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A modular phase I study of lenalidomide and paclitaxel in metastatic castration-resistant prostate cancer following prior taxane therapy

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Abstract

Purpose—Lenalidomide, a highly-potent immunomodulatory derivative of thalidomide, potentiates the action of paclitaxel *in-vitro* against prostate cancer cell lines in co-culture with mononuclear cells. A modular Phase I study of lenalidomide and paclitaxel in men with metastatic castration-resistant prostate cancer (CRPC) was conducted to assess PSA-kinetics with lead-in lenalidomide and the feasibility of the combination.

Methods—Men with metastatic CRPC with prior taxane chemotherapy were planned for single-agent “lead-in” lenalidomide for 21/28 days at dose levels: –1 (5mg), 0 (10mg), +1 (15mg), +2 (20mg), +3 (25mg); followed by lenalidomide at the same dose and schedule in combination with weekly intravenous paclitaxel 100mg/m² over 3 hours on Days 1, 8, 15 every 28 days utilizing a 3+3 dose-escalation design.

Results—Dose-limiting toxicity was observed in 4/6 patients with combination therapy at the 10mg dose-level and 3/6 patients at the 5mg dose-level of lenalidomide respectively. These included Grade 3 neutropenia precluding planned paclitaxel therapy (n=3), grade 3 gastrointestinal toxicity (n=2), chest pain (n=1) and pulmonary embolism (n=1). With lead-in lenalidomide, 2 patients with lymph-node dominant CRPC had a PSA-decline and regression in lymph node disease respectively. Two of 7 evaluable patients had PSA declines by 50% with combination therapy. Progression-free survival was 13 weeks (range 4–35 weeks).

Conclusions—The high DLT rates observed with lenalidomide and weekly paclitaxel require exploration of alternate dose-schedules of the combination in the second-line setting of CRPC. These early observations suggest distinctive toxicity and efficacy outcomes from thalidomide in combination with paclitaxel.

Keywords

Lenalidomide; prostate cancer; second-line; metastases

Introduction

Thalidomide, a drug with immunomodulatory and anti-angiogenic activity, possesses modest single agent activity in castration-resistant prostate cancer (CRPC) (1) and enhanced the activity of front-line docetaxel chemotherapy in a randomized Phase II trial (2). In the second-line setting, thalidomide appeared to reverse taxane-resistance in a subset of patients when combined with paclitaxel and estramustine (3). However, the toxicity profile of the combination was significant when doses of thalidomide exceeded 200mg daily and the median duration of disease control was no better than 3 months.

Based on a hypothesis that the highly-potent immunomodulatory derivatives (IMiDs) of thalidomide (4) offers equivalent or superior biological activity with a lower toxicity profile than thalidomide, the feasibility of lenalidomide in combination with paclitaxel in CRPC with prior taxane therapy was explored in a modular 3+3 Phase I design (5). The primary objective of the study was to estimate the maximum tolerated dose of lenalidomide in combination with fixed-dose paclitaxel.

Methods

Patient Population

Men with CRPC must have exhibited evidence of disease progression on prior docetaxel or paclitaxel based therapy as evidenced by 2 consecutive increments in PSA over 4 weeks; an increase by 30% in measurable disease or new lesion by clinical or radiological criteria, or worsening symptoms attributable to disease progression. An Eastern Cooperative Group performance status of ≤ 2 , serum testosterone level of ≥ 50 ng/ml and anti-androgen withdrawal when relevant, were required. Additionally, an absolute peripheral granulocyte count of $\geq 1,500/\text{mm}^3$, platelet count of $\geq 100,000/\text{mm}^3$, serum bilirubin ≤ 1.5 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2 X the upper limits of normal, and calculated creatinine clearance of ≥ 40 cc/min. Exclusion criteria included New York Heart Association (NYHA) Class III/IV congestive heart failure, arterial or venous thromboembolic events in the last 6 months, prior lenalidomide therapy, oxygen-dependent lung disease, hepatic cirrhosis, $\geq$ grade 2 peripheral neuropathy, or known human immunodeficiency virus infection. The study was performed in accordance with institutional review board guidelines and signed informed consent was obtained in all patients.

Baseline and follow-up evaluations—At baseline, a complete history, physical examination, complete blood count (CBC), serum chemistries including bone-specific and total alkaline phosphatase, ALT, AST, total bilirubin, creatinine, testosterone, thyroid-stimulating hormone, PSA, urine N-telopeptide, Chest X-ray, radionuclide bone scan and computed tomography of the abdomen and pelvis was performed.

Prior to the start of each cycle of combination therapy, histories, physical examinations and laboratory studies were updated and radiological studies repeated after the 1st cycle of combination therapy and thereafter every 2 cycles.

