Neoadjuvant Docetaxel before Radical Prostatectomy in Patients with High-Risk Localized Prostate Cancer

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Abstract

Purpose: To determine the clinical, pathologic, and molecular effects of neoadjuvant docetaxel chemotherapy in high-risk localized prostate cancer.

Experimental Design: Patients with biopsy Gleason scores of 8 to 10, serum prostate-specific antigen levels >20 ng/mL, and/or clinical stage T3 disease received weekly docetaxel (36 mg/m²) for 6 months, followed by radical prostatectomy, and were monitored with weekly visits, serum prostate-specific antigen measurements, and endorectal magnetic resonance imaging (MRI). Frozen tumor specimens were collected for microarray analysis.

Results: The 19 patients enrolled received 82% of the planned chemotherapy. Toxicity was mild to moderate; fatigue and taste disturbance were common. Prostate-specific antigen declines of >50% were seen in 11 of 19 patients (58%; 95% confidence interval, 33-80%) and endorectal MRI showed maximum tumor volume reduction of at least 25% in 13 of 19 patients (68%; 95% confidence interval, 47-85%) and at least 50% in 4 patients (21%; 95% confidence interval, 6-46%). Sixteen patients completed chemotherapy and had radical prostatectomy; none achieved pathologic complete response. Microarray analysis identified coordinate up-regulation of genes involved in androgen metabolism associated with docetaxel therapy. Specifically, RNA expression for genes that decrease cellular levels of bioactive androgens was coordinately increased in response to chemotherapy.

Conclusions: Neoadjuvant docetaxel administered for 6 months before radical prostatectomy is feasible, well tolerated, and often results in prostate-specific antigen declines of >50% and decreased tumor volume on endorectal MRI. No pathologic complete responses were observed. Altered androgen metabolism may partially account for the noted declines in prostate-specific antigen and be a mechanism for chemotherapy resistance.

Most patients who undergo radical prostatectomy are cured, but as many as one third may experience a recurrence of disease (1). These patients are at risk of dying from prostate cancer and new strategies are needed to improve their survival (2). Patients with clinical T3 disease, serum prostate-specific antigen (prostate-specific antigen) levels of 20 ng/mL or higher, prostate-specific antigen velocity of 2 ng/mL/y or higher during the year before diagnosis, and biopsy Gleason scores of 8 to 10 are at high risk for recurrence and death after surgery (3), often due to the presence of early occult metastasis at time of diagnosis (4).

Neoadjuvant systemic therapy is given to cancer patients to decrease local tumor burden and eradicate micrometastatic disease (2). In diseases such as breast cancer, neoadjuvant therapy can result in a pathologic complete response at the time of surgery. Eradication of local disease in response to neoadjuvant therapy strongly predicts improved recurrence-free and disease-specific survival in breast and other cancers (5, 6).

As we increasingly can predict those patients likely to have recurrence following surgery, there is growing interest in neoadjuvant treatment of individuals diagnosed with high-risk prostate cancer. Thus far, however, trials testing the neoadjuvant use of androgen deprivation therapy (7, 8) or early chemotherapy (9) in prostate cancer have been disappointing and have failed to show compelling clinical or survival advantages. Recently, docetaxel, either alone or in combination with estramustine, has shown an excellent biochemical response rate (significant prostate-specific antigen reductions in ≥50% of men; ref. 10), significant palliative benefit, objective radiographic responses, and improved survival for
men with metastatic, hormone-refractory prostate cancer (11, 12). The promising activity of docetaxel in the management of hormone-refractory prostate cancer has led to a reexamination of whether the earlier use of such agents provides clinical benefit if used at the time of diagnosis rather than when the patient has progressive, hormone-refractory disease (13). Several investigators have reported on their experience with neoadjuvant chemotherapy for high-risk localized prostate cancer, although all of these regimens to date have included treatment that induced castration (either with a leutinizizing hormone releasing hormone agonist, estramustine, or both; refs. 14–17). Because docetaxel has significant single agent activity (18), and because estramustine has an unfavorable toxicity profile that includes thromboembolism (19), we designed a phase II trial to determine whether docetaxel alone could induce pathologic complete responses in patients with high-risk localized prostate cancer. Secondary objectives included the assessment of toxicity and clinical measures of response, including serum prostate-specific antigen and endorectal magnetic resonance imaging (MRI) measurements, and a correlative analysis of gene expression in tumors following docetaxel chemotherapy.

