A phase II study of paclitaxel poliglumex in combination with transdermal estradiol for the treatment of metastatic castration-resistant prostate cancer after docetaxel chemotherapy

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Taxanes remain the only agents to extend survival in castration-resistant metastatic prostate cancer, but their impact on the natural history of this disease is modest. We sought to test the hypothesis that increased delivery of taxane chemotherapy to the tumor through the use of a macromolecular polymer–drug conjugate of paclitaxel modulated by estradiol could extend the utility of this class of drugs. Patients with metastatic adenocarcinoma of the prostate who progressed despite standard hormonal therapy and after docetaxel-containing chemotherapy were treated with transdermal estradiol (0.2 mg/24 h) for 4 weeks followed by the same dose of transdermal estradiol and paclitaxel poliglumex (PPX; 150 mg/m^2 intravenous) every 28 days. The primary objective was to determine the level of activity of the regimen measured using a fraction of patients who experienced a confirmed decline in serum prostate-specific antigen (PSA) of 50% or more. A two-stage phase II study designed to identify a response rate of $\geq$ 25% required three responders among 21 patients in the first stage. Twenty-one patients who received a median of two earlier chemotherapy regimens were enrolled in the trial between March 2007 and May 2008. During the estradiol-only treatment phase, no patient had a PSA decline in excess of 50% and lesser PSA declines that ranged from 8.8 to 34.1% were seen in five patients. No patients achieved a $\geq$ 50% PSA decline following the addition of PPX and there were no responses in measurable disease. The median time to progression was 4 weeks. In conclusion, this regimen of low-dose transdermal estradiol induction followed by PPX does not have activity in taxane pretreated patients with castration-resistant prostate cancer. ***Anti-Cancer Drugs*** **21:433–438 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

In 2004, two phase III randomized trials showed a modest survival benefit of docetaxel-based chemotherapy in the treatment of metastatic castration-resistant prostate cancer (CRPC) [1,2] and established the current standard of care. Increasing the delivery of taxane chemotherapy to the tumor may be a method to overcome taxane resistance and enhance the importance of this class of drugs in the treatment of prostate cancer. Paclitaxel poliglumex (PPX) is a macromolecular polymer–drug conjugate of paclitaxel designed to increase intratumoral drug delivery [3–5].

In clinical studies, several phase II and III clinical trials in ovarian and non-small-cell lung cancer (NSCLC) showed antitumor activity with PPX. Most notably, the combination of carboplatin with PPX showed tumor activity in a randomized trial of advanced NSCLC patients with Eastern Cooperative Oncology Group performance status (PS) 2 [3,6]. Compared with patients receiving carboplatin and standard paclitaxel, patients treated with PPX had a lower incidence of myalgias and arthralgias with a delayed time to neuropathy. However, there was no overall difference in survival [6]. In addition, a phase II trial in patients with heavily pretreated ovarian carcinoma showed tumor responses [7].

Taxane cytotoxicity is enhanced by estrogen in prostate cancer xenograft models [8]. Further, estradiol may enhance intratumoral release of free paclitaxel from the PPX macromolecule through interactions with cathepsin B. Cathepsin B is a lysosomal proteolytic enzyme that is frequently expressed in prostate cancer cells [9]. Serum levels of cathepsin B have been linked to prostate cancer progression [10]. The release of free paclitaxel from PPX is mediated by lysosomal enzymes, particularly cathepsin B [5,11]. Estradiol has been shown to upregulate cathepsin B in in-vitro systems [12,13]. In designing this

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study, we hypothesized that cotreatment with estradiol may enhance PPX activity by increasing intracellular cathepsin B-mediated release of free paclitaxel.

We also recognize that estrogens, including transdermal estradiol, have single-agent activity in CRPC [14,15]. However, the dose selected for this study was lower than doses shown to be active as single-agent therapy. This dose of estradiol was selected to maximize the estradiol-mediated upregulation of cathepsin B and intratumoral release of free paclitaxel, but was not designed to capitalize on the potential of estradiol to directly impact prostate cancer. We included a lead-in treatment period that allowed us to distinguish between the direct antitumor activity of estradiol and the activity of the combination.

