. Overall survival in the TAX 327 study.[5] (Reprinted with permission)

Subgroup analysis showed the reduction in hazard ratio of death achieved by q 3 weekly docetaxel was consistent across age groups (less than 65 years versus 65 or over, or 75 or over). It was also consistent across performance status and independent of the presence or absence of pain.

Importantly, docetaxel was well tolerated. Although there was more grade 3/4 neutropenia with docetaxel q 3 weeks (32 events compared with 2 with weekly docetaxel and 22 with mitoxantrone), febrile neutropenia was rare (3 events versus 0 and 2 respectively). Both regimens of docetaxel were associated with greater fatigue, diarrhea, sensory neuropathy and stomatitis than mitoxantrone, but

TABLE 1. **Major outcomes in the TAX 327 study.[5]**

	Mitoxantrone	**Docetaxel**			
		q 3 wks		**weekly**	
	n=337	**n=335**	**p-value**	**n=334**	**p-value**
Median survival (mo)	16.5	18.9		17.4	
% of patients with:					
50% or > fall in PSA	32%	45%	<0.001	48%	<0.001
defined reduction in pain	22%	35%	0.01	31%	0.08
improved quality of life	13%	22%	0.009	23%	0.005

p-values show significance of difference compared to mitoxantrone
mo: months

mitoxantrone was associated with a greater risk of impaired left ventricular function.

In view of these results Tannock and colleagues concluded that, while mitoxantrone remains appropriate for patients who might be susceptible to docetaxel toxicity, "docetaxel plus prednisone is the preferred option for most patients with hormone refractory prostate cancer".[5]

SWOG 99-16[6]

In the SWOG Intergroup 99-16 study, 770 patients with advanced refractory prostate cancer were enrolled to one of two treatments, both given q 3 weeks regimens. Patients received either: mitoxantrone 12 mg/m^2 on day 1 plus prednisone 5 mg twice daily, or estramustine 280 mg tid on days 1-5 plus 60 mg/m^2 docetaxel on day 2. The latter group received dexamethasone premedication. Six hundred and seventy-four patients were eligible.

Patients were stratified by type of progression (established from measurable disease or by PSA), by grade of NCI-CTC bone pain (2 or greater versus less than 2) and by SWOG performance status (0-1 versus 2-3). Baseline prognostic factors were well balanced across treatment arms.

During median follow up of 32 months, there were 235 deaths among patients randomized to mitoxantrone plus prednisone and 217 deaths among patients randomized to docetaxel plus estramustine (Hazard Ratio 0.80). By intent to treat, the median survival in patients randomized to docetaxel plus estramustine was significantly longer than that in patients treated with mitoxantrone plus prednisone (17.5 versus 15.6 months, p=0.02), Figure 2. Treatment with docetaxel and mitoxantrone was associated with significantly longer progression-free survival and with a greater likelihood of PSA response, Table 2. Differences in rate of objective tumor response and in pain reduction were not significant across groups.

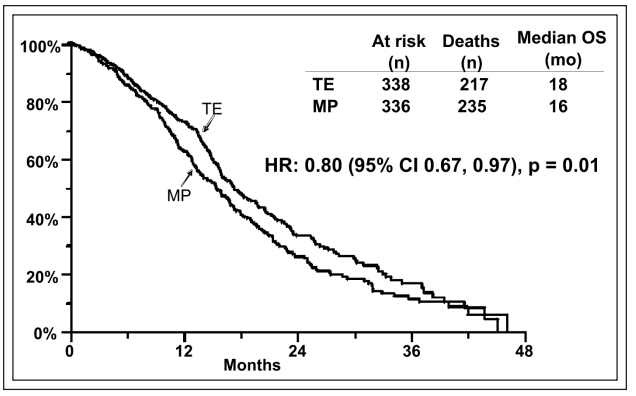

Figure 2. Overall survival of SWOG 99-16.[6] (Reprinted with permission)

Although the difference between treatments in risk of neutropenia was not significant, patients receiving docetaxel plus estramustine were more likely to experience neutropenic fever, nausea and vomiting and cardiovascular events. There were eight treatment-related deaths in patients treated with docetaxel and estramustine and four such deaths in the mitoxantrone arm. This difference between groups was not statistically significant. Neither was the rate of treatment discontinuation.

Given these data, Petrylak and colleagues concluded that the survival benefit seen with the regimen of docetaxel plus estramustine "provides support" for its use in men with metastatic, androgen-independent prostate cancer.[6]

TABLE 2. **Major outcomes of SWOG 99-16, by intent to treat (both regimens were q 3 weeks).[6]**

Number of eligible pts	**Docetaxel plus estramustine n=338**	**Mitoxantrone plus prednisone n=336**	**p-value**
Median overall survival (mo)	17.5	15.6	0.02
Median time to progression (mo)	6.3	3.2	<0.001
% of patients with:			
50% or > fall in PSA	50%	27%	<0.001
Grade 3-5 neutropenia	16%	13%	NS
Grade 3-4 neutropenic fever	5%	2%	0.01
Grade 3-4 nausea and vomiting	20%	5%	<0.001

NS: not significant
mo: months

Recent phase II data in advanced disease

Data from the phase III trials reviewed above are complemented by findings presented in abstract form at the 2004 meeting of the American Society of Clinical Oncology. One area of interest is the future of the weekly regimen of docetaxel.

