A phase II study of lenalidomide in platinum-sensitive recurrent ovarian carcinoma

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Background: Lenalidomide has dual antiangiogenic and immunomodulatory properties and confirmed antitumor activity in hematologic malignancies. A phase II study investigating the safety and efficacy of continuous lenalidomide in recurrent ovarian cancer patients was initiated.

Patients and methods: Patients with histologically confirmed epithelial ovarian, fallopian tube or primary peritoneal carcinoma, with asymptomatic recurrence 6 months after prior therapy were treated with continuous oral lenalidomide (20 mg/day). The primary end point was to evaluate efficacy according to the rate of disease control at 4 months. Secondary objectives were progression-free survival (PFS) and safety.

Results: Most of the 45 patients enrolled and treated had serous histology (78%) and a single line of prior chemotherapy (73%). Median platinum-free interval (PFI) was 11.3 months (range 6.9–56.8). Clinical benefit at 4 months was 38% [95% confidence interval (CI) 23% to 53%]. A 50% disease control rate was reported in patients with a PFI >12 months versus 24% with PFI of 6–12 months (P = 0.023). Four patients had RECIST partial responses and 21 had stable disease. CA125 responses were reported in eight patients, including one complete response. Median PFS was 3.4 months (95% CI 2.4–4.4). Most frequent toxicity was hematologic, notably grade 3–4 neutropenia in 29% of patients, along with fatigue (69%), gastrointestinal toxicity (constipation 53%, abdominal pain 49%, diarrhea 38%, nausea/vomiting 36%) and thrombosis (11%). Eight patients withdrew due to related toxicity.

Conclusions: Lenalidomide shows interesting efficacy in late recurrent ovarian cancer patients. Toxicity was mainly hematologic, gastrointestinal and venous thrombosis. Future studies will evaluate combination of lenalidomide with chemotherapeutic agents.

Clinicaltrials.gov: NCT01111903.

Key words: CA125, CC-5013, lenalidomide, ovarian cancer, platinum-sensitive, recurrent

introduction

Currently the sixth most common cause of death in women [1], ovarian cancer represents a major therapeutic challenge to oncologists. The poor prognosis associated with this disease is mainly due to the high proportion of advanced stage cases at diagnosis (~70%), compounded by limited therapeutic options, with most patients relapsing after first-line therapy. With an overall 5-year survival rate of around 40%, this figure dropping dramatically in late-stage patients, alternative therapies are actively being sought. Carboplatin combination therapy has been the mainstay of management of platinum-sensitive recurrent cancers [2]. The shift of focus to targeted therapies unearthed several candidates with promising clinical outcomes [3, 4]; however, effective new drugs in relapsing ovarian cancer remain an unmet medical need.

Encouraging activity has been reported with the antiangiogenic immunomodulatory agent, thalidomide. Three small monotherapy studies in heavily pretreated ovarian and peritoneal carcinoma patients gave RECIST response rates of 7.7% to 18%, with CA125 reductions ≥50% in 33%–53% of patients [5–7]. However, results of a randomized phase III trial of thalidomide versus tamoxifen in patients with rising CA125 were disappointing in terms of efficacy and toxicity [8]. Lenalidomide (CC-5013) is a less toxic...
analogue which exhibits similar antiangiogenic and more potent immunomodulatory properties than those of the parent compound [9]. It stands apart from thalidomide with a different—but as yet undefined—mechanism of action and a better toxicity profile, notably in terms of neuropathy and constipation [10]. From an immunomodulatory standpoint, lenalidomide inhibits the production of proinflammatory cytokines, potently costimulates T cells which increases secretion cytokine levels, and enhances natural killer cell cytotoxicity [11]. In antiangiogenic models, it affects HIF-1α-mediated proliferation, endothelial cell migration mediated by VEGF, βFGF, and TNFα, as well as adhesion-mediated cellular connections.

Lenalidomide was granted FDA approval in 2006 as second-line or later therapy in association with dexamethasone in multiple myeloma patients. Clinical activity has also been reported as a single agent and combined with chemotherapy in solid tumor patients, including ovarian, prostate, thyroid, hepatocellular, and renal cell cancers [11]. Three dose schedules have been evaluated, two of which—25 mg daily for 21 days every 4 weeks and 10 mg daily—were well tolerated and resulted in antitumor activity [12]. The discontinuous schedule was used in a phase I study in recurrent ovarian cancer patients. Prolonged stabilizations (>6 months) were reported in 4 of the 11 assessable patients [13]. Continuous administration may be better adapted to lenalidomide’s anticipated dual antiangiogenic–immunomodulatory mechanism of action in solid tumors. Toloyna et al. have shown doses up to 20 mg daily are tolerable without drug-related dose-limiting toxicity [14]. The French Investigator Group for Ovarian and Breast Cancer (GINECO) initiated a phase II study to determine the efficacy and safety of continuous lenalidomide in patients with asymptomatic late recurrent ovarian cancer.