Materials and Methods

Patient population

The study was approved by the Institutional Review Board of Dana-Farber/Partners Cancer Care. After providing signed, written informed consent, patients were registered in a central database. Patients were eligible if they had histologically confirmed adenocarcinoma of the prostate and any of the following high-risk features: (a) clinical stage T3 disease; (b) serum prostate-specific antigen ≥20 ng/mL; (c) Gleason sum of 8, 9 or 10; or (d) Gleason sum of 7 with a predominant component of 4 (i.e., Gleason 4 + 3 = 7), with either seminal vesicle involvement on endorectal MRI and/or >5 positive core biopsies involved with cancer (20). Patients were deemed otherwise suitable candidates for radical prostatectomy and had no prior therapy for prostate cancer, including hormonal, radiation, or chemotherapy. An Eastern Cooperative Oncology Group performance status of 0 or 1 was required and no evidence of active infection was allowed. Patients were required to have a WBC count >3,000/µL, hematocrit >30%, platelet count >100,000/µL, normal aspartate aminotransferase, and normal total bilirubin.

Treatment and monitoring

Patients were treated with docetaxel 36 mg/m² weekly. Premedication with oral dexamethasone consisted of 8 mg taken 12 hours and 1 hour before each dose and 12 hours after each dose of docetaxel (a total of 24 mg for each weekly dose). Antiemetics were allowed at the discretion of the treating physician, although additional corticosteroids were specifically not allowed. After a baseline visit and endorectal MRI, patients were seen weekly for assessment of toxicity, physical examination, and complete blood count. Once a month, patients had repeat digital rectal examination, complete chemistries, and serum testosterone and prostate-specific antigen level measurements. After 2 months of therapy, patients were reevaluated with endorectal MRI and, if there was evidence of clinical progression, patients could be removed from the study and given local therapy, including radical prostatectomy or external beam radiotherapy, at the discretion of the patient’s physicians. If patients had evidence of stable disease or response, they continued on treatment for a total of 6 months. At that time (or at the time they completed chemotherapy, if they did not complete 6 months of treatment), endorectal MRI was again repeated. Patients then proceeded to radical prostatectomy.

Patients were allowed to have a one-time dose reduction of docetaxel for significant neutropenia, thrombocytopenia, liver function abnormalities, neuropathy, and cutaneous reactions. The clinical response was defined after 2 and 6 months of treatment. Complete response was defined as complete disappearance of tumor masses by digital rectal exam and endorectal MRI, with no new lesions appearing and prostate-specific antigen <4 ng/mL. Partial response was defined as at least a 25% reduction in bidimensional measurement of a tumor mass by endorectal MRI with no new masses or growth of other lesions. Two independent radiologists (S.S., A.S./C.T.) reviewed all endorectal MRIs, blinded to clinical outcome. Mean values for prostate volume and maximum tumor volume for each patient were calculated. At the same time, prostate-specific antigen had to remain stable or decrease. Stable disease was noted if both measurable disease and prostate-specific antigen did not increase by 25% or more and no new masses were noted. Progression was defined by the appearance of any new areas of tumor, an increase in any previously measurable lesion by 25% or more in bidimensional measurement, any new evidence of extrapulmonary disease, or prostate-specific antigen increases of ≥25% on two successive occasions at least 2 weeks apart, each consecutively increasing.

Pathologic evaluation

The pathologic response to chemotherapy was assessed by central review of a single pathologist (M.L.). A pathologic complete response was defined as complete eradication of tumor. Pathologic downstaging was defined as evidence of decreased pathologic stage or Gleason score when compared with pretreatment clinical stage. The rate of negative surgical margins was also recorded as an indirect measure of response to chemotherapy.

