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SHORT COMMUNICATION

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 (5 mg), 0 (10 mg), +1 (15 mg), +2 (20 mg), +3 (25 mg); followed by lenalidomide at the same dose and schedule in combination with weekly intravenous paclitaxel 100 mg/m^2 over 3 h 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 first-cycle combination therapy at the 10 mg dose-level and 3/6 patients at the 5 mg 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, two patients with lymph-node dominant CRPC had a PSA-decline and regression in lymph node disease, respectively. Two of seven evaluable patients had PSA declines by 50% with combination therapy. Progression-free survival was 13 weeks (range 4–35 weeks).
Conclusions The high dose-limiting toxicity 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

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Introduction

Thalidomide, a drug with immunomodulatory and anti-angiogenic properties, has modest single agent activity in castration-resistant prostate cancer (CRPC) [1] and was shown to enhance the activity of front-line docetaxel chemotherapy in a randomized Phase II trial [2]. In a Phase I–II study in the second-line setting, thalidomide appeared to reverse taxane-resistance when combined with paclitaxel and estramustine [3]. However, the toxicity profile of the latter combination was significant when doses of thalidomide exceeded 200 mg 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] offer 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. The purpose of the modular design was to obtain preliminary insights into the efficacy and toxicity of single-agent lenalidomide at varying dose-levels and link these to outcomes with combination therapy. While men with CRPC currently receive docetaxel as a front-line chemotherapy regimen, paclitaxel was chosen as a template for a second-line combination regimen as the taxanes may not be fully cross-resistant.

Methods

Patient population

Men with CRPC must have exhibited evidence of disease progression after prior docetaxel- or paclitaxel-based therapy as evidenced by two 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 $\leq$2, serum testosterone level of $\leq$50 ng/ml and anti-androgen withdrawal when relevant, were required. Additionally, an absolute peripheral granulocyte count of $\geq$1,500/mm^3, platelet count of $\geq$100,000/mm^3, serum bilirubin $\leq$1.5 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) $\leq$2$\times$ the upper limits of normal, and calculated creatinine clearance of $\geq$40 cc/min were required. 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 two 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 100 mg/m^2 infused over 3 h 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 5 mg (level $-$1), 10 mg (Level 0), 15, 20, 25, 30 and 35 mg (Level +5). Patients who ingested $\geq$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 previously. 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 $\geq$100,000/mm^3 and an absolute neutrophil count $\geq$1,500/mm^3) and all lenalidomide-related adverse events resolved to $\leq$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 300 mg intravenously; dexamethasone 8 mg intravenously 1 h prior to paclitaxel or dexamethasone 8 mg orally 12 and 6 h 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 2 mg 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 Terminology 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 <1,000 and temperature ≥101° Fahrenheit), inability to administer the full 21 days of lenalidomide in the lead-in cycle or all three 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 days 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 5-mg increments to a minimum of 5 mg daily. Paclitaxel dose-reductions were to level −1 (85 mg/m^2) and level −2 (70 mg/m^2).

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 1 ng/ml) to ≥25% above nadir or baseline, measured at least 2 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 six doses, 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 two 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, two African-American and eight Caucasian, median age of 68 years (range, 54–76) were accrued to the study. All patients had received prior taxane-based therapy; a median of two (range 1–3) prior regimens of chemotherapy. All patients had bone metastases with a median baseline hemoglobin of 11 g/dl (range, 8.1–12.3), serum alkaline phosphatase 173 IU/l (range, 83–616), serum lactate dehydrogenase 649 IU/l (range, 256–1,589). Eight patients 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 (10 and 5 mg) proved evaluable. Six patients were treated at lenalidomide 10 mg daily and three at lenalidomide 5 mg daily. After a study modification based on toxicity observations with lenalidomide dose-level of 5 mg daily, the starting dose of paclitaxel was reduced; one patient treated with weekly paclitaxel at 80 mg/m^2 and lenalidomide at 5 mg 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 3 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. Grade 3 neutropenia events qualified as DLT as these prohibited planned retreatment with paclitaxel and lenalidomide at day 8 or 15. Table 2 includes the most frequent qualitative and quantitative toxicities observed over time on-study among the 10 patients. There were two 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 nine 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 seven patients who received at least one cycle of combination therapy four had PSA declines, two 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 three patients with measurable disease at baseline, two were evaluable on-study after at least one cycle of combination therapy. Both patients had minimal regression of multiple neoplastic lymph-nodes.

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

Bone-marker outcomes

Of nine evaluable patients, two 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 five patients for disease progression from 8 to 35 weeks. The median progression-free interval was 13 weeks. Median overall survival was 28 weeks; range, 13–52 weeks with two patients alive at last follow-up at 34 and 47 weeks.

Table 1 Frequency and type of dose-limiting toxicity (DLT) by lenalidomide dose-level

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

Discussion

The results of this Phase I study indicate early dose-limiting toxicity with low-dose lenalidomide and paclitaxel in a group of patients with advanced metastatic CRPC with significant prior chemotherapy exposure. 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 this disease state.

Although the number of observations is limited and subject to case-selection bias, there is evidence that the toxicity and activity of lenalidomide alone and in combination with paclitaxel is 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 eight patients (88%) with prior disease progression on docetaxel-based therapy and two of six 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 with combination therapy. There were no PSA declines in patients with 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 after front-line chemotherapy. Whether lenalidomide possesses unique activity in the lymph-node dominant phenotype of metastatic CRPC requires additional study; nevertheless, 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]. A modular Phase I-II study of lenalidomide with attenuated doses and infusion durations of paclitaxel is currently underway in men with lymph-node dominant castration-resistant metastatic disease defined as radiographic evidence of multiple ($\geq$2) or bulky ($\geq$5 cm diameter) lymph node metastases with <2 discrete sites of bone involvement. Clinical and translational observations from this study will provide insights into the biological effects of lenalidomide in the lymphadenopathic subset of CRPC.

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Conflict of interest statement None.

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