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Clinical paper

Phase II study of i.v. CI-980 in patients with advanced platinum refractory epithelial ovarian carcinoma

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CI-980 is a synthetic mitotic inhibitor that binds to tubulin at the colchicine site, inhibiting the polymerization of microtubules and arresting cellular division in metaphase. Myelosuppression and neurotoxicity were dose-limiting in phase I studies. Sixteen patients with stage III and IV platinum-refractory ovarian cancer received 4.5 mg/m²/day of CI-980 as a continuous i.v. infusion for 72 h, repeated every 3 weeks. Eleven patients had progression and four patients had stable disease. One patient (6%; 95% CI 0–25%) achieved a partial response after 9 months of treatment which lasted for 27 months. The overall median survival was 7 months. Grade 4 granulocytopenia occurred in five patients, with two episodes of neutropenic fever. Neurological toxicity was mild with 12 episodes of transient subclinical recent memory loss documented in four patients by specialized neuropsychological evaluations. One patient each had hallucinations and mild truncal ataxia, and four patients had mild, reversible neurosensory toxicity. One episode of severe hypoxemia and dyspnea occurred in a patient with chronic obstructive pulmonary disease. CI-980 has minimal activity and is tolerable in a population of heavily pretreated patients with platinum refractory ovarian cancer. [© 1998 Lippincott-Raven Publishers.]

Key words: CI-980, CNS toxicity, platinum refractory ovarian cancer, phlebitis tubulin binder.

Introduction

Ovarian cancer accounts for 4% of all cancer diagnoses and 5% of cancer deaths among women. The lifetime risk of developing ovarian cancer is approximately 1.5% and one woman in 100 will die of this disease.[1] Surgery combined with platinum-based chemotherapy is effective with overall and complete response (CR) rates as high as 80 and 50%, respectively.[2–4] Unfortunately, for most patients, disease recurs or becomes resistant to the drugs used during primary induction therapy.[5] Therefore, new drugs that are not cross-resistant are needed.

CI-980 is a synthetic mitotic inhibitor that binds to tubulin at the colchicine binding site, inhibiting the polymerization of microtubules and arresting cellular division in metaphase.[6] A series of *in vivo* and *in vitro* studies has been conducted to investigate its cytotoxic properties. CI-980 had significant activity against a broad spectrum of tumor models with a dose potency equivalent or superior to vincristine.[7,8] It retained activity against tumors that were resistant to vincristine, vinblastine, navelbine and doxorubicin.[7,8] CI-980 is not sensitive to multidrug resistance due to P-glycoprotein overexpression.[7,8] It is widely distributed in tissues and can cross the blood-brain barrier.[7,8] CI-980 exhibited marked schedule dependency *in vitro*. An extended duration of exposure (more than 24 h) resulted in inhibitory concentrations 3 logs less than that required for short exposures (less than 4 h).[7,8] In contrast, the cumulative maximum tolerated dose (MTD) *in vivo* was relatively constant regardless of the regimen employed.

In a phase I study, myelosuppression and CNS effects were the principal toxicities of CI-980 administered as a continuous 72 h infusion.[9,10] Hematological and CNS effects were tolerable at a dose of 4.5 mg/m²/day for 3 days. A higher incidence of CNS adverse events was reported with a single 24 h infusion.[11,12] The present study was conducted to determine the antitumor activity and toxicity of CI-980 when administered as a 72 h continuous i.v. infusion every 3 weeks in patients with advanced platinum refractory-epithelial ovarian cancer, and to monitor the type, incidence and reversibility of CI-980-induced adverse

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events. We have presented this study previously in abstract form[13] and a detailed discussion of its neurologic toxicity has been published.[14]

Materials and methods

Eligibility

Women 18 years and older with histologically confirmed advanced epithelial ovarian cancer FIGO stage III or IV with measurable lesions were candidates for this study. Patients may have received up to three prior chemotherapy regimens, at least one of which was platinum based. Platinum-based regimens that were administered either concurrently or sequentially without intervening evidence of progressive disease were considered as one regimen for purposes of eligibility. However, in reporting patient characteristics the regimens were counted separately as usual. Patients must have had disease refractory to platinum-based therapy, defined as progressive disease (PD) while receiving a platinum-based regimen, relapse within 6 months after completing such therapy or failure to achieve a complete response (CR) after 6 cycles if the last 3 cycles achieved no measurable change in disease. Prior chemotherapy had to be completed at least 4 weeks before first treatment with CI-980.