Therapeutics—Patient cohorts were planned for treatment at five dose levels of lenalidomide on days 1–21 of a 28 day cycle and a standard dose of weekly paclitaxel 100mg/m² infused over 3 hours on Days 1, 8, 15 of a 28-day cycle in a modular Phase I design (5). Prior to initiation of combination therapy, each patient was to be treated at the assigned dose level with a “lead-in” 28-day cycle of single agent lenalidomide given on days 1–21 as with combination therapy. Dose-levels of lenalidomide were 5mg (level –1), 10mg (Level 0), 15mg, 20mg, 25mg, 30mg and 35mg (Level +5). Patients who ingested 80% of the prescribed lenalidomide during the lead-in period and had no dose-limiting toxicity were to be judged compliant and eligible to proceed to combination therapy. Patients who experienced dose-limiting toxicity during the lead-in period would not be eligible to proceed to combination therapy and would be discontinued from study. If three or more patients at any dose level of lenalidomide experienced dose-limiting toxicity during the lead-in period, further enrollment at that level was to be discontinued. Dose level –1 was to be evaluated if the experience with dose level 0 exceeded the toxicity rate specified above. Drug inventory and patient diaries were utilized to confirm drug-compliance.

Prior to the initiation of the first cycle of combination therapy, patients were required to have adequate bone marrow function (defined as a platelet count 100,000/mm³ and an absolute neutrophil count 1500/mm³) and all lenalidomide-related adverse events resolved to Grade 2. Patients were to be treated until progression of disease or the emergence of dose-limiting toxicity.

Supportive care: Premedications to be administered intravenously prior to paclitaxel administration included: diphenhydramine 25–50 mg intravenously, cimetidine 300mg intravenously; dexamethasone 8 mg intravenously one hour prior to paclitaxel or dexamethasone 8mg orally 12 and 6 hours before paclitaxel. Hematopoietic growth factors were not permitted during the lead-in period and first cycle of combination therapy, unless specifically required to manage dose-limiting toxicity. All patients were recommended low-dose warfarin 2mg daily and enteric aspirin 81 mg daily for thromboembolic prophylaxis.

Evaluation and management of toxicity: All toxicities encountered during the study were evaluated by NCI Common Toxicity Criteria version 3.0 and recorded prior to each course of therapy. Dose-Limiting Toxicity (DLT) was defined as Grade 2 non-hematological toxicity that is uncontrolled and intolerable, Grade 3 or higher non-hematological toxicity (excluding alopecia), Grade 4 hematological toxicity, neutropenic fever with elevated temperature (defined as ANC < 1000 and temperature 101 degrees Fahrenheit), inability to administer the full 21 days of lenalidomide in the lead-in cycle or all 3 full doses of paclitaxel and/or the full 21 days of lenalidomide due to toxicity in cycle one, or inability to receive the scheduled Day 1 dose of Cycle 2 combination therapy within 7 days due to treatment related toxicity. For the purposes of evaluating the maximum tolerated dose (MTD) of lenalidomide with paclitaxel, Cycle 1 DLT alone was considered. Patients who experienced DLT in cycle one of combination therapy were permitted to continue therapy if toxicity was manageable by dose modification.

Dose modifications: On Day 8 and 15 of combination therapy both lenalidomide and paclitaxel therapy were withheld for Grade 2 non-hematological toxicity that was

uncontrolled and intolerable, for Grade 3 or 4 hematological or non-hematological toxicity. Upon resolution to tolerable Grade 2 toxicity or less, therapy at reduced dose was permitted. For similar toxicity after one dose reduction, additional dose-reduction in both drugs was required. If such toxicity persisted for 2 weeks, patients were withdrawn from study. Lenalidomide dose-reductions were planned in 5mg increments to a minimum of 5mg daily. Paclitaxel dose-reductions were to level -1 (85mg/m²) and level -2 (70mg/m²).

Definitions of response and progression of disease—For measurable lesions, RECIST criteria were utilized for definitions of objective response and progression. Three consecutive increases in PSA (minimum of 1ng/ml) to 25% above nadir or baseline, measured at least two weeks apart; or the appearance of an unequivocally new lesion on bone scan, worsening symptoms attributable to disease progression qualified as progression. In patients with PSA progression alone without clinical or radiological evidence of disease progression, continued therapy on study at the discretion of the treating physician was permitted.