The dose and schedule of estradiol selected for this study have not been studied earlier. Studies of transdermal estradiol in patients used a higher dose (0.6 mg/day) when the intent was estradiol-based hormonal therapy for prostate cancer [14,16]. When the therapeutic target was hot flash treatment, low-dose estradiol was used (0.05–0.10 mg/day) [17].

The dose for this trial was selected to exceed normal estradiol concentrations in premenopausal women (thought to be sufficient to modulate cathepsin B), but to be less than required for a direct anticancer effect (to avoid confounding the results).

The dose of PPX was based on experience in other cancers. In patients with NSCLC, a dose of 175 mg/m^2 every 3 weeks was well tolerated with rare grade 3–4 neutropenia and a 4% incidence of grade 3 neuropathy [18]. Single-agent studies in late-stage ovarian cancer patients who had received extensive earlier taxane therapy, identified a dose of 175 mg/m^2 as well tolerated for hematologic toxicity, but associated with a higher-than-acceptable rate of neuropathy. Thus, a dose of 135–150 mg/m^2 was suggested for further trials in relapsed ovarian cancer [19]. For this study, a dose of 150 mg/m^2 with every 4-week administration was chosen because the patient population was heavily pretreated with taxanes and thought to be less able to tolerate a more intensive dosing schedule.

Patients and methods

Objectives

The primary objective was to determine the level of activity of the combination of PPX and estradiol. Activity was measured using the fraction of patients who experienced a confirmed decline in serum prostate-specific antigen (PSA; defined as a 50% reduction in serum PSA confirmed by a second serum PSA at least 4 weeks later). Secondary objectives were to characterize the toxicity of the regimen, to describe the response rate in measurable disease, time to disease progression, time to death, and examine blood concentrations of estradiol and bone turnover markers and correlate these with response.

Eligibility

Patients with metastatic adenocarcinoma of the prostate, who progressed despite standard hormonal therapy and after docetaxel-containing chemotherapy, were eligible. Although metastatic disease was required, it was not required that metastases meet criteria for measurable or evaluable disease per RECIST criteria. Earlier therapy with at least two 3-weekly doses or 6 weekly doses of docetaxel, discontinued for any reason, was required. Prior combinations of docetaxel with estramustine or biologic agents were allowed. Standard antiandrogen washout was required when applicable. Patients were required to have an Eastern Cooperative Oncology Group PS 0–2, serum testosterone concentration less than 50 ng/dl, and life expectancy of greater than 3 months. Required laboratory studies included neutrophil count ($\geq$ 1500/mm^3), platelet count ($\geq$ 100 000/mm^3), serum creatinine $\leq$ 1.5 times the upper limit of normal (ULN), total bilirubin $\leq$ 1.5 times ULN, and aspartate transaminase/alanine aminotransferase $\leq$ 2.5 times ULN. Exclusion criteria were significant peripheral neuropathy (NCI CTCAE v3.0 grade 2 or higher), a second active malignancy except adequately treated nonmelanoma skin cancer or other noninvasive or in-situ neoplasm, significant active concurrent medical illness or infection, significant cardiovascular illness defined as New York Heart Association class III or intravenous congestive heart failure, unstable angina, myocardial infarction within 6 months, acute deep venous thrombosis, or acute pulmonary embolism, known or suspected brain metastases, earlier investigational therapy within the past 28 days, treatment with radiotherapy within the past 28 days or treatment with strontium-89 or samarium-153 therapy within 56 days, and earlier therapy with paclitaxel. Written informed consent was obtained from all patients. The study was approved by the institutional review boards at Oregon Health and Science University and the University of California, San Francisco Comprehensive Cancer Center.

Pretreatment evaluation

At baseline, patients were assessed by a physician history and physical examination. Complete blood count, serum chemistry panel including calcium and phosphorus, serum PSA, serum testosterone, lactate dehydrogenase, serum estradiol, bone-specific alkaline phosphatase, and urinary *N*-telopeptide were completed within 28 days of starting the estradiol lead-in period.