Expression analysis

Frozen tumors were collected ex vivo during pathologic examination of the prostate and processed for oligonucleotide microarrays (Affymetrix, Santa Clara, CA) as previously described (21). From the 16 patients enrolled on this protocol who subsequently underwent radical prostatectomy, specimens from seven patients were obtained that had sufficient tumor for microarray analysis, high-quality RNA, and resultant high-quality microarray data. Each tumor collected for this study was matched with two to three previously hybridized, untreated prostate cancer tumors processed asynchronously in the same laboratory by the same person (P.G.F.) using both Gleason score and percent tumor.

To identify genes with differential expression, CEL files were imported into dCHIP and normalized and filtered (SD divided by mean >0.25 and <5, P call percentage ≥20% of samples, and expression ≥200 in ≥50% of samples). For unsupervised analysis, the expression of all genes passing the variation filter was used to organize samples and genes into a hierarchical cluster also using dCHIP (rows were standardized and distance was 1−r, where r is Pearson’s correlation coefficient). For supervised analysis, normalized and filtered gene expression data were exported from dCHIP and imported into GeneCluster 2.1 (Whitehead Institute, Massachusetts Institute of Technology, Cambridge, MA) and a signal-to-noise metric (22) was used to identify genes with differential expression. Random permutations of labeled sample were used to determine genes with differential expression (described previously in ref. 21). Genes were considered significant if their differential expression exceeded that of permuted data with a P value of 0.01.

To identify pathways that may be up-regulated in response to docetaxel therapy in prostate cancer, gene set enrichment analysis was done (23, 24). Here, a curated list of 524 pathways and their associated genes were used to determine if any gene set(s) had increased expression upon treatment with docetaxel.
coordinate differential expression greater than expected by chance alone. A nominal P value of ≤0.05 was taken as statistically significant. Gene set enrichment analysis on a specific pathway for androgen and estrogen metabolism was subsequently done to determine the rank order of genes within the set according to their differential expression between treated and untreated samples.

**Statistical analysis**

**Statistical considerations.** The primary end point of this trial was to define the pathologic complete response rate of docetaxel chemotherapy in patients with untreated, high-risk prostate cancer. The study was designed to distinguish a 10% pathologic complete response rate from an anticipated underlying rate of 1% or less. A two-stage design was specified. In the first stage, 19 eligible patients were entered. If at least one pathologic complete response was observed, the study would enroll an additional 16 eligible patients. If two or more patients among 35 eligible patients exhibited pathologic complete response, the treatment would have been declared worthy of further study. Given these specifications, the study had an 83% probability of stopping early if the true underlying pathologic complete response rate was 1%; 96% probability of rejecting docetaxel if it was inactive; and only 19% chance of finding it inactive if the true pathologic complete response rate was 10% or higher.

The Wilcoxon signed-rank test was used to determine if there were changes in the slope of prostate-specific antigen and testosterone over time. The Wilcoxon rank-sum test was used to test for differences in prostate-specific antigen and testosterone levels between prostate-specific antigen responders and nonresponders. Slopes were calculated using least squares regression. Two-sided exact binomial confidence intervals were used to characterize response rates. Fisher’s exact test was used to test for associations between prostate-specific antigen response and MRI response.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Number of patients</td>
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</tr>
<tr>
<td>Age, median (y)</td>
<td>54</td>
</tr>
<tr>
<td>Time from diagnosis to study entry, median (mo)</td>
<td>2.1</td>
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<tr>
<td>Clinical tumor stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>9 (47)</td>
</tr>
<tr>
<td>T2</td>
<td>7 (37)</td>
</tr>
<tr>
<td>T3</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Biopsy Gleason score</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5 (26)</td>
</tr>
<tr>
<td>7</td>
<td>6 (32)</td>
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<tr>
<td>8</td>
<td>2 (11)</td>
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<tr>
<td>9</td>
<td>6 (32)</td>
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<tr>
<td>Serum prostate-specific antigen at diagnosis</td>
<td></td>
</tr>
<tr>
<td>&lt;20 ng/mL</td>
<td>13 (68)</td>
</tr>
<tr>
<td>≥20 ng/mL</td>
<td>6 (32)</td>
</tr>
<tr>
<td>T2 with seminal vesicle involvement on endorectal MRI</td>
<td>3 (16)</td>
</tr>
<tr>
<td>T2 with Gleason 4 + 3 cancer and &gt;5 (+) biopsies</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Total number of risk factors</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16 (84)</td>
</tr>
<tr>
<td>2</td>
<td>3 (16)</td>
</tr>
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</table>

