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PHASE II STUDIES

Phase II study of KOS-862 in patients with metastatic androgen independent prostate cancer previously treated with docetaxel

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Summary Based on the pre-clinical spectrum of activity in taxane-resistant cell lines, we evaluated KOS-862 (epothilone D; 12,13-desoxyepothilone B) as second-line chemotherapy in androgen-independent prostate cancer.

Thirty-eight men with metastatic androgen-independent prostate cancer and evidence of progression following docetaxel-based chemotherapy were treated with KOS-862, 100 mg/m^2 (maximum of 240 mg) i.v. weekly for 3 weeks, repeated every 4 weeks. The primary objective for this study was to determine the antitumor activity, measured by PSA decline by more then 50% confirmed 4 weeks later.

Two patients (5.3%, 90% CI 1–16%) met criteria for confirmed PSA decline. While both of these patients had previously been treated with docetaxel, neither had confirmed docetaxel-refractory disease. None of the 24 patients with measurable disease had a confirmed partial response. Seventy-three percent of patients had an adverse event leading to dose delay, reduction, or treatment discontinuation. Neurological toxicity and fatigue predominated. Seventeen patients (44.7%) had treatment related grade 3 neurological adverse events including peripheral sensory neuropathy (n=4, 10.5%), ataxia (n=3, 7.9%), peripheral motor neuropathy (n=1, 2.6%), involuntary muscle contractions (n=1, 2.6%) and neuropathic pain (n=1, 2.6%). One subject (2.6%) had a grade 4 treatment peripheral motor neuropathy.

Further study of this dose and schedule of KOS-862 in this patient population cannot be recommended due to both lack of activity and excessive toxicity.

Keywords Prostate cancer · Docetaxel

Background

Chemotherapy has recently been recognized as useful in the management of advanced prostate cancer that is unrespon-

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sive to hormonal manipulation. After mitoxantrone with prednisone was established as a palliative regimen, [1] docetaxel with prednisone was shown to improve survival, as well as pain control and quality of life over mitoxantrone plus prednisone [2]. This advance was modest, however, since survival improvement was relatively brief and the median time to disease progression was approximately six months. There remains an urgent need for new agents to treat patients who have already been treated with docetaxel.

KOS-862 (epothilone D; 12,13-desoxyepothilone B) is a cytotoxic macrolide capable of causing mitotic arrest by stabilizing tubulin polymerization. KOS-862 has demonstrated in vitro cytotoxic activity in a panel of human cell lines, equipotent to that of paclitaxel. KOS-862 is more potent than paclitaxel in p-glycoprotein overexpressing cell lines that demonstrate multiple drug resistant activity [3]. KOS-862 has also been shown to be active in the androgen-independent PC-3 human prostate cancer cells with IC_{50} of 0.0128 μM [4]. In vivo, KOS-862 has shown significant antitumor activity in a range of xenograft models, including those that are resistant to paclitaxel [3].

The dose limiting toxicity for KOS-862 in phase I studies has been neurologic including both central and peripheral neurologic toxicity. Approximately 75% of patients enrolled in phase I studies experienced at least one neurologic toxicity. Based on the pre-clinical spectrum of antitumor activity, particularly activity in taxane-resistant cell lines, we evaluated KOS-862 as second-line chemotherapy in androgen-independent prostate cancer.

Methods

Patients

Eligible patients had histologically confirmed adenocarcinoma of the prostate with radiographically documented metastases and evidence of progression on standard androgen deprivation therapy and following treatment with a docetaxel-containing regimen. Progression was defined as either PSA progression defined by consensus criteria, [5] or objective disease progression. One of the PSA values or the imaging studies showing objective progression must have been at least 4 weeks after flutamide discontinuation or 6 weeks after bicalutamide or nilutamide discontinuation. Patients could be enrolled if their disease progressed at any time following docetaxel-based chemotherapy. Patients who met progression criteria and had previously received docetaxel-containing chemotherapy for metastatic prostate cancer were eligible. Other inclusion criteria were: ECOG performance status ≤ 2, age ≥ 18 years, testosterone ≤ 50 ng/dl, hemoglobin ≥ 8 g/dl, neutrophil count ≥ 1.5×10^9/l, platelet count ≥ 75×10^9/l, serum creatinine ≤ 2.0 mg/dl, serum bilirubin ≤ 1.8 mg/dl, aspartate aminotransferase (AST) ≤ 2.5 × upper limit of normal (ULN) (≤ 5×ULN in case of hepatic metastasis), and serum prostate specific antigen (PSA) ≥ 5 ng/ml. All adverse events caused by prior chemotherapy, surgery or radiotherapy must have resolved to NCI-CTCAE grade ≤ 1, and a minimum of 3 weeks must have passed since the last receipt of chemotherapy, radiotherapy, surgery, or any investigational agent (8 weeks for radiopharmaceuticals).