Treatment

Patients began with estradiol (0.2 mg/24 h) delivered using 7-day estradiol patches (Climara, Bayer HealthCare Pharmaceuticals, Wayne, New Jersey, USA). During the lead-in, PSA was monitored every 2 weeks for the first 8 weeks and then every 4 weeks. After 4 weeks of

estradiol, the patients began treatment with the combination unless their serum PSA had declined by more than 10%. Patients with a PSA decline of more than 10% continued estradiol monotherapy for up to 12 weeks or longer if their PSA declined by 50% or more within 12 weeks. Patients with clinical evidence of disease progression discontinued lead-in therapy and started active therapy with the two-drug combination immediately. Patients were assessed by whole body bone scan and computed tomography scan of the abdomen and pelvis, before the initiation of PPX therapy.

Patients then received PPX (150 mg/m^2 intravenous infusion) through peripheral vein or central line over 10–20 min on day 1 of every 28-day cycle. Estradiol therapy continued at the same dose.

Monitoring

Every 4 weeks during combination therapy, adverse events were assessed when a physical exam was performed, and complete blood count with differential, PSA, serum chemistry profile including liver tests, calcium, and phosphorus were obtained. After the first two cycles, serum estradiol, bone-specific alkaline phosphatase, and urinary *N*-telopeptide were collected. A computed tomography scan of the abdomen and pelvis was obtained every 8 weeks if measurable disease was present at baseline. Radionuclide bone scan was obtained every 16 weeks.

Dose reductions

It was planned to discontinue estradiol treatment for the following drug-related toxicities: angina, cholecystitis, and gynecodynia or gynecomastia, which are unacceptable to the patient. PPX dose delay was planned for absolute neutrophil count ($< 1500/\mu l$), platelets ($< 75\,000$), or ongoing nonhemotologic toxicities greater than grade 2 until resolution to grade 1 or 0. Any delay greater than 3 weeks resulted in removal from study therapy. The dose of PPX was reduced for any of the following toxiticies: febrile neutropenia (fever $\geq 38.5^{\circ}C$ when absolute neutrophil count is $< 1000/\mu l$), grade 4 neutropenia lasting for more than 7 days, grade 3 or 4 thrombocytopenia, any grade 2 neuropathy, and any drug-related clinically significant grade 3 or 4 nonhematologic toxicity except manageable nausea, vomiting, gynecomastia, gynecodynia, and fatigue. In addition, dose reduction was planned in the event of dose delays in two consecutive cycles. Up to two dose reductions were allowed, to dose levels of 135 and 110 mg/m^2.

Statistical methods

This study design was one of a single-arm two-stage phase II clinical trial according to the optimal criteria of Simon's two-stage design with a 10% significance level and 90% power [20]. For the purposes of this study, a PSA response rate of 10% was considered poor whereas that of 25% was considered promising. In the first stage, at least three responders of the 21 patients enrolled were required to continue to the second stage. Response was defined as a 50% reduction in serum PSA confirmed by a second serum PSA at least 4 weeks later. A total of 50 patients were to be accrued to the entire study with a minimum of eight responders required to recommend further study of the regimen.

Results

Patient characteristics

Twenty-one patients enrolled in the trial between March 2007 and May 2008. Baseline patient characteristics and earlier therapies are shown in Table 1. Notably, this was a relatively heavily pretreated group with a median of two earlier chemotherapy regimens (range 1–5). The prevalence of cancer-related pain was 86%, also indicating the relative adverse patient selection to this trial. Enrollment was stopped at the end of the first stage because of inadequate activity.

Treatment delivery and activity

Estradiol lead-in

Of the 21 patients treated in the study, 17 completed the entire 4-week estradiol lead-in period before progressing.