Clinical response. The study was open from January 2000 to October 2001. All patients were node negative by imaging studies and free from metastatic disease at diagnosis (Table 1). The median age of the patients was 54 years, reflecting a younger than average group of men with prostate cancer. The high-risk features most commonly noted were biopsy Gleason score of 8 or higher (43%) and/or a serum prostate-specific antigen over 20 ng/mL (32%; Table 1). Only 3 (16%) patients had clinical T3 disease and the same number of men (3) had more than one high-risk factor for eligibility into this trial.

Weekly docetaxel had a significant effect on serum prostate-specific antigen for most men (Fig. 1A). After 2 months, the median reduction in prostate-specific antigen compared with baseline was 34%. After 6 months, the median reduction in prostate-specific antigen was 64%. One patient who received a single dose of chemotherapy was not evaluable for response but is included in the denominator for computing all response rates. Eleven patients (58%; 95% confidence interval, 33-80%) showed at least a 50% reduction in serum prostate-specific antigen.

Prostate tumor volumes, as measured by endorectal MRI, also decreased with docetaxel therapy. Median tumor volumes

![Fig. 1. Prostate-specific antigen and testosterone levels during docetaxel therapy. Mean serum prostate-specific antigen (A) and testosterone (B) at baseline and each month during therapy (± SD).](https://example.com)
decreased by 25.8% after 2 months and by 48% after 6 months (Table 2). Whereas 13 of 19 patients (68%; 95% confidence interval, 47-85%) achieved a marginal response of at least a 25% reduction in maximum tumor volume during therapy, only 4 patients (21%; 95% confidence interval, 6-46%) achieved a partial response of 50% reduction in maximum tumor dimension in an intent-to-treat analysis.

During therapy, there was a modest reduction in circulating testosterone potentially caused by either dexamethasone premedication or docetaxel itself (Fig. 1B). Although some decline in circulating testosterone was noted, testosterone levels stayed within the reference range and there was no correlation between serum prostate-specific antigen and serum testosterone levels (Table 3). In addition, prostate volume (a hormonally sensitive measure; ref. 25) remained relatively stable with reductions compared with baseline of 14% at 2 months and 12.5% at 6 months (Table 2). Thus, the effects of docetaxel therapy were likely to have been a direct effect on the disease rather than an indirect effect through circulating androgen levels.

Toxicity. Docetaxel caused mild to moderate toxicity and most patients (13 of 19, 68.4%) completed 6 months of weekly therapy as planned. Toxicity consisted of mostly grade 1 and 2 fatigue (84%) and mild gastrointestinal effects such as taste disturbance, nausea, and diarrhea (Table 4). One patient experienced a significant infusion reaction after his first dose of docetaxel and was removed from study. Three patients experienced grade 3 toxicity: the aforementioned patient who had an infusion reaction (transient bradycardia and syncope), another patient who had a cough-induced vasovagal reaction related to an atypical pneumonia that developed on therapy, and a third patient with grade 3 hypernatremia and hypokalemia after treatment with loop diuretics for edema. Although of unclear etiology, one patient had constrictive pericarditis that was diagnosed in the postoperative period. Other toxicities included nail bed changes in 32% and epiphora (excessive tearing) in 26%. Remarkably, no hematologic toxicities were noted, no patients required dose reduction, and only one patient experienced a single dose delay.

