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A prospective clinical trial of lenalidomide with topotecan in women with advanced epithelial ovarian carcinoma

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Abstract

Background—Lenalidomide is an anti-angiogenic IMiD® immunomodulatory drug. The objective of this study was to determine the maximum tolerated dose (MTD), overall safety profile, and activity of oral lenalidomide in combination with topotecan in women with advanced epithelial ovarian or primary peritoneal carcinoma.

Methods—In this Phase I/II open-label, dose-escalation study, patients with histologically or cytologically confirmed advanced ovarian or primary peritoneal carcinoma with disease progression or recurrence following first-line therapy with a platinum agent and paclitaxel were eligible. The Phase I trial utilized a standard dose-escalation design to define the MTD and evaluate the safety profile of lenalidomide and topotecan. The starting doses were lenalidomide 5 mg, days 1–14, and intravenous topotecan 1.25 mg/m^2, days 1–5 of a 21-day cycle. Only the lenalidomide dose was escalated, in 5-mg increments up to 25 mg. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events. The Phase II portion was designed to evaluate the antitumor activity based on objective response rate of lenalidomide and topotecan.

Results—Five women with advanced epithelial ovarian carcinoma were enrolled, each receiving 5 mg oral lenalidomide and 1.25 mg/m^2 topotecan. Four patients discontinued because of dose-limiting toxicity, most commonly grade 4 neutropenia (n = 3). One patient discontinued because of lack of therapeutic effect. The study was terminated early for reasons of toxicity.

Conclusion—The addition of lenalidomide to topotecan is not a feasible drug combination in women with advanced epithelial ovarian carcinoma because of dose-limiting toxicity.

Keywords

Lenalidomide; Topotecan; Advanced epithelial ovarian carcinoma; Safety; Neutropenia

Introduction

Ovarian cancer is the leading cause of death from gynecological malignancies, and it is responsible for an estimated 14,000 deaths annually in the United States [1]. Primary treatment with platinum- and taxane-based regimens results in a 75% response rate [2]. Although the majority of these women develop recurrent disease, long-term therapy can

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improve survival in some patients. However, there is a need for new treatment options that can prolong the treatment-free interval while maintaining the woman's quality of life.

We have previously reported the results of a Phase II trial of thalidomide plus topotecan compared to topotecan alone in women with recurrent ovarian cancer [3]. The overall response rate was 47% among patients who received thalidomide plus topotecan versus 21% in those who received topotecan alone ($P = 0.03$). Lenalidomide (Celgene, Summit, NJ, USA) is an anti-angiogenic IMiD® immunomodulatory drug designed to have increased clinical activity in cancer patients with less toxicity. Our goal was to conduct a Phase I/II, dose-escalation study in women with advanced epithelial ovarian or primary peritoneal carcinoma to determine the maximum tolerated dose (MTD), overall safety profile, and activity of lenalidomide in combination with topotecan.

Patients and methods

Patients

This multicenter trial was initiated at three institutions, and appropriate regulatory approval was obtained from the relevant institutional review boards. After providing informed consent, women with histologically or cytologically confirmed advanced ovarian or primary peritoneal carcinoma with radiographic or clinical evidence of measurable disease (≥ 2 cm in diameter) were enrolled. To be eligible, women had to have disease progression or recurrence following first-line therapy with a platinum agent and paclitaxel plus an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were ineligible if they had any of the following: inadequate hematological counts [absolute neutrophil count (ANC) <1,500 cells/mm^3 or platelet count <100,000 cells/mm^3]; abnormal renal or hepatic function [serum creatinine >1.5 mg/dl, serum aspartate transaminase (AST) or alanine transaminase (ALT) >3.0 times the upper limit of normal, or serum total bilirubin >2.0 mg/dl]; more than one prior chemotherapy regimen (with the exception of patients with platinum-sensitive disease who were retreated with a platinum-containing regimen); prior grade ≥3 rash or any desquamating rash while taking thalidomide; prior grade ≥3 allergic reaction/hypersensitivity to thalidomide; use of any standard or experimental anticancer drug therapy within 28 days of the initiation of study drug; or known active hepatitis C.

