Phase I Study of Weekly Mitoxantrone and Docetaxel before Prostatectomy in Patients with High-Risk Localized Prostate Cancer

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ABSTRACT

Purpose: The purpose is to determine the dose-limiting toxicity (DLT) and maximum-tolerated dose (MTD) of mitoxantrone and docetaxel administered weekly before prostatectomy in men with localized prostate cancer at high risk for recurrence.

Experimental Design: Twenty-two patients were treated with four cycles of docetaxel 35 mg/m² and increasing doses of mitoxantrone starting at 2 mg/m² repeated weekly for 3 weeks of a 4-week cycle before prostatectomy. The MTD was defined as that dose at which fewer than one-third of patients experienced a DLT (≥grade 4 hematological or ≥grade 3 nonhematological toxicity). Changes in serum prostate-specific antigen and serum testosterone, and pathological outcome with surgery were secondary endpoints.

Results: The MTD for mitoxantrone in combination with this dose of docetaxel was 4 mg/m². Neutropenia was the DLT for the combination. Ten of 12 patients treated at the MTD completed the planned 16 weeks of chemotherapy, whereas 2 discontinued therapy early because of toxicity. The median reduction in PSA was 41% (range, 4–88%). Serum testosterone levels remained constant postchemotherapy.

Conclusions: In this patient population, the planned Phase II regimen is 4 mg/m² mitoxantrone and 35 mg/m² docetaxel weekly for 3 of every 4 weeks. Delivery of this regimen before prostatectomy is feasible with acceptable toxicity. Additional studies are needed to determine whether this combined modality approach will reduce cancer recurrence rates in this high-risk population. Because extent of disease and exposure to prior therapy may impact treatment tolerance these safety data may not be applicable to patients with advanced prostate cancer.

INTRODUCTION

Effective systemic therapy regimens capable of eradicating microscopic metastases are needed to improve the outlook for patients with high-risk localized prostate cancer. The addition of hormonal therapy to prostatectomy has been tested in several randomized studies. Although postoperative hormonal therapy in men with nodal metastases discovered at prostatectomy was beneficial in one trial (1), multiple studies have shown that 3 months of preoperative androgen deprivation does not reduce the risk of prostate cancer recurrence (2, 3). Studies examining longer androgen deprivation before prostatectomy are ongoing (4). Furthermore, surgical margin status loses its predictive value in the setting of neoadjuvant androgen deprivation, perhaps as a result of effects of therapy on cellular characteristics (5). The failure of androgen deprivation to produce complete pathological responses or reduce cancer recurrence suggests that androgen-independent prostate cancer cells that contribute to postoperative recurrence may be present early in the disease process. Agents that are active against androgen-independent prostate cancer (AIPC) may therefore be necessary to improve the long-term outcome of men with high-risk localized prostate cancer.

In addition to mitoxantrone, the activity of which was tested in two Phase III studies (6, 7), several new cytotoxic chemotherapy agents tested only in Phase II trials have significant activity against AIPC (8, 9). The availability of such agents has stimulated their experimental application in combination with surgery in the treatment of patients with high-risk prostate cancer, an approach that has been successfully applied to breast cancer (10). Although systemic therapy can be added before or after surgery, only preoperative treatment allows assessment of tumor response and collection of pre- and posttreatment tumor tissue for molecular interrogation.

Three groups have reported results with neoadjuvant chemohormonal therapy (11–13). These trials demonstrated the feasibility of combining chemotherapy with surgery in the treatment of prostate cancer. The contribution of chemotherapy to the observed treatment effects [such as prostate-specific antigen (PSA) reduction or incidence of negative surgical margins] is difficult to determine from these studies because of the inclusion of androgen deprivation.

Two reports of the application of chemotherapy without hormonally active agents before prostatectomy are available. The studies examined different schedules of docetaxel alone...
(14, 15). The available data from these studies are limited, and no conclusions regarding efficacy can be made.

The goal of the current study was to develop a new non-hormonal regimen for neoadjuvant treatment of high-risk prostate cancer that combined mitoxantrone and docetaxel, two of the most active chemotherapy agents in AIPC. The Phase I development of the combination was undertaken in the target population rather than in older, heavily pretreated patients with advanced prostate cancer because it was anticipated that higher doses of chemotherapy would be tolerated in younger, more fit patients and to evaluate the morbidity of the combination of chemotherapy and surgery.