Surgery and follow-up. Thirteen patients had a radical prostatectomy done by a single surgeon (J.P.R.) and three patients had surgery at an outside hospital. Of the three patients who went off the study, one patient started hormones after 2 months despite having stable disease and eventually proceeded with surgery; one had an infusion reaction after the first dose (see toxicity) and went on to receive hormones and radiation; and the third patient had a stable prostate-specific antigen but progression, based on MRI evidence of new extracapsular disease and digital rectal exam, and was treated with hormones and external beam radiation.

Median estimated blood loss during radical prostatectomy was 675 mL (range, 400-1,750 mL) and patients were hospitalized for a median of 3 days (range, 2-6 days). Surgical complications included a need for blood transfusion in three patients and pulmonary embolus in one patient; no toxicity resulted in residual sequelae. With subsequent follow-up, only one patient had noted persistent urinary incontinence, although all reported significant erectile dysfunction. Median estimated blood loss, complication rate, and number of hospital days for patients on this trial were typical for comparable stage patients (1). Postsurgical treatment was not defined in the trial, but most patients did not receive additional therapy. One patient received adjuvant radiation to the prostate and a second one received adjuvant androgen deprivation therapy. Two others subsequently had androgen deprivation therapy for increasing prostate-specific antigen whereas a third had external beam radiation for this indication. At a median of

Table 2. Prostate volume and maximum tumor assessment by endorectal MRI

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
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<th>Month 2</th>
<th></th>
<th></th>
<th>Month 6</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median</td>
<td>Range</td>
<td>n</td>
<td>Median</td>
<td>Range</td>
<td>n</td>
<td>Median</td>
</tr>
<tr>
<td>Prostate volume (cm³)</td>
<td>19</td>
<td>28.9</td>
<td>21.9-53.5</td>
<td>18</td>
<td>24.8</td>
<td>16.9-47.3</td>
<td>15</td>
<td>25.3</td>
</tr>
<tr>
<td>Maximum tumor volume (cm³)</td>
<td>19</td>
<td>3.1</td>
<td>0.8-11.7</td>
<td>18</td>
<td>2.3</td>
<td>0.5-9.8</td>
<td>15</td>
<td>1.6</td>
</tr>
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</table>

Table 3. Comparison of prostate-specific antigen and testosterone levels and endorectal MRI results based on level of prostate-specific antigen decline

<table>
<thead>
<tr>
<th></th>
<th>Prostate-specific antigen decline ≥50%</th>
<th>No prostate-specific antigen decline ≥50%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>7</td>
<td>0.55</td>
</tr>
<tr>
<td>Median baseline prostate-specific antigen</td>
<td>12.4</td>
<td>19.8</td>
<td>0.13</td>
</tr>
<tr>
<td>Median final prostate-specific antigen</td>
<td>3.9</td>
<td>12.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Median baseline testosterone</td>
<td>386</td>
<td>241.5</td>
<td>0.31</td>
</tr>
<tr>
<td>Median final testosterone</td>
<td>279</td>
<td>243</td>
<td></td>
</tr>
<tr>
<td>MRI response (25% reduction)</td>
<td>7</td>
<td>6</td>
<td>0.66</td>
</tr>
<tr>
<td>MRI response (50% reduction)</td>
<td>1</td>
<td>3</td>
<td>0.26</td>
</tr>
</tbody>
</table>

NOTE: One patient was not evaluable for prostate-specific antigen response.
26.5 months following surgery (range 4.5-40 months), 3 of 16 patients received salvage radiation therapy, 3 patients received hormonal therapy, and 7 patients continued to have an undetectable prostate-specific antigen.

**Pathologic response.** Although docetaxel therapy resulted in significant decreases in levels of serum prostate-specific antigen and tumor volume, there were no pathologic complete responses. Of the 16 radical prostatectomy specimens available for pathologic analysis, 38% had organ-confined disease (pT2, n = 6), 62% had extracapsular penetration (pT3, n = 9, or pT4, n = 1), and 0% had lymph node involvement. Half of the patients had seminal vesicle involvement (8 of 16, 50%). The study was stopped per protocol, as there were no pathologic complete responses among the first 19 enrolled patients. When the Gleason score of the diagnostic biopsy was compared with the Gleason score of the prostatectomy specimen, most men had no change in their Gleason score (n = 9), four men had an increase in their Gleason score, and three men had a decrease in their Gleason score. Also noted was a “treatment effect” on the prostate epithelium that seemed similar to that seen with androgen ablation. Whereas the sample size is too small for statistical analysis, it is likely that the difference between biopsy and prostatectomy Gleason scores for men within this study is similar to that of a general population; neoadjuvant docetaxel does not seem to be associated with a significant decrease in Gleason score.