Treatment plan

This Phase I trial utilized a standard dose-escalation design to define the MTD of lenalidomide and topotecan. The starting doses were oral lenalidomide 5 mg, days 1–14 and intravenous topotecan 1.25 mg/m^2, days 1–5 of a 21-day cycle. Lenalidomide dose was to be escalated in increments of 5 mg up to 25 mg, whereas topotecan was fixed at 1.25 mg/m^2. Five dose levels were planned with six patients enrolled in each level. The following escalation rules were used: (1) initially, six patients were to enter into a dose level; (2) if two or more of the initial patients experienced dose-limiting toxicity (DLT), then the MTD had been exceeded; and (3) if none or one of the initial patients experienced DLT, then subsequent patients were to be enrolled into the next higher dose level.

The MTD of lenalidomide and topotecan combination therapy was defined as the highest dose level at which no more than one of six patients experienced DLT. DLT was defined as any one of the following: (1) inability to deliver 14 doses of daily lenalidomide on days 1–14 in combination with topotecan due to toxicity (if doses were missed inadvertently, they could be given during the 7-day rest period); (2) grade ≥3 nonhematological toxicity (excluding alopecia); (3) grade ≥3 nausea, vomiting, or diarrhea despite receiving optimal symptomatic treatment; (4) febrile neutropenia (absolute neutrophil count <1,000 cells/mm^3 and fever >38.3°C), (5) platelet count <10,000 cells/mm^3; or (6) inability to initiate cycle 2,

day 1 of therapy due to toxicity. Patients at the lenalidomide 5 mg/day dose level who developed DLT during cycle 1 were to be discontinued from the study. Patients in subsequent dose levels that developed DLT during cycle 1 were to be allowed to continue study therapy after the doses of study drugs had been reduced. Patients who discontinued the study before the completion of the first cycle of study treatment for reasons other than DLT were to be replaced. The use of hematopoietic growth factors was not allowed during cycle 1 but was to be allowed during subsequent cycles.

During the Phase II part of this study, objective response rate was planned to be determined as means of antitumor activity of lenalidomide and topotecan. However, because of dose-limiting toxicity the study was terminated before entering the Phase II stage.

Assessment

At each visit, patients were evaluated by physical examination, complete blood count with differential, platelet counts, serum chemistries, CA 125 levels, and ECOG performance status. Patients were monitored for safety by evaluating laboratory data and adverse events on days 8 and 15 of cycle 1 and on day 1 of each subsequent cycle. Adverse events were graded using version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v. 3.0).

Statistical analysis

The data were summarized using descriptive statistics, frequency tabulations, graphs, and data listing as appropriate for each dose level in the stage. Data from all patients who received one or more doses of the drugs were incorporated into the safety analyses. Adverse events, vital sign measurements, clinical laboratory information, and electrocardiogram (ECG) interpretations were tabulated and summarized by regimen and phase. All toxicities were summarized by relative and absolute frequency, severity grade based on the NCI CTCAE v. 3.0, and relationship to treatment. Serious adverse events were listed separately.

Results

Five women with advanced epithelial ovarian carcinoma were enrolled in the first cohort (5 mg lenalidomide/fixed dose topotecan). The study was closed after these five patients were enrolled. All five women had stage III disease and had received prior therapies including a platinum agent and paclitaxel. Baseline demographics are summarized in Table 1.

Four patients discontinued the study because of DLT and one patient discontinued because of lack of therapeutic effect. The study was therefore terminated due to toxicity. The median time on study for these patients was 6.9 weeks (range, 3.1–11.1 weeks). Mean duration of drug exposure was 3.8 weeks (range, 1.9–8.1 weeks), and mean daily dose was 4.4 mg (range, 3.1–5.0 mg).