Phase I studies combining the two drugs on an every 3-week schedule confirmed that neutropenia is the dose-limiting toxicity (DLT) of the combination (16). Weekly administration, associated with substantially less neutropenia, was therefore chosen for this study. Although the primary goals of this investigation were to identify the DLT and maximum-tolerated dose (MTD) of the combination of docetaxel with mitoxantrone in this patient population and to examine the morbidity of surgery after this chemotherapy regimen, preliminary evaluation of efficacy, including PSA reduction and pathological findings (including surgical margin status), as well as the effect of chemotherapy on circulating testosterone levels, were the secondary objectives.

**MATERIALS AND METHODS**

**Patients.** Eligibility criteria included the following criteria: histologically confirmed adenocarcinoma of the prostate; prostatectomy planned as primary therapy; ≥10 years life expectancy; and any of the following high risk features: clinical stage T2c or surgically resectable T3a, or PSA ≥ 15 ng/ml, or Gleason grade ≥ 4 + 3 (4 + 3, 4 + 4, or any 5 elements).

Patients could not have bone metastases on radionuclide bone scan, lymph nodes ≥ 2 cm in diameter on pelvic computed tomography scan (scan required only in patients with a PSA ≥ 40 ng/ml), Eastern Cooperative Oncology Group performance status ≥ 2, and left ventricular ejection fraction ≤ 50% by multiple gated acquisition technetium scan. Patients were also excluded for the following: any prior therapy for prostate cancer; significant active medical illness; second malignancy other than nonmelanoma skin cancer within 5 years; ≥ grade 2 peripheral neuropathy; hypersensitivity to drugs formulated with polysorbate-80; significant contraindications to corticosteroids; WBC count < 3000/mm³; neutrophil count < 1500/mm³; platelet count < 100,000/mm³; or conjugated bilirubin > upper limit of normal (ULN), alkaline phosphatase > 4.0 × ULN, alanine transaminase (ALT) > 2.0 × ULN, or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN.

Written informed consent was obtained from all patients. The protocol was approved by the Institutional Review Boards of Oregon Health and Science University, Portland Veterans Affairs Medical Center, the University of Washington, and the Portland Legacy Health Systems.

**Treatment.** Mitoxantrone administered by i.v. infusion over 3–5 min and dosed according to the dose escalation scheme followed by docetaxel given at a fixed dose of 35 mg/m² i.v. over 15–30 min was administered weekly for 3 weeks and repeated on a 4-week cycle for four cycles. Four mg p.o. of dexamethasone 12 and 1 h prior and 12 h after docetaxel infusion was given. Patients who weighted >130% of their ideal body weight (defined as 50 kg + 2.3 kg/inch for each inch of height over 5 feet; Ref. 17) had their body surface calculated based on adjusted weight equal to ideal body weight + 0.5 (actual weight – ideal body weight).

**Planned Dose Modifications and Supportive Care.** In addition to the rules for dose escalation, dose modifications were planned for individual patient’s toxicity. Omitted doses were not made up. For hematological toxicity, therapy with both agents was withhold for platelet count < 75,000/mm³ or neutrophil count < 1000/mm³ until both counts were above these parameters. The mitoxantrone dose was reduced by 25% if recovery took longer than 1 week, two consecutive doses produced counts below these parameters, or for any grade 4 hematological toxicity. The dose of docetaxel was reduced by 25% if a patient again met these criteria despite the mitoxantrone dose reduction. Patients who had a had a platelet count < 75,000/mm³ or neutrophil count < 1000/mm³ that persisted longer than 2 weeks or had any grade 4 hematological toxicity despite the 25% dose reduction of both agents were to be removed from the study.

The dose of docetaxel and mitoxantrone was to be reduced by 25% for aspartate aminotransferase of 1.6–5 × ULN. Therapy was withheld for bilirubin > ULN, alkaline phosphatase > 5 × ULN, or ALT > 5 × ULN. Therapy was resumed at a 25% dose reduction in patients whose liver function tests recovered within 3 weeks. Mitoxantrone was to be discontinued for any objective evidence of cardiotoxicity (including >10% decline in ejection fraction). For all other persistent and clinically significant ≥ grade 3 nonhematological toxicity, therapy was to be withheld until resolution of toxicity and treatment resumed with a 25% reduction in the dose of both agents.