Patients were excluded from the study if they had any pre-existing neuropathy of CTCAE grade ≥ 2, or if they had a documented hypersensitivity reaction CTCAE grade ≥ 3 to prior therapy containing Cremophor. Patients were ineligible if they had treatment with a second-line chemotherapy regimen for metastatic disease, however prior adjuvant, neoadjuvant, or radiosensitization chemotherapy did not affect eligibility. Patients were also excluded for known CNS metastases, leptomeningeal metastases requiring steroids, a known personal or family history of congenital long QT syndrome, or any medical conditions that, in the investigator's opinion, would impose excessive risk to the patient were also excluded from the study. The study was approved by Institutional Review Boards at all participating institutions and written informed consent was obtained from all patients before any study-specific procedures were performed.

Objectives

The primary objective for this study was to determine the antitumor activity of KOS-862, measured by PSA decline, [5] in patients with hormone resistant prostate cancer whose disease had progressed following docetaxel-based chemotherapy for metastatic disease. The secondary objectives included: safety, objective response rate in patients with measurable disease, time to tumor progression, time to PSA progression, duration of PSA and tumor response, and overall survival.

Additional pre-specified exploratory analysis were: the PSA decline rate in docetaxel-refractory patients (those progressing while receiving, or within 60 days of receiving, docetaxel-based therapy) vs. docetaxel-relapsed patients (progression > 60 days after the last dose of docetaxel-based therapy) and measured PSA velocity during the first 3 months of therapy as described by SWOG 9916 investigators [6].

Treatment

Patients were treated with KOS-862, 100 mg/m^2 (maximum body surface area of 2.4 m^2) administered by intravenous infusion over 90 min weekly for 3 weeks, repeated every 4 weeks until progression or unacceptable toxicity. All patients were pre-medicated with antihistamines (H1 and

Table 1 Patient demographic and baseline characteristics

Characteristic	*N*=38
Age (mean), years	69.2
Median (Range)	69.0 (56, 87)
Age Group [*n*, (%)]	
<65 years	10 (26.3)
≥65 years	28 (73.7)
ECOG Performance Status [*n*, (%)]	
0	11 (28.9)
1	21 (55.3)
2	6 (15.8)
PSA (ng/ml)[a]	
Median (Range)	103.2 (2.4, 2825)
Testosterone (ng/dl)	
Median (Range)	16.0 (0.0, 38.0)
Alkaline Phosphatase (u/l)	
Median (Range)	98.5 (40, 1016)
Serum LDH (u/l)	
Median (Range)	222.5 (127, 2011)
Hemoglobin, g/dl	
Median (range)	11.5 (9.3, 15.4)
Time Since Original Diagnosis (years)	
Median (range)	6.2 (1, 16)
Time Since Progression (years)	
Median (range)	0.4 (0, 14)
Prior Radiotherapy for Malignancy [*n*, (%)]	
Yes	28 (73.7)
No	10 (26.3)
Radiopharmaceuticals [n, (%)]	
Yes	1
No	37 (97.4)
No. of prior hormonal therapies for prostate cancer [*n*, (%)]	
1	3 (7.8)
2	12 (31.6)
3	11 (28.9)
≥4	12 (31.6)
No. of prior chemotherapy regimens for prostate cancer [b][*n*, (%)]	
1	32 (84.2)
2	6 (15.8)
Prior chemotherapy experience docetaxel[a] [*n*, (%)]	
Docetaxel refractory	8 (21.1)
Docetaxel relapsed	30 (78.9)

[a] At Screening (within 14 days prior to start of treatment)
[b] Any stage of disease

H2 blockers) and corticosteroids (methylprednisolone 40–80 mg IV *or* dexamethasone 10–20 mg IV) 30–60 min prior to the infusion of KOS-862.

Monitoring

Baseline evaluation included a physical examination, three electrocardiograms (done at least 5 min apart), toxicity evaluation, a neurological assessment and mini-mental status exam (MMSE), vital signs, complete blood count (CBC) with differential, prothrombin time and partial thromboplastin time (PT/PTT), serum chemistry, PSA, testosterone, urinalysis, bone scan and tumor measurements by computed tomography.

The physical examination, toxicity evaluation, neurological assessment, CBC with differential, PT/PTT, serum chemistry, PSA, and urinalysis were repeated prior to each 4-week treatment cycle. Tumor measurements and bone scans (if positive at baseline) were repeated every 8 weeks.

