Weekly Neoadjuvant Ixabepilone on Surgical Feasibility and Clinical Outcomes in Locally Advanced High-Risk Prostate Cancer: A Phase II Clinical Trial

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Abstract: *Background*: Men diagnosed with locally advanced high-risk prostate cancer have up to a 40% risk of biochemical recurrence after prostatectomy. The authors performed a phase II trial of neoadjuvant weekly ixabepilone prior to radical prostatectomy.

Methods: Enrollment criteria included patients with high-risk prostate cancer defined by D'Amico criteria or high-volume Gleason 4+3 with a palpable nodule. Patients received ixabepilone 20 mg/m^2/week or 16 mg/m^2/week for 3 weeks every 28 days for 4 cycles followed by surgery 2-8 weeks later.

Results: Sixteen patients were enrolled with a mean age of 56.5 years (range 43-70). PSA values decreased by a mean of 47% in 14/16 men with patients receiving a mean of 8.25 weeks of treatment (range 2-12). Nine men experienced an adverse event requiring dose modification or premature cessation of chemotherapy. Pathologic staging in 9 patients showed T3a, 5 with T3b, and 1 with T2c disease; 8 had R1 disease and 2 demonstrated nodal involvement. Mean operative time, blood loss, and hospital stay were 189 minutes, 184 mL, and 1.5 days, respectively. At median follow-up of 32 months (range 15-45), 4 patients experienced biochemical recurrence.

Conclusions: Neoadjuvant weekly ixabepilone had a good PSA response and no increased surgical morbidity; however, a higher dose is associated with significant persistent neuropathy. There were no complete pathologic responses, but biochemical recurrence rate is low. Further assessment of time to treatment failure will require continued, planned follow-up to evaluate the long-term potential clinical benefit of this study.

Keywords: Ixabepilone, prostate cancer, neoadjuvant chemotherapy, taxanes, epothilone.

INTRODUCTION

It is estimated that 239,000 American men will be diagnosed with prostate cancer with a projected 29,700 deaths in 2013 [1]. Widespread screening with prostate specific antigen (PSA) has led to an increased detection of prostate cancer at an early stage, when the tumor is confined to the prostate and potentially curable [2]. Depending on clinical stage and Gleason score, potential definitive treatment modalities include radical prostatectomy, external beam radiation therapy, brachytherapy, proton beam radiation therapy, or cryotherapy. Radical prostatectomy has been the standard curative procedure for localized prostate cancer for several decades.

Men with adverse features of prostate cancer at diagnosis are at high risk of recurrence up to 40 percent [3]. Features that predict recurrence after prostatectomy include more aggressive tumor histology as reported by Gleason score, elevated PSA and increased stage. Kattan *et al.* has described a nomogram based on PSA, Gleason score and stage that is predictive of tumor relapse [4]. The 2010 updated AJCC system incorporates the pretreatment serum prostate specific antigen (PSA) and Gleason score to divide patients into prognostic categories. It is hypothesized that neoadjuvant therapy may decrease this risk of recurrence by treating micrometastatic disease.

Neoadjuvant or adjuvant hormone therapy does not improve survival in combination with prostatectomy [5, 6]. Furthermore, recent data demonstrates that exposure to hormonal therapy may be associated with increased cardiovascular mortality [7, 8]. Neoadjuvant chemotherapy prior to prostatectomy is a promising approach and has been investigated. Docetaxel, an active conventional agent in metastatic, castrate resistant prostate cancer, has been investigated with or without estramustine in patients with high-risk localized prostate cancer. Gleave reported that 2 of 64 patients had a pathologic complete response following 24 weeks of neoadjuvant docetaxel in combination with hormonal therapy [9]. Febbo reported that 58% of patients had a decline in PSA of >50% and decreased tumor volume on endorectal MRI, but no pathologic

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complete responses following 6 months of neoadjuvant docetaxel [10]. Similarly, Magi-Galluzzi *et al.* demonstrated no pathologic complete responses with neoadjuvant docetaxel [11]. Ross *et al.* evaluated docetaxel in combination with bevacizumab and reported no complete pathologic responses, a PSA decline ≥50% in 22% of patients however 49% of patients experienced biochemical recurrence at last follow-up [12].

Non-taxane based therapies have also been utilized. Pettaway *et al.* evaluated neoadjuvant ketoconazole, doxorubicin, vinblastine, and estramustine prior to radical prostatectomy. While activity was demonstrated, there were no pathologic complete responses, the positive margin rate was 17%, and lymph node metastases were seen in 37% of patients [13].