Birch and colleagues recently argued that weekly administration could be preferable in patients with comorbidities which may enhance drug toxicity.[9] In a randomized phase IIb trial involving 62 chemotherapy-naive HRPC patients, Birch et al compared weekly and q 3 week schedules of docetaxel plus estramustine. Both regimens had substantial activity, achieving a greater than 50% reduction in PSA in the majority of patients. Median survival was not significantly different across schedules but weekly docetaxel was associated with significantly less hematologic toxicity: G-CSF was required for 4% of patients given weekly drug but for 40% of those on the q 3 week schedule (p=0.0022). Dose reduction or delay was required significantly more often in the latter group. Although non-hematologic toxicities were not less severe with weekly administration, Birch et al concluded that, overall, the weekly regimen has a more favorable therapeutic index.

Another area of interest is the exploration of novel docetaxel-based combinations in HRPC. Dreicer et al reported a phase I/II study of docetaxel plus the proteasome inhibitor bortezomib (Velcade) in a total of 31 patients with castrate testosterone levels and documented evidence of progression following anti-androgen withdrawal.[10] Nineteen patients had had prior chemotherapy, including a taxane in 14 cases. At the dose and schedule used, the combination was well tolerated, with grade 3 diarrhea, peripheral neuropathy, hyperglycemia, neutropenia and fatigue seen in fewer than 5% of patients. The activity of the regimen was described as promising: of 22 patients evaluable for response, eight (36%) showed a greater than 50% decline in baseline PSA and two of twelve patients with measurable disease had a partial response.

The ASCO meeting also heard a report on the use of docetaxel plus a high-dose of the COX-2 inhibitor celecoxib.[11] COX-2 is overexpressed in 90% of patients with HRPC and is an independent prognostic factor. Preliminary data suggest that the combination of taxane plus celecoxib is well tolerated and active, inducing objective tumor responses in 65% of patients.

Other studies are investigating the combination of chemotherapy with zoledronic acid, atrasentan, imatinib (Glivec), gefitanib (Iressa), bcl-2 antisense/oblimersen sodium, and radioisotopes such as strontium 89.

Discussion

For many years cytotoxic therapy for hormone refractory prostate cancer was considered inefficient. More recently, the United States (US) Food and Drug Administration (FDA) approved treatment with Mitoxantrone and Prednisone and although the real standard treatment for hormone refractory prostate cancer remained unclear, this treatment was widely used in the US and in Europe.

Urologists often apply different lines of hormonal treatment, before referring their patients to the medical oncologist, because the effect of cytotoxic chemotherapy was felt by many of the urologists to be too disappointing. Therefore many patients were initially treated with castration (surgical or LHRH) and then subsequently with maximal androgen blockade. In the case of biochemical or clinical progression the anti-androgen would be stopped in order to obtain an anti-androgen withdrawal effect. The subsequent progression would often be treated with Estramustine phosphate, Ketoconazole, Aminogluthetimide, Cortisone or Progestagens. While each hormonal manipulation could induce a short lived biochemical or clinical regression, the patient's general condition deteriorated with the patient ultimately being in an unfit state for receiving cytotoxic chemotherapy.

Newer chemotherapeutic agents have offered fresh hope for the treatment of hormone refractory prostate cancer. Docetaxel is one of the newer agents which offered promising activity in the treatment of this disease. A number of mechanisms underlie the cytotoxicity of docetaxel.[12] In addition to disrupting microtubule disassembly and hence mitosis, it induces cell death by inhibiting bcl-2, an anti-apoptotic gene implicated in the progression of androgen-refractory prostate cancer.[13] However, docetaxel is also active in bcl-2 negative tumors, probably because it encourages expression of p27, a cell cycle inhibitor which is frequently lost in hormone refractory prostate cancer.

With the results of the two randomized docetaxel studies, it is questionable whether the secondline endocrine manipulations still have a place before initializing docetaxel-based chemotherapy.[14] In the TAX 327 design the prednisone dosage was identical across arms and hence the difference in outcomes achieved was based on docetaxel. For the first time, the randomized trials have shown that cytotoxic chemotherapy with a 3-weekly docetaxel regimen prolongs survival. This has now become a new standard to which newer treatments or combinations for hormone refractory or androgen-independent prostate cancer need to be compared. A logical approach for hormone refractory prostate cancer

in a patient under maximal androgen blockade would therefore be first to stop the anti-androgen and in case of progression consider chemotherapy, whenever possible in the frame of a randomized controlled trial where docetaxel is the standard arm versus combinations or other treatments.