All five patients experienced at least one adverse event, most commonly neutropenia ($n = 5$) and thrombocytopenia ($n = 4$) (Table 2). Furthermore, all subjects experienced at least one grade 3 or 4 adverse event, and four subjects reported at least one adverse event that was suspected to be related to the study drug: neutropenia ($n = 3$), thrombocytopenia ($n = 2$), anemia ($n = 2$), fatigue ($n = 1$), and pulmonary embolism ($n = 1$) (Table 2).

Two patients had at least one serious adverse event: intestinal obstruction ($n = 1$) and pulmonary embolism ($n = 1$). Of these, only pulmonary embolism was suspected to be drug related. Four patients discontinued treatment because of grade 3 or 4 adverse events and one patient discontinued treatment because of lack of therapeutic effect. The most common adverse event leading to study drug discontinuation was grade 4 neutropenia ($n = 3$). Other

adverse events leading to study drug termination were grade 3 thrombocytopenia ($n = 2$), grade 4 pulmonary embolism ($n = 1$), and grade 3 anemia ($n = 1$). None of the patients died during the study or within 30 days of the last dose of the study drug. One patient died of progressive disease approximately 3 months after administration of the last dose of study drug.

Discussion

This Phase I/II, dose-escalation study was designed to determine the MTD and overall safety of oral lenalidomide administered on days 1–14 as combination therapy with topotecan 1.25 mg/m^2 on days 1–5 of a 21-day cycle in women with advanced epithelial ovarian or primary peritoneal carcinoma. This study was terminated after the enrollment of five patients because of excessive toxicity and an inability to determine the MTD. There was no dose escalation beyond the 5 mg/day lenalidomide dose. DLTs were grade 3/4 neutropenia, thrombocytopenia, anemia, and pulmonary embolism.

The treatment dosage and schedule for this study was chosen with the intention to minimize toxicities anticipated from therapy with lenalidomide and topotecan while maintaining drug efficacies. Lenalidomide is often given orally on days 1–21 of a 21-day cycle for the treatment of multiple myeloma. When administered in combination with a treatment regimen given on day 1 of a 21-day cycle, lenalidomide has been demonstrated to have better tolerability when decreasing the schedule to be given on days 1–14 of a 21-day cycle [4, 5]. When dosed at 1.5 mg/m^2 on days 1–5 of a 21-day cycle, topotecan is associated with significant toxicity from myleosuppresion. Several studies have shown that patients who are at high risk for toxicity, including those who were heavily pretreated or have received prior platinum regimens, have a reduced rate of grade 3/4 myelosuppression when topotecan is given with a reduced dose of 1.25 mg/m^2 on days 1–5 of a 21-day course [6, 7]. In efforts to decrease toxicity with the combination of topotecan and lenalidomide, we chose to administer lenalidomide orally on days 1–14 and topotecan 1.25 mg/m^2 on days 1–5 of a 21-day course.

A previous study has indicated that the addition of thalidomide to topotecan results in an improved overall response rate compared to topotecan alone (47% vs. 21%), with no differences in grade 3 or 4 toxicities between the two regimens [3]. This finding suggests that the addition of an anti-angiogenic drug, such as thalidomide, may be important in the treatment of ovarian cancer. Tumors are composed of a disorganized irregular vasculature containing permeable endothelial junctions, which impairs the penetration of chemotherapy agents into the tumor. A proposed mechanism of action of anti-angiogenic agents is that they induce normalization of these vessels to allow for improved delivery of traditional cytotoxic chemotherapy agents to the tumor, which may at least partly explain the improved response rates with the combination of thalidomide and topotecan.

The exact antitumor mechanisms of lenalidomide are unknown, but a number of postulated mechanisms include: (1) anti-angiogenic activity through the inhibition of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-alpha [8, 9], (2) immunomodulatory effects by stimulating T-cell proliferation [10–13], and (3) induction of apoptosis or G_1 cell-cycle arrest in multiple myeloma cells possibly overcoming drug resistance [14, 15]. There is likely a dual mechanism of action in which tumoricidal effects lead to direct tumor cell death and immunomodulatory effects keep the tumor in remission [16]. Additive antitumor effects have been described with the combination of lenalidomide and cytotoxic agents in solid tumors, particularly in combination with docetaxel in prostate cancer [17].