Epothilones are a newer class of tubulin polymerization agents obtained by fermentation of the myxobacteria *Sorangium cellulosum* [14]. The cytotoxic activities of the epothilones, like those of the taxanes, have been linked to stabilization of microtubules which results in mitotic arrest at the G2/M transition [15, 16]. Ixabepilone (BMS-247550) is a semisynthetic analog of the natural product epothilone B and was specifically designed to overcome the metabolic instability of its natural precursor. Ixabepilone is active against various taxane-resistant cell lines, including those overexpressing the multidrug resistance gene (MDR) or with mutations in the beta-tubulin gene. In nonclinical pharmacology studies, ixabepilone has demonstrated antitumor activity superior to paclitaxel in five paclitaxel-resistant tumors (four human tumor xenographs and one murine tumor) [17].

Phase II and III studies demonstrated the activity of ixabepilone in a variety of tumors including hormone-refractory prostate cancer. Study 081, a phase II, multicenter, single-arm study, was designed to assess the objective response rate (ORR) of single-agent ixabepilone 40 mg/m^2 in patients resistant to anthracyclines, taxanes, and capecitabine [18]. Ixabepilone demonstrated clinically meaningful activity in these heavily pretreated patients with resistant disease. Ixabepilone administered every 21 days has demonstrated activity in metastatic, castrate resistant prostate cancer [19]. Weekly ixabepilone may be better tolerated and achieve an intensive dose-dense neoadjuvant treatment without adverse effects on surgical or clinical outcomes.

METHODS

Patient Population

This study was designed as a single arm phase II trial conducted by the Brown University Oncology Research Group and Division of Urology. Enrollment criteria included patients with newly diagnosed, histologically proven adenocarcinoma of the prostate that were candidates for radical prostatectomy. High-risk disease was classified using D'Amico criteria or high-volume Gleason 4+3 with a palpable nodule [20]. Patients with histologic components with small cell, neuroendocrine, or transitional cell carcinomas were not eligible. Gleason sum scores were determined by central review based on biopsy or transurethral resection of the prostate (TURP) at the time of registration. Patients were eligible if they had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and with an expected survival of > 10 years [21]. Other eligibility criteria included adequate kidney and liver functions and hematologic parameters. Informed consent was obtained from all eligible patients.

Pretreatment Evaluation

Patients had a complete medical evaluation including a physical exam and digital rectal exam (DRE). Baseline studies included complete blood counts, liver function tests, electrolytes, creatinine, prostate specific antigen (PSA), and testosterone. Radiographic studies included staging CT or MRI of the abdomen and pelvis and a bone scan. Patients with radiographic evidence of metastatic disease or pelvic lymph nodes > 1 cm were excluded. Patients were excluded if they had pre-existing >Grade 1 neuropathy (motor or sensory) or hearing loss at study entry [21].

Treatment Plan

Enrolled patients were pre-medicated with an H1 and H2 antagonist 30-60 minutes prior to each treatment and received ixabepilone intravenously over 60 minutes. A maximum body surface area (BSA) of 2.2 m^2 was used to calculate chemotherapy dosing. Ixabepilone was administered weekly x 3, in 4 week cycles for an anticipated total of 4 cycles. Given an unexpected higher rate of grade 3/4 neuropathy in the first 8 patients receiving 20 mg/m^2/week, the ixabepilone dose was reduced to 16 mg/m^2/week following the same cycle schedule. Neoadjuvant treatment was not extended beyond 12 weeks to

administer doses missed due to toxicity. Patients were reassessed after completion of chemotherapy for surgical appropriateness. Prostatectomy was performed at 2-8 weeks after completion of neoadjuvant treatment to allow complete recovery from chemotherapy, as assessed by complete blood counts, electrolyte evaluation and physical exam.

Response Assessment

Antitumor response was evaluated by obtaining PSA values at enrollment, pre-prostatectomy, post-operatively then at least every 6 months during the post-operative period. Surgical outcomes including tumor margin status, and pathologic responses were assessed.

RESULTS

Patient Characteristics

Sixteen patients were enrolled with a mean age of 56.5 years (range 43-70) and median follow-up of 32 months (range 15-45). The majority of patients had cT1c (31.3%) or cT2b (25%) and a median baseline PSA of 8.02 ng/mL (range 4.4-99.4) (Table **1**).