Growth factors could be used at the treating physician’s discretion; however, the addition of growth factor support was not a substitute for required dose reductions.

**Statistical Design.** The dose of docetaxel was fixed at 35 mg/m², whereas the starting dose of mitoxantrone was 2 mg/m². Three patients were enrolled at each dose level. Doses were not escalated within patients. The mitoxantrone dose was to be increased in subsequent cohorts of patients in increments of 1 mg/m² until 6 mg/m² or until one-third or more of the patients experienced DLT, defined as grade 3 nonhematological or grade 4 hematological toxicity during the first cycle of therapy. The dose escalation stopped if 2 or 3 patients experienced a DLT. If 1 of 3 patients experienced a DLT, an additional 3 patients were enrolled at the same dose level. If none of the additional 3 patients experienced a DLT, the dose escalation resumed. If any of the additional 3 patients experienced a DLT, the dose escalation stopped. The MTD and proposed Phase II dose were defined as the dose at which fewer than one-third of patients experienced a DLT. A total of 12 patients at the proposed Phase II dose was enrolled to develop more robust toxicity data.

**Monitoring.** A complete blood count with automated differential was obtained during every treatment visit, and chemistry panel and PSA were collected every 4 weeks. Serum testosterone was measured before chemotherapy and again after four cycles of treatment. A physical examination, including a
prostate examination and assessment of toxicity, was performed every 4 weeks. Prostate imaging was not used to follow disease status. All perioperative surgical morbidity, operative time, and blood loss was recorded in all patients.

**Translational Studies.** Patients underwent a transrectal ultrasound-guided 10-core prostate biopsy from which all specimens were snap frozen in liquid nitrogen before chemotherapy administration. Unfixed portions of both cancer and noncancer tissue were selected from the prostatectomy specimen and rapidly frozen. These paired pre- and posttherapy specimens will be used for both hypothesis-driven and exploratory investigation of markers of prostate cancer progression, drug resistance, and prognosis using immunohistochemistry, in situ hybridization to mRNA, and RNA amplification and gene expression analysis.

**RESULTS**

**Patients.** Twenty-two patients were enrolled between January 2001 and July 2002. All patients were eligible. The median age was 63 (range, 52–74 years). Median Eastern Cooperative Oncology Group performance status was 0. The median PSA was 16.0 ng/ml (range, 4.2–46.3 ng/ml), and the median Gleason score was 8 (range, 6–9; Table 1).

**Treatment.** Of the 22 patients, 3 received mitoxantrone at 2 mg/m², 3 at 3 mg/m², 12 at 4 mg/m², and 4 at 5 mg/m². Nineteen patients completed the planned 16 weeks of chemotherapy. One patient withdrew consent after two doses of chemotherapy. The interpretation of changes in serum PSA are challenging in this setting. Unlike the setting of androgen-independent prostate cancer, there are no validated PSA end points. In patients whose PSA is relatively low, a significant fraction of serum PSA would be expected to originate from the normal gland and therefore be unaffected by chemotherapy. Furthermore, the short duration of therapy limits PSA results as a maximum of four measurements after starting therapy are

| Number | 22 |
| Age (years) | Median 63, Range 52–74 |
| Eastern Cooperative Oncology Group PS | 0: 19, 1: 3 |
| PSA | Median 16.0, Range 4.2–46.3 |
| Clinical stage (2002 criteria) | T1c: 3, T2a: 3, T2b: 2, T2c: 6, T3a: 8 |
| Biopsy Gleason score | 6: 4, 7: 6, 8: 6, 9: 6 |

**Toxicity.** The MTD and the planned Phase II dose for mitoxantrone in combination with this dose of docetaxel was 4 mg/m². Two of 4 patients treated with 5 mg/m² mitoxantrone experienced DLTs during the first cycle of therapy. In both cases, the DLT was grade 4 neutropenia. No DLTs were recorded during the first cycle of therapy with mitoxantrone doses of 2–4 mg/m².