Table 1 Baseline patient characteristics

Characteristics	
Number enrolled	21
Median age, years (range)	71 (48–80)
ECOG performance status	
0	4 (19%)
1	12 (57%)
2	5 (24%)
Bony metastasis	20 (95%)
Cancer-related pain	18 (86%)
Soft Tissue metastasis	13 (62%)
Lymph nodes	8 (38%)
Visceral organ	4 (19%)
Soft tissue mass	5 (24%)
Serum PSA, median (range)	234.6 (15.0–3671.8)
Serum lactate dehydrogenase, median (range) ($n=20$)	202.5 (119–601)
Hemoglobin, g/dl, median (range)	11.5 (9.5–13.9)
Prior therapies	
Local therapy	
Prostatectomy	8 (38%)
Radiation to prostate	8 (38%)
Salvage radiotherapy	3 (14%)
Brachytherapy	2 (10%)
Number of prior hormonal therapy regimens	
1	1 (5%)
2	6 (29%)
3	7 (33%)
4 or more	7 (33%)
Number of prior chemotherapy regimens	
1	9 (43%)
2	8 (38%)
3 or more	4 (19%)
Number of nonchemo, nonhormonal investigational regimens	
1	3 (14%)
2	1 (5%)
3 or more	0
Prior palliative radiation	11 (52%)

Three patients had PPX therapy started earlier as a result of clinical progression and one patient received radiation (considered progression) before the completion of 4 weeks of estradiol. No patient had a PSA decline in excess of 50% during the estradiol lead-in and lesser PSA declines were seen in five patients and ranged from 8.8 to 34.1%.

Paclitaxel poliglumex delivery

The median number of cycles delivered was 2 (range 1–8). Only five patients received more than two cycles. Seventeen patients discontinued therapy for cancer progression. Two patients had treatment discontinued because of an adverse event. One developed cholecystitis, possibly related to estradiol, the other developed a gastric ulcer and thrombocytopenia. He had preexisting grade 1 thrombocytopenia. One patient was removed per investigator discretion (mental and PS decline). One patient was removed as a result of referral to a hospice.

Response to paclitaxel poliglumex and estradiol combination therapy

No patients achieved $\geq 50\%$ PSA decline on PPX and estradiol combination therapy. Potentially, clinically meaningful disease stabilization, defined as the absence of progression at 16 weeks, was seen in two patients. Of the 12 patients with measurable disease at baseline, only six remained on the study long enough to obtain follow-up scans. Among the six patients for whom follow-up scans were available, no patients responded (three stable, three progression). The median time to disease progression was 28 days (95% CI 26–30 days). The median overall survival was 7.8 months (95% CI 4.8–10.8 months).

Toxicity

All 21 patients were evaluable for toxicity. There were no treatment-related deaths. As shown in Table 2, the most common adverse events of any severity were anemia, lymphopenia, fatigue, nausea, vomiting, hyponatremia, and aspartate transaminase elevation. One patient with preexisting grade 1 thrombocytopenia experienced grade 4 thrombocytopenia; two patients had grade 4 anemia and one patient experienced grade 4 hyperbilirubinemia likely because of cholecystitis.

Correlative studies

Serum estradiol increased from a mean of 14.5 (range 6–51) to 105.3 pg/ml (range 17–340 pg/ml) during the estradiol lead-in and 206.7 pg/ml (range 20–528 pg/ml) during combination therapy ($P < 0.01$). Mean bone-specific alkaline phosphatase was 56 µg/l (range 7–279.5 µg/l) at baseline. Mean bone urinary *N*-telopeptides were 115.2 mmol (range 14–772 mmol) BCE at baseline. We did not detect a statistically significant change in either bone-specific alkaline phosphatase or urinary *N*-telopeptides with therapy.

Table 2 On-study toxicity (excluding unrelated)