These two trials have not solved all the questions. Some experts have questioned the role of Prednisone as they have felt that Prednisolone might give better results. The reasoning behind this is that Prednisone may interfere with the metabolism of docetaxel in the liver, possibly resulting in the inactivation of docetaxel.

The 3-weekly schedule is more effective but also associated with more toxicity. Therefore the weekly schedule can be used in patients with a predisposition to greater severe toxicity.

It is unclear how long treatment should be continued and when chemotherapy should be started in hormone refractory prostate cancer patients. Indeed, hormone refractory prostate cancer remains ill defined. Is hormone refractory prostate cancer occurring after first-line, second-line, third-line, fourth-line of fifth-line hormonal treatment? In any case the possibility of giving docetaxel must be discussed with the patient who has to accept the potential toxicity in order to gain in survival.

Enhanced interactions between urologists, that treat most patients with prostate cancer until they become hormone refractory, and medical oncologists that administer docetaxel chemotherapy is highly warranted. This can only be achieved by a multidisciplinary team, the set-up of which must be encouraged.

Another question regarding docetaxel, is if this active agent should find a role wider than that of advanced disease?

Given the substantial risk of recurrence even after radical local treatment, there is a pressing need for effective and well tolerated adjuvant therapy in patients at high risk. In this context, Rosenbaum and colleagues are conducting a pilot study of 6 months' adjuvant docetaxel after radical prostatectomy.[15] Rapid accrual to their trial suggests a good level of interest among patients and physicians. Although no data on outcome are available as yet, the study is powered to detect a 3 year progression free survival rate of 69%, compared with an expected rate of 50%.

Experience with the first fifty patients suggests weekly adjuvant docetaxel is feasible. Toxicity is moderate and reversible. Other possibilities would be to use docetaxel in the neoadjuvant setting prior to radical prostatectomy or early, combined with hormonal therapy, in patients with newly diagnosed metastatic disease. □

References

1. Yagoda A, Petrylak D. Cytotoxic chemotherapy for advanced hormone-resistant prostate cancer. *Cancer* 1993;71:1098-1109.
2. Tannock I, Gospodarowicz M, Meakin et al. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989;7:590-597.
3. Tannock IF, Osoba D, Stockler MR et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756-1764.
4. Martel CL, Gumerlock PH, Meyers FJ, Lara PN Jr. Current strategies in the management of hormone refractory prostate cancer. *Cancer Treat Rev* 2003;29:171-187.
5. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *New England J Med* 2004;351:1502-1512. Copyright © 2004 Massachusetts Medical Society. All rights reserved.
6. Petrylak DP, Tangen CM, Maha HA et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *New England J Med* 2004;351:1513-1520. Copyright © 2004 Massachusetts Medical Society. All rights reserved.
7. Osoba D, Tannock IF, Ernst DS, Nevill A. Health-related quality of life in men with metastatic prostate cancer treated with prednisone alone or mitoxantrone and prednisone. *J Clin Oncol 1999*;17:1654-1663.
8. Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. *J Urol* 2002;168:2439-2443.
9. Birch R, Kalman L, Holt L et al. Randomized phase IIb trial comparing two schedules of docetaxel plus estramustine for metastatic hormone refractory prostate cancer. *J Clin Oncol* 2004;22(14S):Abs 4622.
10. Dreicer R, Roth B, Petrylak D et al. Phase I/II trial of bortezomib in patients with advanced androgen-independent prostate cancer. *J Clin Oncol* 2004;22(14S):Abs 4654.
11. Kasimis B, Cogswell J, Hwang S et al. Phase II trial of docetaxel and high dose celecoxib in patients with hormone resistant prostate cancer. *J Clin Oncol* 2004;22(14S):Abs 4616.
12. Debes JD, Tindall DJ. Mechanisms of androgen-refractory prostate cancer. *New England J Med* 2004;351:1488-1490.
13. McDonnell TJ, Navone NM, Troncoso P et al. Expression of bcl-2 oncoprotein and p53 protein accumulation in bone marrow metastases of androgen independent prostate cancer. *J Urol* 1997;157:569-574.
14. Eisenbergen M.A., Carducci M.A. Chemotherapy for hormone-resistant prostate cancer. In: Campell's urology, Saunders, 2002 Ed P. Walsh, A.B. Retik, E. D. Vaughan, A.J. Wein, pp 3209.
15. Rosenbaum E, Kibel A, Roth BJ et al. Adjuvant weekly docetaxel for high-risk prostate cancer patients after radical prostatectomy: preliminary data of a multicenter pilot trial. *J Clin Oncol* 2004;22(14S):Abs 4649.