Treatment-related toxicity for the entire four-cycle course of therapy is detailed by dose level in Table 2. Neutropenia was the most common treatment-related hematological toxicity. Hyperglycemia, expected with dexamethasone premedications, and onycholysis, commonly reported with weekly docetaxel, were the most common nonhematological toxicities. One patient suffered a calf deep venous thrombosis below the popliteal vein while receiving chemotherapy.

**Surgery after Chemotherapy.** Similar to systemic toxicity, the interpretation of these surgical results is limited by the sample size. Variation in individual pelvic anatomy as well as variations in technique among surgeons additionally limit the interpretability of surgical morbidity data. However, observed operative morbidity compared favorably to published data for prostatectomy without prior chemotherapy. In the absence of direct measures of technical difficulty, we evaluated commonly used surrogates. The median operative time was 3.6 h (mean, 3.9 h; range, 2.4–6.5 h). The median estimated blood loss was 575 ml (mean, 768 ml; range 100–2000 ml). There were no intraoperative complications [0%, 95% confidence interval (CI), 0–15%]. Postoperative complications were limited to a wound infection in one patient (5%, 95% CI, 0–23%). There were no postoperative deep venous thromboses. None of the three surgeons felt that surgery was more difficult after chemotherapy. In a prior prospective study of high-risk patients undergoing radical prostatectomy without preoperative therapy, mean operative time was 3.9 h (18). In that study, major injuries to either the rectum or ureter were reported in 4.2% of patients. Operative blood loss data are not available from other high-risk series; however, estimated blood losses in the current study were lower than other contemporary series of standard-risk prostatectomy in which losses ranged from 844 to 1200 ml (19–21).

**Effect on Testosterone.** There was no change in serum testosterone with therapy. The mean serum testosterone concentration was 401.3 ng/dl before therapy (95% CI, 320.3–582.3 ng/dl; range, 118–914 ng/dl) and 364.7 ng/dl after therapy (95% CI, 275.3–454.1; range, 118–914 ng/dl; n = 20, P = 0.42 by paired t test).

Treatment Effects. Twenty-one patients, those who received at least one cycle of chemotherapy, were available for analysis of treatment effects. These analyses should be viewed as hypothesis generating and are not intended to represent definitive measures of efficacy.

**PSA Changes.** The interpretation of changes in serum PSA are challenging in this setting. Unlike the setting of androgen-independent prostate cancer, there are no validated PSA end points. In patients whose PSA is relatively low, a significant fraction of serum PSA would be expected to originate from the normal gland and therefore be unaffected by chemotherapy. Furthermore, the short duration of therapy limits PSA results as a maximum of four measurements after starting therapy are
obtained. On the other hand, because testosterone concentrations were unaffected by this treatment, observed changes in PSA likely reflect direct tumor kill. PSA reduction was observed in all but 1 patient, whose PSA increased 4% on treatment. The PSA reduction over time is summarized in Table 3.

**Initial Operative Outcome.** Pathological outcome at surgery is summarized in Table 4. Negative margins were obtained in 16 of 21 (76%, 95% CI, 52–92%) patients. Postoperative PSA was <0.2 ng/ml in 14 of 21 (67%, 95% CI, 43–85%) of patients. The rate of detectable PSA after surgery is consistent with the pathological stage of the patient population. Elevated PSA after surgery has been associated with both locally advanced disease and with the subsequent development of metastases (22, 23). In one study, an elevated postoperative PSA (>0.5 ng/ml) was detected in 61% of cases with extracapsular extension, but only 13% of patients with organ confined prostate cancer (23). In our study, extracapsular disease was detected in 12 of 21 cases (48%). It is therefore not surprising that 33% had a detectable PSA after surgery.

None of the patients had a pathological complete response, although 1 patient with Gleason 4/4 adenocarcinoma in seven of eight biopsy cores had an 88% reduction in PSA and had an estimated tumor volume of 0.2 ml in a 38-g prostate specimen.

**DISCUSSION**

The combination of 35 mg/m² docetaxel with 4 mg/m² mitoxantrone administered weekly on a 3 of 4-week schedule is the planned Phase II regimen based on the results of this Phase

### Table 3  
Prostate-specific antigen (PSA) reduction by cycle of therapy

A negative number indicates an increase in serum PSA (n = 21).