**Expression analysis.** Gene expression in local tumors treated with docetaxel was measured using oligonucleotide microarrays and compared with untreated prostate tumors. In unsupervised analysis, treatment status did not drive sample organization when tumors were clustered based on the expression of the 2,271 genes passing a variation filter (Fig. 2A). Interestingly, whereas there were 332 genes with small but significant expression differences between the two groups (P < 0.01; Fig. 2B), there were no genes with large (>5-fold) expression changes between treated and untreated prostate tumors. However, any negative finding needs to be interpreted with caution given the relatively small number of samples available for analysis.

To implicate potential mechanisms involved in docetaxel resistance, we applied gene set enrichment analysis. In this analysis, genes are grouped according to their association with a signaling pathway or other biological phenomena and their shared differential expression is tested between two sample classes. When applied here, a gene set composed of genes involved in androgen and estrogen metabolism was found to be coordinately up-regulated in treated samples (Fig. 2C and D). Although no single androgen metabolism gene had significant differential expression, the consistent increase in expression of these genes as a set in the treated samples was significant and its potential importance is underscored by the specific patterns for genes that either increase or decrease androgen availability. Specifically, the RNA expression of metabolic enzymes that decrease levels of active androgen (e.g., CYP11B1, HSD11B2, HSD17B2, HSD3B1, and UGT2B15) increased whereas that of enzymes that increase the levels of active androgens decreased (HSD11B1 and CYP11B2; Fig. 2E). This suggests that one response of prostate tumors to neoadjuvant cytotoxic chemotherapy is to decrease androgen bioavailability.

**Conclusions**

In this pilot trial, men with high-risk localized prostate cancer received 6 months of neoadjuvant docetaxel chemotherapy and experienced significant decreases in serum prostate-specific antigen levels and maximum tumor volume, but did not show pathologic complete responses. The regimen was well tolerated. Fatigue, gastrointestinal symptoms, and nail bed changes were the most common toxicities, but they seldom limited and only once delayed therapy. Also, neoadjuvant chemotherapy did not seem to increase the complication rate of radical prostatectomy. With a median follow-up of over 26 months after surgery, seven men continued to have an undetectable prostate-specific antigen test and did not receive additional therapy.

The decrease in prostate-specific antigen observed in most men receiving neoadjuvant docetaxel is likely due to multiple factors. The regulation of prostate-specific antigen in prostate cells and prostate cancer is driven by androgen activity but other chemical and biological factors can influence prostate-specific antigen secretion (26, 27). Although there was a trend toward a decline in circulating testosterone levels in men treated with neoadjuvant docetaxel, the levels of testosterone remained within the reference limits. In addition, testosterone levels did not correlate with serum prostate-specific antigen levels, and the
slight decline in testosterone was not associated with a decrease in prostate gland volume, a hormonally sensitive measure (25). Thus, the decrease in prostate-specific antigen did not seem to be due to docetaxel-altering circulating androgens. It is likely that antitumor effects accounted for at least some of the observed decline in prostate-specific antigen. This is supported by the decrease in tumor volume observed when the baseline endorectal MRI was compared with those repeated at 2 and 6 months.