Event	Grade 1	Grade 2	Grade 3	Grade 4
Blood				
Hemoglobin decreased	1	4	2	2
Leukopenia	2	1		
Lymphopenia	3		3	
Neutrophil count decreased		1		
Platelet count decreased	2		1	1
Constitutional symptoms				
Fatigue	4		2	
Fever	1			
Cardiac				
Hypotension	1			
Dermatology				
Rash	2	1		
Gastrointestinal				
Anorexia	1	2	1	
Constipation	4	1		
Diarrhea	4			
Dyspepsia	1			
Dysphagia		1		
Nausea	5	4	1	
Vomiting	3	2	2	
Hemorrhage/bleeding				
Gastric hemorrhage			1	
Hepatobiliary/pancreas				
Cholecystitis			1	
Infection				
Urinary tract NOS			1	
Lymphatics				
Edema limbs	1	1		
Metabolic/laboratory				
Alanine aminotransferase increased			1	
Alkaline phosphatase increased	1	1		
Aspartate aminotransferase increased	10		1	
Bicarbonate, serum low	1			
Creatinine increased	1			
Hyperbilirubinemia	1			1
Hyperglycemia	3	1		
Hyperkalemia	2			
Hypoalbuminemia	5			
Hypocalcemia	3	2		
Hypokalemia	3	1		
Hyponatremia	6			
Hypophosphatemia		2	1	
Musculoskeletal				
Muscle weakness	1			
Neurology				
Confusion		1		
Memory impairment	1			
Peripheral sensory neuropathy	2			
Speech disorder			1	
Pain				
Abdominal pain		1		
Pain – other		1		
Pulmonary				
Dyspnea	2			
Pneumonia			1	
Sexual/reproductive function				
Breast pain	4			
Gynecomastia		4		

NOS, not otherwise specified.

Discussion

Although well tolerated, this regimen of low-dose transdermal estradiol and PPX did not have activity in taxane pretreated patients with CRPC. The patients enrolled in this study were heavily pretreated and suffered from relatively advanced disease as noted by a high prevalence of pain, visceral disease, and reduced PS at baseline.

This was particularly evident in the fact that several patients had disease progression during the 4-week lead-in period with the estradiol patch. We cannot determine whether the regimen would have been more active in a more favorable group of patients.

The estradiol lead-in period proved unnecessary as no patients responded to this dose of estradiol. As the lead-in period represents 4 weeks without effective therapy, we would recommend against this strategy in future studies.

When compared with standard paclitaxel, the administration of PPX is considerably simpler. Standard paclitaxel must be administered over 3 h with premedications to avoid the adverse effects associated with the cremophor formulation. In contrast, PPX is administered over 20 min, without premedications.

The regimen was well tolerated. In particular, hematologic toxicity was quite modest. One interpretation of this finding is that the dose and schedule of PPX selected for this trial were less than optimal and either a higher dose or a shorter dosing interval may have been more desirable. We did not examine PPX pharmacokinetics (PK), but while we hypothesized that estradiol may enhance the release of the active paclitaxel molecule in the cell, we know of no reason to suspect that the addition of estradiol accelerated systemic drug clearance. Although PK analyses were not conducted in this study, earlier comparisons of PPX PK in men and women showed similar PK suggesting no major effect of circulating estrogen on PPX PK.

In addition, the underlying hypothesis that estradiol increases cathepsin B in the tumor microenvironment, while attractive, was unable to be tested in this setting. A more thorough study of the role of cathepsin B and its interactions with estrogens may be of use in the development of alternate strategies of chemotherapy delivery.

Interestingly, Amato *et al.* [21] recently reported the preliminary results of a similar effort that examined PPX on the same schedule or every 21 days alone and in a subsequent subset of patients with transdermal estradiol. The response, measured by PSA, was seen in four of 29 patients. Two of these patients had received taxanes earlier, as opposed to this trial, in which all patients had received at least one earlier taxane, with 57% of patients having two or more earlier chemotherapy regimens. At the same time, toxicity was much more pronounced with seven of 29 patients experiencing grade 3 or higher neutropenia. At the last report, this trial was continuing to enroll patients using every 3-week dosing of PPX with transdermal estradiol. Thus, this study should provide further insights into the potential of this combination at a higher dose intensity of PPX.

Although the Amato results reported to date are somewhat more encouraging than ours, neither study has seen a level of activity necessary to have significant promise in advanced prostate cancer. Recently, satraplatin failed to improve survival [22] after reporting a 25% PSA decline rate and a median time to progression of 11.4 weeks in CRPC patients who had earlier received chemotherapy [23]. These results suggest that a more robust level of activity is needed to give us the confidence that novel agents studied in chemotherapy pre-treated CRPC patients have sufficient disease activity to warrant randomized phase II or phase III studies. On the basis of our results, we cannot recommend further studies of PPX in CRPC patients who have been treated with docetaxel. Despite this, given its excellent tolerability and ease of administration, further consideration may be given to the role of this and similar agents in the taxane-nave patient population.

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