Statistical Design—The primary objective of the study was to estimate the maximum tolerated dose (MTD) of oral lenalidomide in combination with paclitaxel. Up to 6 dose levels of lenalidomide were to be considered as described earlier. A 3+3 design for dose escalation was employed. Dose-escalation was planned on DLT frequencies observed during the lead-in period as well as those observed through the first 28 days of combined paclitaxel and lenalidomide therapy. A DLT rate of 33% was defined as the MTD. If 2 DLT events were observed at a dose-level, then the MTD was exceeded and further accrual to that dose-level or dose-escalation was not permitted. Secondary objectives included a description of qualitative and quantitative toxicity, PSA and bone marker outcomes with lead-in lenalidomide and objective response, PSA-declines, bone marker outcomes and freedom-from-progression with combination therapy.

Results

Patient characteristics

Ten men, 2 African-American and 8 Caucasian, median age of 68 years (range, 54–76) were accrued to the study. All patients had received prior taxane-based therapy and up to 3 prior regimens of chemotherapy. All patients had bone metastases with a median baseline hemoglobin of 11g/dl (range, 8.1–12.3), serum alkaline phosphatase 173 IU/L (range, 83–616), serum lactate dehydrogenase 649 IU/L (range, 256–1589). All patients had bone metastases and 8/10 had > 10 lesions on bone scan. Eastern Co-operative Oncology Group Performance status was 0 in 3 patients and 1 in 7 patients.

Toxicity

Two dose-levels of lenalidomide (10mg and 5mg) proved evaluable. Six patients were treated at lenalidomide 10mg daily and three at lenalidomide 5mg daily. After a study modification based on toxicity observations with lenalidomide dose level of 5mg daily, the starting dose of paclitaxel was reduced; one patient treated with weekly paclitaxel at 80mg/m² and lenalidomide at 5mg daily. An administrative decision to halt the study was

made following lengthy administrative delays imposed by the Food and Drug Administration to modify consent procedures relating to putative teratogenicity of lenalidomide.

Adverse events with lead-in lenalidomide

While a total of 32 adverse events, 24 Grade 1, 7 Grade 2 and 2 Grade 3, were documented among 9 patients during the 28 days of lenalidomide monotherapy. Grade 2 events were observed as non-troublesome and included constipation, edema, rash, leucopenia and anemia. A Grade 3 anemia was attributed to advanced metastatic disease. Another patient experienced typical anginal chestpain three days after initiation of lenalidomide. He underwent cardiac catheterization and was found to have severe occlusive coronary artery disease and was removed from study. This event was categorized as a DLT.

Adverse events with combination therapy

DLTs by dose-level for Cycle 1 of combination therapy are described in Table 1. A disparate set of adverse events defined dose-limiting toxicity within the dose-levels that were evaluated. Table 2 includes the most frequent qualitative and quantitative toxicities observed over time on-study among the 10 patients. There were 2 events of Grade 4 bone pain that were attributed to disease progression. Miscellaneous Grade 3 adverse events included bone pain (n=1), abdominal pain (n=1), infections (n=3), hyperglycemia (n=1), chest pain (n=1), dehydration (n=1) and muscle weakness (n=1). There were no episodes of febrile neutropenia. Four patients were removed from study for toxicity events, the remainder for progressive disease.

PSA outcomes during lead-in period and combination therapy

Of 9 patients evaluable for PSA outcomes with lead-in therapy, one patient with a lymph-node dominant distribution of disease had a PSA-decline < 50% of baseline. The overall median change in PSA over 4 weeks was 2.0 fold. Of 7 patients who received at least one cycle of combination therapy 4 had PSA declines, 2 by 50% of baseline (cycle 1 day 1), including one patient with lymph-node dominant disease who had a marked regression in a lymph-node mass in the neck during lead-in therapy.

Objective responses with combination therapy

Of 3 patients with measurable disease at baseline, 2 were evaluable on-study after at least one cycle of combination therapy. Both patients had minimal regression of multiple neoplastic lymph-nodes.

Bone-marker outcomes

Of 9 evaluable patients, 2 had >50% decline in urine N-telopeptides from baseline during lead-in lenalidomide monotherapy. No bone-specific alkaline phosphatase declines >10% were noted during lead-in therapy. This pattern did not change with combination therapy.

Progression-free and overall survival

Of 10 patients, three were removed from study for toxicity at 4, 7 and 8 weeks; one by patient choice at 34 weeks for fatigue; one for physician choice at 10 weeks for PSA-based concerns of progression and the remaining 5 patients for disease progression from 8–35 weeks. The median progression-free interval was 13 weeks. Median overall survival was 28 weeks; range, 13–52 weeks with 2 patients alive at last follow-up at 34 and 47 weeks.

Discussion

The results of this Phase I study indicate early dose-limiting toxicity of a disparate manner in a group of patients with advanced metastatic CRPC in the second-line setting. Grade 3 neutropenia that limited scheduled delivery of weekly paclitaxel accounted for nearly half of the dose-limiting toxicity. Alternate dose-schedules of paclitaxel in combination with lenalidomide may provide additional insights into tolerance of this combination in the second-line disease state of metastatic CRPC.