<table>
<thead>
<tr>
<th>Cycle</th>
<th>2 mg/m² (n = 3)</th>
<th>3 mg/m² (n = 3)</th>
<th>4 mg/m² (n = 14)</th>
<th>5 mg/m² (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% PSA reduction, median (range)</td>
<td>19 (−16 to 66)</td>
<td>33 (2 to 83)</td>
<td>43 (−4 to 88)</td>
<td>41 (−4 to 88)</td>
</tr>
</tbody>
</table>

* Two patients started treatment at the 5 mg/m² dose level but had their dose reduced to 4 mg/m² once the maximum-tolerated dose was determined. The toxicity experience of these patients at each of the dose levels they received is shown separately.
Table 4 Operative outcome (n = 21)

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2a</td>
<td>1</td>
</tr>
<tr>
<td>T2b</td>
<td>2</td>
</tr>
<tr>
<td>T2c</td>
<td>6</td>
</tr>
<tr>
<td>T3a</td>
<td>2</td>
</tr>
<tr>
<td>T3b</td>
<td>2</td>
</tr>
<tr>
<td>T3c</td>
<td>6</td>
</tr>
<tr>
<td>T4a</td>
<td>2</td>
</tr>
<tr>
<td>Node positive</td>
<td>6</td>
</tr>
</tbody>
</table>

Surgical Gleason Score

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>8–10</td>
<td>8</td>
</tr>
</tbody>
</table>

Negative margin | 16 (76%) |

Prostate-specific antigen <0.2 ng/ml | 14 (67%) |

I trial. The regimen was generally well tolerated with <10% of patients discontinuing therapy because of toxicity before completing the planned four cycles of therapy. As expected, hematological toxicity was dose limiting for the combination. This treatment regimen was not associated with an increase in observed perioperative morbidity. Also, unlike other regimens that include hormonal therapy, this combination did not increase the difficulty of the surgery because of periprostatic desmoplasia.

This study was not designed to measure efficacy of therapy. Only preliminary comments about treatment effects are therefore possible. Because this regimen did not include hormonally active agents and preservation of serum testosterone concentrations was confirmed, changes in PSA likely reflect antineoplastic effects. The nearly universal reduction in serum PSA is encouraging.

The initial surgical results are also encouraging. Seventy-six percent of patients who received at least one cycle of chemotherapy had negative surgical margins. This result compares favorably to previously reported outcomes of surgery alone in similar high-risk populations where only 52–54.5% of patients had negative surgical margins (2, 3). Surgical margin status in patients treated with surgery alone is an independent prognostic factor for prostate cancer recurrence (24, 25). Studies of neoadjuvant androgen deprivation have shown that improvements in surgical margin status after hormonal therapy do not translate into reductions in disease recurrence (2, 3). However, negative margins in this setting were likely low because of difficulties in recognizing tumor after a course of androgen deprivation (5). Ours is the first report that includes pathological outcome after neoadjuvant chemotherapy devoid of hormonally active agents. Additional studies are needed to determine whether surgical margin status in this setting has prognostic value.

Because this regimen combines two agents with significant activity in AIPC, testing it in more advanced prostate cancer may be of interest. Brief safety studies in AIPC should be carried out before or in conjunction with efficacy testing because the population studied here was younger and more fit than typical AIPC patients.

In this study, we developed a new regimen that combines weekly docetaxel with mitoxantrone. The delivery of this regimen before prostatectomy is feasible and is associated with acceptable toxicity. No patient experienced tumor progression by prostate examination and only one patient had a slight (4%) increase in serum PSA with treatment. Serum testosterone was not reduced with this therapy. Phase II evaluation of this regimen in the neoadjuvant setting is under way. Randomized studies will be required to determine the impact of this regimen on cancer recurrence. At the present time, it is not known if the addition of hormonal therapy to this regimen would be of value.

In the setting of surgery, only long-term androgen deprivation after prostatectomy in men who had nodal involvement has been shown to be beneficial (1). As more is learned about the efficacy of preoperative chemotherapy, it may be of interest to combine this approach with long-term postoperative hormonal therapy in future clinical trials.

REFERENCES

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