Table 1: Clinical Stage of Enrolled Patients

Clinical Stage	N (%)
T1c	5 (31.3)
T2a	3 (18.8)
T2b	4 (25)
T2c	3 (18.8)
T3	1 (6.3)
Biopsy Gleason Score	
6	1 (6.3)
7	5 (31.3)
8	9 (56.3)
9	1 (6.3)
10	0
Enrollment PSA	
<4	0
4-10	11 (68.8)
10-20	1 (6.3)
>20	4 (25)

Treatment Delivery

The first eight patients received ixabepilone at 20 mg/m^2/week with a mean of 7.5 treatments (range 5-12). The next eight patients went on to receive ixabepilone at16 mg/m^2/week for a mean of 9 treatments (range 2-12). Nine men experienced an adverse event requiring dose modification or premature cessation of chemotherapy (Table **2**). Allergic reactions included: one anaphylactic reaction, one hypersensitivity reaction, and one patient developed angioedema. PSA values decreased by a mean of 47% in 14/16 men (Figure **1**) with a ≥50% decline in 44% of patients.

Table 2: Most Common Side Effects Triggering Dose Modification or Cessation of Neoadjuvant Chemotherapy

Toxicity requiring dose modification or cessation	N (%)
Neuropathy	5 (31.3)
Allergic Reaction	3 (18.8)
Diarrhea	1 (6.3)

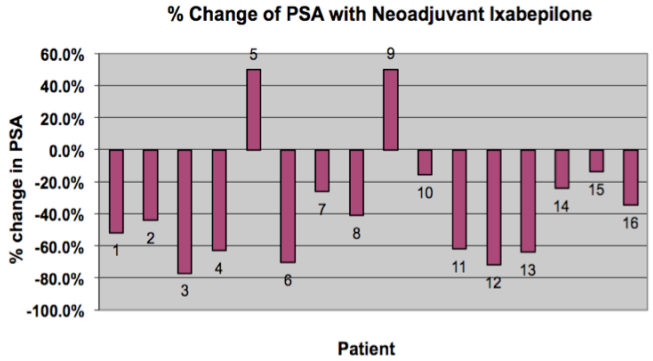

Figure 1: Percent PSA change after neoadjuvant chemotherapy completed.

Radical Prostatectomy

All 16 patients went to prostatectomy, one at an outside institution (thus with incomplete operative data). Preoperative PSA and pathologic staging for all 16 patients is noted in Table **3**.

Pathologic staging in 9 patients showed pT3a, 5 with pT3b, 1 with pT2c disease, 8 had R1 disease, and 2 demonstrated nodal involvement. There were no complete pathologic responses. Mean operative time, blood loss, and hospital stay were 189 minutes (range 150-360 minutes), 184 mL (range 100-750 mL), and 1.5 days (range 1-7 days), respectively for the 15 patients with full surgical data available. Two patients experienced a post-operative complication; one developed a DVT and another an anastomotic leak and ileus that resolved with conservative management.

Table 3: Post-Chemotherapy PSA and Pathologic Staging

Pre-Prostatectomy PSA	N (%)
<4	8 (50)
4-10	3 (18.8)
10-20	3 (18.8)
>20	2 (12.5)
Pathologic Stage	
T2c	1 (6.3)
T3a	9 (56.3)
T3b	5 (31.3)
Nodal Status	
Nx	1 (6.3)
N0	13 (81.3)
N1	2 (12.5)
Margin Status	
R0	8 (50)
R1	8 (50)

Adjuvant Therapy and Post-Treatment Follow-Up

All 8 patients with positive surgical margins were offered adjuvant radiation therapy. Due to patient preference, only 3 opted to receive IMRT, 2 of which received androgen deprivation for up to one year. Ten patients reported continued neuropathy at most recent follow-up: patients 1, 3-9, 11 and 13. At last review, 4 patients experienced biochemical recurrence, none of who had received adjuvant radiation or hormonal therapy. One patient with biochemical recurrence is receiving intermittent androgen blockade (Table **4**).