Additional criteria included WHO performance status of 0, 1 or 2; expected survival of over 9 weeks, and adequate liver (total bilirubin $\leqslant 2.0$ mg/dl), renal (creatinine $\leqslant 2.0$ mg/dl) and bone marrow (absolute granulocyte count $\geqslant 1500$ μl, platelet count $\geqslant 100\,000/\mu l$) function. Patients were ineligible if they had concurrent cancer chemotherapy, radiotherapy or surgery, concurrent serious infection, history of any other cancer (except non-melanoma skin cancer or carcinoma *in situ* of the cervix), confirmed or suspected brain metastases, or overt psychosis or mental disability. They were also excluded if they had concurrent life-threatening illnesses (unrelated to tumor), severe cardiac risk factors or hypertension that was not controlled by medication.

Dosage and drug administration

Patients initially received three consecutive 24 h continuous i.v. infusions of CI-980 at a dose of 4.5 mg/m^2/day (dose level 0). The total dose per course was 13.5 mg/m^2 administered over 72 h. Subsequent courses were administered every 3 weeks. The dose of CI-980 was titrated in subsequent courses based on each patient's tolerance to therapy. The dose of CI-980 was reduced by 1.0 mg/m^2/day (dose level -1) if the absolute granulocyte count nadir from the previous course was below 500 μl for 5 days or more or if it was associated with a fever above 100.4°F (38°C) or a documented infection, if the platelet count nadir was below 40 000 μl, if clinically significant treatment related grade 3 or 4 non-hematologic adverse events or grade 2 CNS adverse events occurred. The dose of CI-980 was reduced by 2.0 mg/m^2/day (dose level -2) if a patient developed a grade 3 treatment-related CNS adverse event. The dose of CI-980 was increased by 0.5 mg/m^2/day (dose level +0.5) if the prior course was well tolerated.

Antiemetic therapy

Ondansetron 10 mg i.v. was used as premedication 30 min prior to chemotherapy followed by 8 mg orally every 8 h as needed.

Removal of patients from the study

CI-980 was discontinued in patients who developed grade 4 non-hematologic adverse events or progression of their disease after two courses of CI-980.

Patient evaluation

Prior to first treatment, patients had a history, physical examination, neurologic and neuropsychologic examination, electrocardiogram (EKG), CT scan (usually of abdomen and pelvis), chest X-ray, and laboratory tests performed including complete blood count with differential and platelet count, glucose, blood urea nitrogen, serum creatinine, total protein, albumin, calcium, serum glutamic-pyruvic transaminase, alkaline phosphatase, total bilirubin, sodium, chloride, potassium, urinalysis and CA-125. All of these except for EKG, CT scan and chest X-ray were repeated prior to each course of CI-980. CT scan and chest X-ray were repeated after every second course if utilized for tumor response evaluation. The EKG was repeated on completion of the study. The complete blood count with differential and platelets were repeated weekly. The neurologic and neuropsychologic examinations were repeated after the 72 h infusion of CI-980 was completed and prior to each course. All patients who received at least one complete course of therapy were evaluable for treatment response. The primary efficacy parameter was the change in the size of the

bidimensional sentinel lesion(s), categorized as CR, partial response (PR), stable disease (SD) or PD according to WHO criteria. Secondary efficacy parameters of duration of response, time to response, time to progression and survival were evaluated.

Results

Sixteen patients with stage III or IV platinum refractory ovarian cancer were treated. Patient characteristics are shown in Table 1. One patient received one course, 10 patients received two courses, two patients received three courses, and one patient each received 12, 27 and 31 courses of CI-980, for a total of 97 courses. The dose level was increased in four patients. One patient required a dose reduction by one level because of grade 4 granulocytopenia.

Response

All patients were evaluable for response. Eleven patients showed PD, four patients (25%) had SD and one patient achieved a PR (6%, 95% CI 0–25%) (Table 2). Surprisingly, the single response occurred 9 months after the initiation of treatment with CI-980 and continued for 27 months. The disease was measured by CT scan and pelvic examination. The reduction in tumor size was noted early; however, it did not qualify as a partial response until 9 months of treatment. The CA-125 in this patient was always normal. This patient was taken off study after receiving 31 treatment courses over 33 months because of severe hypoxemia and dyspnea. The patient had asthma and moderate to severe chronic obstructive pulmonary disease. She had exacerbations of her pulmonary disease several times during the administration of prior chemotherapy regimens with carboplatin and cyclophosphamide and paclitaxel. Serial neuropsychological examination of this patient during her treatment with CI-980 revealed that her verbal learning and fine motor dexterity showed a transient mild decline after each infusion which resolved prior to the next treatment. Furthermore, she developed mild truncal ataxia and sensory neuropathy during treatment. The patient developed PD documented by CT scan and pelvic examination 36 months after the start of treatment with CI-980, 3 months after CI-980 treatment was discontinued due to the respiratory events.