Statistical considerations

This study was a single-arm, open-label clinical trial, and was conducted at multiple centers throughout the United States. A response rate (proportion with at least 50% decline in serum PSA) of at least 25% was considered worthy of further study (alternative hypothesis), whereas a response rate of only 10% or less (null hypothesis) was

considered uninteresting. The sample size calculation was based on the Simon two-stage optimal design [7] with the aforementioned null hypothesis and alternative hypotheses, and selected two-sided type I error (α) = 0.10 and type II error (β) = 0.10. A maximum sample size of 50 evaluable patients was required, with a first-stage accrual of 21 patients. Accrual beyond stage one was permitted until evaluation of stage one patients was completed. Three or more PSA responses in stage one were required for the trial to accrue stage two fully, after which 8 or more confirmed PSA responses in 50 evaluable patients were required for KOS-862 to be considered worthy of further study in prostate cancer.

Results

Patient characteristics

The trial was stopped prematurely due to insufficient activity after 39 men were enrolled between January and October 2005. One patient withdrew prior to receiving any therapy. The remaining 38 patients are included in the intent-to-treat (ITT) analysis. Eight patients were not evaluable for efficacy analyses for the following reasons: received two or fewer infusions of KOS-862 without documented disease progression or death (n=6, 15.8%), did not have a confirmatory PSA level for response/progressive disease at a minimum of a 4 week interval (n=4, 10.5%), or violated clinically significant inclusion/exclusion criteria (n=2, 5.2%). Results for the entire ITT (n=38) dataset are reported. Pretreatment characteristics are summarized in Table 1. All patients had progressed following initial docetaxel-based chemotherapy for metastatic disease. Seven patients had active peripheral neuropathy prior to study entry (either peripheral motor or sensory neuropathy).

Treatment

Eighty-two treatment cycles were administered. The median number of cycles was 2.0 (range 1, 7). Most subjects were treated for one cycle (n=10, 26.3%) or two cycles (n=19, 50%). The median dose intensity was 68.9 mg/m^2/week (range: 49, 75). The median relative dose intensity was 91.9% (range: 66, 100). Seventeen patients (44.7%) had a dose delay; for 11 patients (28.9%), the delay was due to toxicity. Six patients (15.8%) had a dose decrease as a result of recalculated BSA (n=3, 7.9%) or toxicity (n=3, 7.9%).

Toxicity

All patients experienced a treatment related adverse event. Six patients (15.7%) experienced a serious adverse event considered to be related to the study drug. 73% (n=28) of patients had an adverse event leading to dose delay, dose reduction, or treatment discontinuation. Eighteen patients (47%) experienced an adverse event that led to patient discontinuation of study drug.

The most frequently observed treatment-related adverse events that occurred in ≥ 10% of patients, graded by using the maximum grade for a patient, are indicated below in Table 2.

As expected from the phase 1 experience, neurological toxicity and fatigue predominated. Most neurological events were assessed by the investigator as having a maximum intensity of grade 1–2. These grade 1–2 events

Table 2 Summary of most frequently experienced treatment related adverse events (>10 %) by MedDRA preferred term (n=38)

Preferred term	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Number patients (%)
Peripheral sensory neuropathy	16 (42.1)	11 (28.9)	4 (10.5)	0 (0)	31 (81.6)
Fatigue	5 (13.2)	7 (18.4)	8 (21.1)	0 (0)	20 (52.6)
Nausea	11 (28.9)	4 (10.5)	0 (0)	0 (0)	15 (39.5)
Dizziness	9 (23.7)	3 (7.9)	0 (0)	0 (0)	12 (31.6)
Diarrhoea	8 (21.1)	3 (7.9)	0 (0)	0 (0)	11 (28.9)
Dysgeusia	5 (13.2)	4 (10.5)	0 (0)	0 (0)	9 (23.7)
Anorexia	3 (7.9)	3 (7.9)	2 (5.3)	0 (0)	8 (21.1)
Flushing	7 (18.4)	1 (2.6)	0 (0)	0 (0)	8 (21.1)
Vomiting	6 (15.8)	2 (5.3)	0 (0)	0 (0)	8 (21.1)
Arthralgia	5 (13.2)	1 (2.6)	0 (0)	0 (0)	6 (15.8)
Balance disorder	4 (10.5)	2 (5.3)	0 (0)	0 (0)	6 (15.8)
Hypoaesthesia	4 (10.5)	2 (5.3)	0 (0)	0 (0)	6 (15.8)
Constipation	3 (7.9)	2 (5.3)	0 (0)	0 (0)	5 (13.2)
Memory impairment	5 (13.2)	0 (0)	0 (0)	0 (0)	5 (13.2)
Oedema peripheral	4 (10.5)	1 (2.6)	0 (0)	0 (0)	5 (13.2)
Ataxia	0 (0)	1 (2.6)	3 (7.9)	0 (0)	4 (10.4)