**patients and methods**

**patient population**

Eligible patients were over the age of 18 with histologically confirmed epithelial ovarian, fallopian tube or primary peritoneal carcinoma, with asymptomatic late recurrence (>6 months from the last dose of platinum) defined according to Gynecological Cancer Intergroup (GCIG) criteria as a confirmed doubling in CA125 counts relative to the upper limit of normal or nadir [15], with or without measurable disease and up to two lines of prior therapy (all platinum-based and at least one taxane-based). An Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic, renal, hepatic and coagulatory functions were also required. Patients with borderline or mixed histology tumors were excluded, as were patients having received radiotherapy or lenalidomide, having grade 2 or higher neuropathy, a history of heart failure (NYHA >2), arrhythmia, or a history within 6 months of gastrointestinal hemorrhage, gastrointestinal ulcer, myocardial infarction, or thromboembolism, with prior febrile neutropenia, grade 4 thrombocytopenia, a 2-week delay due to hematologic toxicity or transfusion with prior chemotherapy, rash with desquamation following prior thalidomide or equivalent, or of child-bearing potential. All patients gave written informed consent.

**study design and treatment**

In this multicentric phase II study, patients received lenalidomide (Revlimid®, Celgene Corporation Summit, NJ) as a continuous dose of 20 mg/day orally until progression or unacceptable toxicity. Prophylactic antiemetics and anticoagulants were administered, erythropoietin was permitted and G-CSF in cases of febrile neutropenia. In the event of grade 4 neutropenia, febrile neutropenia, grade 3-4 thrombocytopenia lasting >7 days, grade 2-3 rash without desquamation, grade 2 cardiac arrhythmia, grade 3 or repeat grade 2 neurotoxicity, grade 2 hypersensitivity or moderate renal insufficiency, treatment was interrupted until recovery to grade 2 (grade 1 for neurotoxicity) and a dose reduction (15 mg then 10 mg) was implemented. Lenalidomide was also interrupted until recovery if any other clinically significant grade 4 toxicity or hyper- or hypothyroidism occurred. Treatment was stopped if there was further toxicity after dose reduction to 10 mg, a 2-week delay due to toxicity, grade 3 rash with desquamation, grade 4 rash, grade 2-4 erythema multiforme, grade 3 cardiac arrhythmia, thrombosis or embolism, grade 4 neurotoxicity, grade 3-4 hypersensitivity or severe renal insufficiency. The study was approved by the local and national ethics committees, and was conducted in accordance with national and local requirements and the declaration of Helsinki. An ancillary exploratory analysis is currently being conducted to investigate the correlation between lenalidomide efficacy and immunologic parameters such as lymphocyte phenotype and cytokines.

**evaluations**

Patients underwent a complete clinical examination at baseline and were assessed throughout the study for adverse events, hematology and serum chemistries which were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v3.0). CA125 and coagulation factors were measured monthly, and thyroid-stimulating hormone and radiologic tumor assessments were carried out every 2 months. Response was determined according to RECIST v1.0 [16] and CA125 using GCIG criteria (≥50% reduction compared with baseline in two consecutive measurements at a minimum 1-month interval; complete response required CA125 levels within the normal range) [15]. The date of progression was documented according to CA125 or RECIST, whichever was earlier. Patients were followed up every 3 months for 1 year.

**statistical analysis**

The primary objective was to evaluate the efficacy of lenalidomide according to the rate of disease control at 4 months. Sample size was calculated according to a Simon two-stage design. The null hypothesis was a 5% rate of disease control at 4 months in the absence of treatment [17] (responses plus stable disease, according to CA125 or RECIST, with RECIST retained in the event of inconsistent outcomes), and an alternative hypothesis of a 20% rate at 4 months, as the minimum anticipated rate of disease control. Forty-one patients allowed for 90% power to differentiate between these rates, with 5% accuracy. Assuming a 10% dropout rate, a total of 45 patients were planned. If disease control at 4 months was reported in at least 2 of the first 21 assessable patients, additional patients were recruited.

Secondary end points were progression-free survival (PFS) defined as the interval from inclusion to the date of documented progression or death from any cause, and safety. The Kaplan–Meier method was used to calculate time-related variables. Analyses were carried out with SPSS®, v20.0.