DISCUSSION

Our study demonstrates the feasibility of neoadjuvant ixabepilone for high-risk prostate adenocarcinoma. Use of neoadjuvant ixabepilone in our study did not increase surgical complications of robotic-assisted radical prostatectomy compared to institutional norms or accepted national standards. The

Table 4: Treatment Details, Pathologic Staging, and Adjuvant Treatments Offered for Each Patient Enrolled

Patient Enrolled	Patient Age	Race	Assigned starting dose	Enrollment PSA ng/mL	Weeks of Ixabepilone Treatment	Cause of Treatment Cessation	Preoperative PSA ng/mL	Pathologic stage	Postoperative PSA ng/mL	Adjuvant Treatment Offered	Adjuvant Treatment Accepted
1	56	A.A.	20 mg/m^2	6.6	7	Grade 3 Neuropathy	3.2	T3aN0R1	0.01	XRT	^XRT
2	66	C	20 mg/m^2	6.93	6	Allergic Reaction	3.9	T3aN0	<0.03	XRT	
3*	56	C	20 mg/m^2	44	4	Grade 3 Neuropathy	10.2	T3aN0R1	0.08	XRT	#IAD
4	57	C	20 mg/m^2	9.6	6	Grade 3 Neuropathy	3.6	T3aN0	0.03	XRT	
5	50	C	20 mg/m^2	99.4	7	Grade 3 Neuropathy	149	T3aN0R1	<0.01	XRT	
6	69	C	20 mg/m^2	9.1	12	Completed	2.72	T3bN0R1	0	XRT	
7	69	C	20 mg/m^2	6.6	4	Completed	4.9	T3aN0R1	0.2	XRT	
8*	54	C	20 mg/m^2	31.5	6	Grade 3 Neuropathy	18.7	T3aN0R1	0.2	XRT	
9*	43	C	16 mg/m^2	35.2	10	Rising PSA levels	52.9	T3bN1	<0.01	XRT	
10	53	C	16 mg/m^2	5.68	1	Allergic Reaction	4.8	T3bN1	<0.1	XRT	XRT + ADT x8 months
11	67	C	16 mg/m^2	4.95	12	Completed	1.9	T3aNx	<0.1	XRT	
12*	55	C	16 mg/m^2	9.9	12	Completed	2.8	T2cN0	0.01		
13	57	C	16 mg/m^2	6.3	12	Completed	2.3	T3aN0R1	0.1	XRT	
14	55	C	16 mg/m^2	18.4	5	Grade 2 Neuropathy	13.98	T3bN0R1	0.13	XRT	XRT + ADT x1 year
15	70	C	16 mg/m^2	4.4	4	Allergic Reaction	3.8	T3apN0	<0.04	XRT	
16	63	C	16 mg/m^2	6.4	12	Completed	4.2	T3bN0R1	0.1	XRT	

A.A. = African American, C = Caucasian.
*Patients with biochemical relapse.
^XRT = Radiation Therapy.
#IAD = Intermittent Androgen Deprivation Therapy (ADT).

vast majority of our patients experienced a decline in their PSA. In a recent systematic review article, many neoadjuvant chemotherapy trials demonstrated PSA response, however, the clinical significance of these responses remains unclear [22]. Of note, in spite of the high-risk profile of our patients a relatively small percentage (25%) has had a biochemical relapse at a median follow-up of 32 months (mean 30.25 months).

The rate of grade 3 peripheral neuropathy proved to be more prevalent and of lasting clinical effect than expected from previously published data evaluating weekly ixabepilone at 20 mg/m^2/week. This side effect led to a dose modification half way through accrual and limited the number of treatments received in the first half of patients. This study was not powered to detect differences in treatment response between the utilized doses.

Given the reported, although modest, activity of taxanes and the demonstrable activity of ixabepilone in docetaxel-resistant tumors, we hypothesized improved activity in high-risk locally advanced prostate cancer. In this study, similar to previously published data, there were no complete pathologic responses and the indication for adjuvant treatment was typical of high-risk disease. Despite an apparent minimal affect on measurable disease burden as indicated by the rate of extracapsular extension, positive surgical margins, and lymph node involvement, biochemical recurrence rate remains relatively low at time of most recent follow-up suggesting a possible benefit of neoadjuvant ixabepilone on micrometastatic disease.

In summary, our study demonstrates the safety of neoadjuvant ixabepilone and surgical feasibility following treatment. The role of neoadjuvant chemotherapy in high-risk prostate cancer requires ongoing randomized clinical trials.

DISCLOSURES

Dr. J.F. Renzulli II is a speaker for Dendrion, Sanofi-Aventis, Astellas, and Ferring pharmaceuticals and is a managing partner for PrimeBiomedical consulting firm. Dr. A.E. Mega is a speaker for Sanofi-Aventis and Astellas and has received research support from Sanofi-Aventis.

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