We were unable to continue enrollment after four of the five first subjects enrolled experienced DLT because of the safety criteria in the study protocol for termination of the study. The most common adverse events were grade 3 or 4 neutropenia (n = 5, 100%) and grade 3 or 4 thrombocytopenia (n = 3, 60%). Previous studies of topotecan as a single agent or in combination with non-cytotoxic agents have demonstrated high rates of myelosuppression. A phase I study of topotecan in combination with tensirolimus resulted in four of seven subjects with grade 3 neutropenia and three of seven subjects with grade 3 or 4 thrombocytopenia [18]. Our previous study of topotecan given as a single agent versus in combination with thalidomide showed minimal differences in rates of toxicity; however, the majority of subjects experienced myelosuppression, with grade 3 or 4 neutropenia occurring in 72% of the single-agent topotecan group and in 87% of the combination group. Granulocyte colony-stimulating factors were utilized in 35% of the single-agent topotecan group and in 41% of the combination group [3]. It is well known that when lenalidomide is used as a single agent in the treatment of multiple myeloma it is well tolerated, but the most common adverse events include myelosuppression and venous thromboembolic complications early in the course of treatment [16]. In previous studies of multiple myeloma, lenalidomide has shown superior efficacy over thalidomide; however, lenalidomide has an increased risk of hematological toxicity that is often easily resolved with dose reduction or granulocyte colony-stimulating factors [19, 20]. In this study, we attribute the high rate of myelosuppression primarily to toxicity from topotecan. Lenalidomide has a higher risk of hematological toxicity compared to thalidomide, and the addition of thalidomide to topotecan resulted in significant hematologic toxicity that led to discontinuation of the trial because of DLT in this pretreated patient population.

It is unclear whether combination therapy with lenalidomide and a less myelosuppressive cytotoxic chemotherapeutic agent could have a better toxicity profile in women with recurrent ovarian cancer. Both topotecan and liposomal doxorubicin are indicated for the treatment of advanced ovarian carcinomas refractory to prior platinum-based therapies. In a randomized Phase III clinical trial of women with recurrent epithelial ovarian cancer, liposomal doxorubicin (50 mg/m^2 as a 1-h infusion every 4 weeks) compared to topotecan (1.5 mg/m^2/day as a 30-min infusion daily for 5 days every 3 weeks) showed no difference in overall response rate (19.7% vs. 17.0%), progression-free survival (16.1 vs. 17.0 months), or overall survival (60.0 vs. 56.7 weeks) [21]. However, more hematological toxicities were associated with the topotecan arm. Adverse hematological events were seen in 90% of women in the topotecan arm, and 77% were grade 3 and 4 compared with 12% in the liposomal doxorubicin arm. These events led to significantly more frequent use of hematopoietic growth factors, blood transfusions, and dose modifications in the topotecan group compared to the liposomal doxorubicin group.

To address the question of whether lenalidomide would be better tolerated and whether it would be effective in combination with a less cytotoxic agent, we have initiated a Phase I/II trial of lenalidomide with liposomal doxorubicin in women with recurrent ovarian carcinoma.

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Table 1

Baseline characteristics

Patients *n*	5
Age, years	
Median	67
Range	40–74
Race, *n*	
White	4
Hispanic	1

Table 2

Hematological and nonhematological adverse events in five enrolled patients

Adverse event, *n*	Grade 1, 2	Grade 3, 4	Drug related[a]
Neutropenia	0	5	3
Thrombocytopenia	1	3	2
Anemia	1	2	2
Fatigue	1	0	1
Intestinal obstruction	0	1	0
Pneumonia	1	0	0
Pulmonary embolism	0	1	1
Pruritis	1	0	0

[a] Adverse events at least suspected to be related to study drug