**results**

**patient characteristics**

Forty-five patients were enrolled in 17 French centers between May 2009 and September 2010. Patient and disease characteristics are summarized in Table 1. Median age was 63 years (range 43–78 years). The majority of patients had advanced disease (91% with FIGO stage III–IV), serous histology (78%) and had received a single line of prior chemotherapy (73%). Prior-line
therapy included carboplatin and taxanes for all patients. Of the 12 patients who had undergone second-line chemotherapy, 11 received carboplatin. The median platinum-free interval (PFI) was 11.3 months (range 6.9–56.8 months) and 58% of patients had a PFI of 6–12 months.

disease control, best overall and serologic responses

Among the first 21 patients, 8 (38%) were not progressive at 4 months. Of the 45 patients treated, 3 were ineligible for CA125 response evaluation due to lack of confirmed CA125 doubling. Clinical benefit at 4 months was 38% [95% confidence interval (CI) 23% to 53%]. Disease control at 4 months was significantly more frequent in patients with a PFI >12 months (10 of 17 assessable patients, 59%), compared with those with PFI of 6–12 months (6 of 25 patients, 24%; P = 0.023).

RECIST partial responses were reported in 4 patients (9%, Table 2) lasting from 2.1 to 3.7 months, and 21 patients (47%) had stable disease, 7 lasting more than 4 months (median 3.6 months, range 1.4 to 13.5+ months). Eight patients had CA125 responses (19%, Table 2), one of which was a complete response, while 30 patients (71%) had stable disease (all but one confirmed).

progression-free survival

After a median follow-up of 14 months, 40 patients had progressed giving a median PFS of 3.4 months (95% CI 2.4–4.4). PFS was significantly longer in patients with a PFI >12 months (median 6.4 versus 3.2 months respectively; P = 0.012; Figure 1). Five patients had died and median overall survival had not been reached.

safety

Patients received a median of four cycles (range 1–12) and a total of 191 cycles. Dose reductions and delays (mean 6.4-day duration) caused by toxicity occurred in 14 and 28 cycles, respectively, for hematologic toxicity (8 and 15 cycles, respectively).

Toxicity, summarized in Table 3, was mostly grade 1–2. Hematologic toxicity was common, notably neutropenia in 82% of patients including grade 3 in 10 patients and grade 4 in 3. Two patients with grade 4 neutropenia required G-CSF, one of whom ultimately discontinued treatment. Anemia was reported in 60% of patients, all of which was grade 1–2. No patients required blood transfusions. Nonhematologic events included fatigue (69% of patients) and gastrointestinal toxicity (constipation 53%, abdominal pain 49%, diarrhea 38%, nausea/vomiting 36%). Seven patients (16%) had infections including one grade 3 event.

Eight women withdrew due to related toxicity, two for grade 2–3 allergic reaction, two for grade 4 pulmonary embolisms and one each for grade 3 venous thrombosis, grade 3 cardiac arrhythmia, grade 4 neutropenia and grade 4 cough. Five patients of 30 who did not receive antithrombotic prophylaxis had treatment-related thromboembolism including three cases of grade 4 pulmonary embolism.

discussion

Administration of continuous daily lenalidomide has shown efficacy in this patient population with late recurrent ovarian or peritoneal cancer, a setting where approved chemotherapies are lacking but some activity of single targeted agents has been
reported. Given lenalidomide’s predominantly immunomodulatory mechanism of action, disease stabilization was considered a more appropriate end point to assess than response rate. The 38% rate of clinical benefit at 4 months exceeded the study hypothesis of 20%. The 56% overall rate of RECIST disease control, including 9% partial response, compares favorably to rates reported with the antiangiogenic agents sunitinib malate (39%) [18] and pazopanib (36%) [19], although these studies included ovarian cancer patients with resistant disease. Disease control is lower than the 73% rate reported in a phase II study with single-agent bevacizumab [20].

Results are more encouraging than those with thalidomide in a phase III study with tamoxifen as the control arm which was prematurely interrupted in the absence of apparent benefit with thalidomide [8]. The trend seen in their study for better PFS in patients with a longer PFI treated with thalidomide (4.9 months for PFI >12 months versus 3.8 months for PFI 6–12 months) was more pronounced here with lenalidomide (6.4 versus 3.2 months, respectively). However, in the thalidomide study, patients with measurable lesions were excluded and nearly 20% were platinum-resistant, making a direct comparison with our population difficult.

It may be argued that platinum-sensitive relapse may better benefit from a chemotherapy combination than a single targeted agent such as lenalidomide. Asymptomatic rising CA125, however, is not an indication for chemotherapy, but should be followed up [21] and as such is considered an acceptable entry criterion for clinical trials [2]. The value of this model in evaluating novel agents which may interfere with CA125 secretion remains questionable. This might be applicable in our study where a clear difference was observed between disease control rates with RECIST (56%) versus CA125 (90%).

The eligibility criteria to select patients for this study were designed to obtain a homogenous population where potential activity of single-agent lenalidomide could be optimally evaluated. The choice of a platinum-sensitive asymptomatic population with low tumoral volume and after hematologic and immunologic recovery was designed to maximize the opportunity for any signs of efficacy with this immunomodulatory drug to become apparent, rather than using a platinum-resistant population where patients are rapidly symptomatic.