The median time to progression was 1.5 months. Fifteen patients have died (14 of cancer and one of a pulmonary embolus). Median survival was 7 months. The patients whose best tumor response was SD survived 4, 10, 27 and 33 months from start of CI-980 therapy. The patient with the PR remains alive 38 months after the start of treatment with CI-980.

Table 1. Patient characteristics

Number of patients entered	16
Age [median (range)]	58 (35–71)
Performance status, Zubrod	
0	1
1	13
2	2
Histology	
clear cell adenocarcinoma	1
mixed carcinoma	3
serous carcinoma	2
serous surface papillary carcinoma	10
Prior therapy	
chemotherapy	16
hormones	4
immunotherapy	2
surgical resection	16
Prior chemotherapy[a]	
no. of regimens	
1	2
2	4
3	7
>3	3
no. of agents	
1	1
2	1
3	6
>3	8

[a]The platinum regimens administered sequentially are counted as one for purposes of eligibility; however, in patient characteristics they are reported separately in the usual manner.

Side effects

At dose level 0, grade 3 or 4 granulocytopenia occurred in 3 and 5 patients, respectively. At dose level +0.5, grade 3 or 4 granulocytopenia occurred in two patients. Two episodes of neutropenic fever occurred. Thrombocytopenia was observed only in one patient each at dose level 0 and +0.5.

Neurological toxicity was usually mild. Four patients had 12 episodes of transient subclinical recent

Table 2. Response

	n	%	95% CI
SD	4	25	5–55
PR	1	6	0–25
PD	11	69	40–90

memory loss, as determined by specialized neuropsychological tests. Methodology of this evaluation has been reported.[14] One patient had hallucinations, four patients had sensory loss and one patient had mild truncal ataxia. All of these were reversible. One patient with pre-existing adrenal insufficiency showed transitory unresponsiveness concurrent with severe hyponatremia (105 mmol/l). The patient had omitted her corticoid replacement therapy while under CI-980 treatment. She recovered completely after corticoid medication was resumed. Two patients reported dyspnea and one patient had stomatitis. Alopecia grade 1 was seen in two patients. Eight patients developed phlebitis at the injection site which appeared to be associated with the use of polyurethane catheters. We hypothesized that CI-980 accumulated in the catheter material to cause local irritation. Subsequent laboratory tests confirmed this finding (personal communication, WG). Therefore, silastic central venous catheters were required for CI-980 infusions, which abolished local complications.[13] Fatigue and gastrointestinal toxicity were mild and manageable. Table 3 shows grade 3 and 4 toxicity.

Discussion

Most women with advanced ovarian cancer eventually die of their disease. Therefore, it is important to find new drugs with improved efficacy against this tumor. CI-980 is a cytotoxic agent that arrests cellular division by binding to tubulin at the colchicine binding site. Unlike colchicine, it crosses the blood-brain barrier.[8,14] In phase I studies the main side effects of CI-980 were CNS disturbances.[9-12] Rowinsky *et al.* reported CNS toxicities of neurocortical and cerebellar manifestations and mood alterations with doses above 3.75 mg/m^2/day.[10] We reported previously the neurotoxicity of CI-980 in this trial.[14] Subclinical reversible loss of recent memory, and a slight decline of motor speed and dexterity were documented after each course. These largely resolved prior to the next course. No patient required a dose reduction for neurological toxicity. Granulocytopenia grade 3 and 4 occurred in eight patients, but only one patient required a dose reduction due to myelosuppression. Nausea and vomiting were mild. Overall, CI-980 toxicities were tolerable. No evidence of cumulative toxicity was observed in patients who received many treatment courses.

Table 3. Toxicity grade 3 and 4 at dose 4.5 mg/m^2/day

Toxicity	Number of courses	
	Grade 3	Grade 4
Anemia	3	0
Granulocytopenia	8	6
Thrombocytopenia	1	0
Dyspnea	1	0
Local reaction	1	0
Hyponatremia	1	0
Urinary tract infection	1	0

Conclusion

CI-980 showed minimal activity and was tolerable in a population of heavily pretreated patients with advanced platinum refractory ovarian cancer. One partial response was documented among 16 patients. This response occurred late, i.e. 9 months after beginning treatment with CI-980; it lasted for 27 months. Phlebitis was eliminated by using Silastic i.v. catheters. Further trials of CI-980 are feasible and are warranted in other tumor types.

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