Although the number of observations is limited, there is some evidence that the toxicity and activity of lenalidomide alone and in combination with paclitaxel may be distinct from thalidomide. Only 2/7 men with combination lenalidomide and paclitaxel therapy had PSA-declines that reached the 50% decline threshold. These are in contrast to the 76% PSA-decline rate and objective responses in 45% of patients with measurable disease receiving thalidomide in combination with paclitaxel and estramustine in the second-line setting (3). With thalidomide, seven of 8 patients (88%) with prior disease progression on docetaxel-based therapy and two of 6 patients with prior paclitaxel failure (33%) had a >50% decline in PSA. However the overall median progression-free survival with the thalidomide combination was 13 weeks, similar to that observed with lenalidomide in this study. With thalidomide in combination, toxicities were principally fatigue, edema, dizziness, somnolence, constipation and venous thrombosis, the latter despite prophylaxis with mini-dose warfarin and aspirin. In this study, Grade 3 toxicities with lenalidomide in combination with paclitaxel were dominated by uncomplicated neutropenia and gastrointestinal distress.

A provocative observation from this study was the singular observation of rapid regression of a neck mass during lead-in lenalidomide, 50%-decline in PSA with subsequent combination lenalidomide and paclitaxel therapy and a progression-free interval of 35 weeks. Another patient with lymph-node dominant disease had a PSA-decline <50% with lenalidomide monotherapy during the lead-in but unfortunately was removed from study for an intervening deep venous thrombosis, prior to additional clinical observations on efficacy. There were no PSA decline in bone-dominant disease during lead-in with lenalidomide monotherapy although one patient with bone-dominant disease had a 50% PSA-decline with combination paclitaxel and lenalidomide therapy lasting 34 weeks before the patient decided to discontinue therapy. Effects on bone-markers were restricted to declines in urine N-telopeptides alone in 2/9 evaluable patients during lead-in lenalidomide monotherapy.

In summary, modified dose-schedules of lenalidomide and paclitaxel will be required to assess the feasibility and toxicity of this regimen in CRPC in the second-line setting. Whether lenalidomide possesses unique activity in the lymph-node dominant phenotype of

metastatic CRPC is a matter of speculation but these early observations with lower dose-levels of lenalidomide suggest differential biological effects from thalidomide in bone-dominant CRPC. Lenalidomide is 50–100 times more potent than thalidomide in stimulating the proliferation of T-cells following primary induction by T-cell receptor activation; 50–100 times more potent than thalidomide in augmenting the production of interleukin-2, interferon-gamma, granulocyte-macrophage colony stimulating factor and interleukin-3 following activation of peripheral blood mononuclear cells or T-cells (6). The specific role of these pathways toward control of CRPC in the distinctive microenvironment of the neoplastic lymph-node requires elucidation. A Phase I-II study of lenalidomide and attenuated doses and infusion durations of paclitaxel, with correlative studies embedded, is currently underway in men with lymph-node dominant castration-resistant metastatic disease defined as radiographic evidence of multiple (≥ 2) or bulky (5 cm diameter) lymph node metastases with < 2 discrete sites of bone involvement.

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Table 1

Frequency and type of dose-limiting toxicity (DLT) by lenalidomide dose-level

Cohort	Patients (n)	Lenalidomide dose-level	Paclitaxel dose-level	DLT frequency	DLT (type/grade)
1	3	10mg	100 mg/m ²	1	Diarrhea/Vomiting: Grade 3
2	3	10mg	100 mg/m ²	3	Neutropenia: Grade 3 Neutropenia: Grade 3 Chest pain: Grade 3
3	3	5mg	100 mg/m ²	2	Infection/neutropenia: Grade 3 Dehydration/infection: Grade 3
4	1	5mg	80 mg/m ²	1	Pulmonary embolism: Grade 4

Table 2

Type and frequency of toxicity events by grade of severity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total
Anemia	9	11	2	0	22
Neutropenia	9	6	3	0	18
Thrombocytopenia	8	2	0	0	10
Diarrhea	7	2	1	0	10
Nausea/Vomiting	4	1	5	0	10
Constipation	4	2	0	0	6
Edema	5	2	0	0	7
Neuropathy	5	3	1	0	9
Thromboembolic	0	0	0	1	1
Transaminase	9	0	0	0	9
Fatigue	11	10	1	0	22
Rash	3	2	0	0	5
Dyspnea	0	0	1	0	1
Arrhythmia	1	0	0	0	1