Toxicity with continuous daily administration of 20 mg lenalidomide was generally manageable in this pretreated asymptomatic population. The toxicity profile corresponds to that described previously for lenalidomide [13], with mostly mild to moderate events. Limiting toxicities associated with thalidomide (constipation, neuropathy, fatigue) were mild and manageable, as reported with an alternative lenalidomide regimen [13]. While the rate of hematologic toxicity was higher than that with thalidomide [8], it could be managed by dose reductions and G-CSF administration, and associated infection was rare. Thromboembolism is a recognized side-effect of lenalidomide, albeit to a lesser degree than with thalidomide. It is a concern for ovarian cancer patients, and the 11% rate reported here is high albeit consistent with a recent publication reporting a 10.8% rate of deep vein thrombosis and 7.2% of pulmonary embolism in over 600 patients diagnosed over a 10-year period [22]. It is of note that the five patients who experienced thromboembolism in this study did not receive the antithrombotic prophylaxis recommended in the protocol.
In conclusion, this study has shown that lenalidomide has activity in ovarian cancer. Potential approaches for the clinical development of lenalidomide in this asymptomatic population include using it to prolong the PFI following recurrence after first- or second-line carboplatin. The potential for this strategy is to improve efficacy with subsequent platinum treatment. The benefit/risk ratio of lenalidomide may be improved by selection of patients who could be more prone to respond. The ongoing immunological translational study may provide an exploratory biomarker track. The path forward with lenalidomide undoubtedly lies in its combination with other anticancer agents; however, following in the footsteps of successful thalidomide combinations should be approached with caution. Experience has shown that while the addition of thalidomide to topotecan in a phase II ovarian cancer study offered solid improvement in efficacy over topotecan alone, with a 2-month PFS advantage [23], a lenalidomide/topotecan combination was prematurely terminated due to unacceptable toxicity [24]. Given that hematologic toxicity appears more likely with lenalidomide than thalidomide, particular attention should be paid to the hematologic profile of any proposed combination therapy. A phase I study is currently underway evaluating lenalidomide with carboplatin and liposomal doxorubicin in platinum-sensitive relapsed ovarian cancer (NCT011111903).

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Disclosure

The authors have declared no conflicts of interest.

References


Table 3. Adverse events, N patients (%)

<table>
<thead>
<tr>
<th>Grade (NCI-CTCAE)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (29%)</td>
<td>11 (24%)</td>
<td>10 (22%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16 (36%)</td>
<td>12 (27%)</td>
<td>5 (11%)</td>
<td>–</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12 (27%)</td>
<td>12 (27%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>19 (42%)</td>
<td>8 (18%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (40%)</td>
<td>13 (29%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>18 (40%)</td>
<td>6 (13%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>17 (38%)</td>
<td>6 (13%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (22%)</td>
<td>9 (20%)</td>
<td>3 (7%)</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (22%)</td>
<td>6 (13%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>10 (22%)</td>
<td>4 (9%)</td>
<td>2 (4%)</td>
<td>–</td>
</tr>
<tr>
<td>Cutaneous toxicity</td>
<td>8 (18%)</td>
<td>5 (11%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>6 (13%)</td>
<td>5 (11%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dyspnea/cough</td>
<td>4 (9%)</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>–</td>
<td>5 (11%)</td>
<td>3 (7%)</td>
<td>–</td>
</tr>
<tr>
<td>Infection</td>
<td>–</td>
<td>6 (13%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6 (13%)</td>
<td>1 (2%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (7%)</td>
<td>2 (4%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>–</td>
<td>–</td>
<td>2a (4%)</td>
<td>3b (7%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>–</td>
<td>2 (2%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Allergy</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3 (7%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>–</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
</tbody>
</table>

*a*Patients with thrombosis were not treated with antithrombotic prophylaxis.

*b*Venous thrombosis.

*p*Pulmonary embolism.
Background: Distant metastasis is the major cause of cancer-related death, and epithelial-to-mesenchymal transition (EMT) has a critical role in this process. accumulating evidence indicates that EMT can be regulated by microRNAs (miRNAs). miR-29c has been implicated as a tumor suppressor in several human cancers. However, the role of miR-29c in the progression of colorectal cancer (CRC) metastasis remains largely unknown.

Patients and methods: The expression of miR-29c was examined by qRT-PCR in a cohort of primary CRC (PC) and distant liver metastasis (LM) tissues. A series of in vivo and in vitro assays were carried out in order to elucidate the

original articles

MiR-29c mediates epithelial-to-mesenchymal transition in human colorectal carcinoma metastasis via PTP4A and GNA13 regulation of β-catenin signaling

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