Despite some likely antitumor activity, no pathologic complete responses were observed for the men who underwent radical prostatectomy on this trial, a finding consistent with a prior report testing 6 weeks of neoadjuvant docetaxel on 29 patients with intermediate to high-risk prostate cancer (28). Although disappointing, the absence of pathologic complete responses that occurred in either trial is not surprising. It is notable that the rate of pathologic complete response is low even

![Expression analysis of docetaxel treated tumors. A, hierarchical cluster of tumors based on the expression of all genes passing initial filtering (n = 2,271). Treated cancers (Rx) do not cleanly separate from untreated cancers. B, heat map of the 332 genes with significant differential expression between untreated and treated prostate cancers. Mean normalized gene expression; red, high expression; blue, low expression. C, gene set enrichment analysis pathway results for the top 15 pathways ranked according to their normalized enrichment score (P < 0.05). D, gene set enrichment analysis result for genes included in the "androgen and estrogen metabolism" pathway. The running score (red line) is based on the distribution of the genes (blue lines) after all genes (n = 22,275) were ranked based on a signal-to-noise metric measuring the differential expression between treated and untreated cancers with those genes with increased expression in the treated tumors ranked at the top and those genes with decreased expression in the treated tumors ranked at the bottom. E, percent change in mean expression (± SD) for each gene in treated cancers when compared with untreated cancers ordered according to their signal-to-noise rank and represented as the percent of the untreated mean. Gene symbols and metabolic effects on bioactive androgens [increase (red) or decrease (blue)] are provided.](image-url)
in relatively chemotherapy-sensitive tumors such as breast cancer (5-15%; ref. 5). As the achievement of pathologic complete response has been associated with improved survival across tumor types, it is important to understand the potential mechanisms of resistance so that combination therapies can be planned.

Expression analysis suggests that surviving cells may alter their metabolism of androgens such that there is a decrease in active androgens available to the prostate cancer cells. Specifically, enzymes that convert androgens to inactive or less active metabolites, such as CYP11B1 (29), HSD17B2 (30), HSD3B1 (31), and UGT2B15 (32), have increased expression in the prostate cancers treated with docetaxel compared with untreated cancers, whereas enzymes that are associated with increased androgen activity, such as HSD17B3 (30) and CYP11B2 (29), have decreased expression. Androgens are critical to the development and progression of prostate cancer, and androgen deprivation therapy remains the most effective therapy in halting cellular proliferation and decreasing the symptoms associated with metastatic prostate cancer (33, 34). Although still requiring further confirmation, it is plausible that the prostate cancer cells surviving docetaxel therapy have altered their androgen metabolism such that they decrease the availability of active androgens, divide less often, and are less sensitive to the antimitotic effects of the microtubule-stabilizing activities of docetaxel. Such a shift in hormone metabolism may move the prostate cancer cells back toward a more primitive, prostate tumor stem cell, which in murine models is generally quiescent and less sensitive to hormone manipulation (35).

This study cannot address the benefit of neoadjuvant docetaxel with respect to overall and disease-free survival. However, most men had a >50% decline in serum prostate-specific antigen and decreases in tumor volume on endorectal MRI (36). Given the regulation of the expression of prostate-specific antigen being complex, such clinical responses are encouraging and, together with the feasibility herein established, warrant definitive studies. Cancer and Leukemia Group B 90203 is a randomized phase III study comparing neoadjuvant docetaxel and androgen ablation followed by surgery to surgery alone for men with high-risk localized prostate cancer, and will have 90% power to detect a 36% decrease in 5-year recurrence rate (37). This study will provide critical data both addressing the benefit of neoadjuvant chemotherapy and assessing the merits of radical prostatectomy in patients with high-risk disease. Our finding about androgen metabolism as a mechanism of resistance to docetaxel raises some concern on combining androgen ablation with docetaxel, but androgen ablation remains the most effective therapy for metastatic disease, and our findings are too preliminary to preclude trials of the combination.

In summary, neoadjuvant docetaxel is feasible and may have a role in improving the clinical course of men diagnosed with high-risk prostate cancer who are candidates for surgery. Although significant clinical responses were seen, no pathologic complete responses were obtained. Furthermore, there was a suggestion that metabolic shifts within tumors cells may occur, which help protect the tumors against the cytotoxicity of chemotherapy. Randomized trials powered to assess disease-free and overall survival are warranted to test the benefit of neoadjuvant docetaxel in prostate cancer.

References


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