MedDRA Medical Dictionary for Regulatory Activities (Version 7.1)

included peripheral sensory neuropathy, ataxia, dizziness, dysgeusia, balance disorder, hypoaesthesia, memory impairment, paresthesia, headache, restless leg syndrome and disturbance in attention. Seventeen patients (44.7%) had treatment related neurological adverse events with a maximum intensity of grade 3. These included peripheral sensory neuropathy (n=4, 10.5%), ataxia (n=3, 7.9%), peripheral motor neuropathy (n=1, 2.6%), involuntary muscle contractions (n=1, 2.6%) and neuropathic pain (n=1, 2.6%). One subject (2.6%) had a treatment related grade 4 peripheral motor neuropathy.

Efficacy

The primary efficacy variable was PSA decline. Only two patients (5.3%, 90% CI 1%–16%) met criteria for confirmed PSA decline. Both of these patients were in the docetaxel-relapsed group. No patients who were docetaxel-refractory had a confirmed PSA decline. No confirmed partial responses in patients with measurable disease (n=24) were observed.

The median time to tumor progression, defined as time from the first day of treatment to the first documentation of progressive disease based upon imaging studies, was 9.0 weeks (90% CI 7.9–19.4 weeks with 45.8% patients censored) in efficacy evaluable patients. Median overall survival was 32 weeks.

Other analyses

PSA velocity was measured based on the first 3 months of therapy [6]. Specifically, mean PSA velocity was 96.2 ng/ml/mo (Standard deviation 215.4, N=38). PSA velocity values varied considerably, ranging from 0.11 ng/ml/mo to 1007.99 ng/ml/mo. These data may prove useful for design of future clinical trials in this patient population.

Discussion

KOS-862 did not have sufficient antitumor activity to recommend further evaluation in this patient population. Treatment was also associated with frequent severe neurotoxicity (45%), particularly toxicity affecting the central and peripheral nervous system. The incidence of severe neurologic toxicity exceeded that expected from the phase I experience and from prior phase 2 single-agent trials in metastatic breast [8] and lung cancer [9]. In these studies, the incidence of grade 3 or higher neurologic toxicity was 21% and 22% respectively. The reasons for higher than expected severe neurotoxicity in our study are not known.

This study does not allow us to confidently comment about the viability of microtubules and the mitotic spindle as a therapeutic target in docetaxel-treated AIPC patients. The high frequency of treatment discontinuation due to toxicity may have contributed to the low level of activity observed. The median progression-free survival duration observed in this study was similar to those reported in both arms of the randomized study of prednisone with or without satraplatin, [10] and in studies of mitoxantrone and epothilone B in similar patient populations. We cannot determine if a lower dose of KOS-862 that would presumably have produced less toxicity would have yielded more encouraging results.

Other approaches to targeting microtubules in this patient population, including novel taxanes and epothilone class agents are under investigation. Preliminary data from studies of other epothilones suggest that this class of agents has important activity in prostate cancer. In chemotherapy-naïve patients, ixabepilone has been studied in two multi-institutional phase II studies. PSA decline rates of 48% [11] and 33% [12] were reported and activity in measurable disease was seen.

It is less clear if this class of agents has important activity in docetaxel-treated AIPC patients, as the activity levels seen in these patient populations to date are of marginal interest. Ixabepilone therapy was associated with a 17% PSA decline rate in patients whose androgen-independent prostate cancer progressed on or within 60 days of docetaxel-based chemotherapy [13]. Treatment with EPO906 was associated with a 22% PSA decline rate in 37 patients that included both chemotherapy-naïve and chemotherapy pre-treated AIPC patients [14]. Studies of several members of this class of drugs in prostate cancer are ongoing.

Grade 1 or 2 neurotoxicity was reported in 19% of patients and no grade 3 or higher neurotoxicity was noted in the preliminary report of EPO906 in advanced prostate cancer [14]. Severe neurotoxicity was reported in 17% of prostate cancer patients treated with ixabepilone [12]. It is possible, therefore, that the frequency and severity of neurotoxicity varies across members of this drug class, but comparisons of this sort across small phase II studies are not reliable and additional studies would be needed to definitively comment on this question.

Overall survival in this challenging population remains poor highlighting the need for new therapies and the development of new agents capable of treating this lethal form of prostate cancer remains a top priority for the field.

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