original reports abstract

Pazopanib and Oral Cyclophosphamide in Women With Platinum-Resistant or -Refractory Epithelial Ovarian Cancer

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PURPOSE Women with recurrent, multiply-treated epithelial ovarian cancer (EOC) have unfavorable prognosis with limited treatment options after failure of platinum-based regimens. We report here a retrospective analysis of women with recurrent, platinum-resistant EOC treated with an oral regimen of pazopanib and cyclophosphamide.

PATIENTS AND METHODS Women with recurrent platinum-resistant or -refractory EOC were treated with pazopanib (600 mg orally daily in 2 divided doses, 400 and 200 mg) and cyclophosphamide (50 mg orally daily for 21 days every 28 days) until disease progression or unacceptable toxicity.

RESULTS Twenty patients (17 with platinum-resistant and 3 with platinum-refractory disease) were treated between April 2014 and April 2018. Patients had a median age of 52 years (range, 40-60 years) and median of 4 previous lines of chemotherapy (range, 2-8 previous lines), including 3 patients with progressive disease on bevacizumab. Patients received a median of 6 cycles (range, 2-48 cycles) of pazopanib and cyclophosphamide, with best responses of partial response in 9 patients (45%, including 1 of 3 patients treated previously with bevacizumab), stable disease in 6 patients (30%), and disease progression in 5 patients (25%). The median progression-free survival time was 5.5 months, and median overall survival was 9.5 months. Common adverse events (grade 3 or 4) were fatigue (25%), diarrhea (15%), hand-foot syndrome (10%), mucositis (10%), transaminitis (5%), and hypertension (5%). Dose reduction as a result of toxicity was required in 14 patients (70%), and no patient stopped treatment as a result of toxicity.

CONCLUSION Pazopanib plus oral cyclophosphamide is a well-tolerated regimen with clinically relevant benefit in patients with platinum-resistant or -refractory EOC.

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INTRODUCTION

Women with recurrent, multiply-treated epithelial ovarian cancer (EOC) have unfavorable prognosis with limited treatment options after failure of platinum-based regimens. Only 10%-20% of patients with platinum-resistant EOC demonstrate response to various chemotherapeutic agents.[1-4] Angiogenesis plays an important role in growth and development of cancer. The addition of antiangiogenic therapies (bevacizumab) in platinum-resistant EOC improves response rates to 25%-30% and progression-free survival (PFS) to 6 months (compared with 4 months with chemotherapy alone), but there is no overall survival (OS) benefit.[5]

Bevacizumab is the most frequently studied antiangiogenic drug in ovarian cancer. There is a need for an alternative drug that is cost effective and easy to administer. Pazopanib is an oral angiogenesis inhibitor that targets multiple kinase protein receptors (VEGFR, PDGFR, FGFR, and c-Kit).[6] Preclinical and clinical data suggest promising efficacy of pazopanib in ovarian cancer.[7] Evidence of clinical activity and efficacy of pazopanib in ovarian cancer has been demonstrated in phase II and III studies. A phase II trial evaluated single-agent pazopanib in patients with recurrent EOC. Participants received oral pazopanib 800 mg daily until clinical or radiologic evidence of disease progression. Eleven (31%; 95% CI, 16% to 48%) of 36 patients had a CA-125 response to pazopanib. Twenty patients (56%) had stable disease.[8] Another phase II trial of pazopanib in patients with recurrent platinum-resistant EOC evaluated the clinical benefit rate (CBR). Median PFS was 1.83 months (95% CI, 1.67 to 2 months), with a 40% CBR (10 of 25 patients).[9] In the AGO-OVAR-16 trial, pazopanib maintenance therapy for 24 months after completion of first-line platinum-based therapy improved PFS by 5.6 months compared with placebo.[10]

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CONTEXT

Key Objective

Is there an efficacious regimen for patients with platinum-resistant or -refractory epithelial ovarian cancer (EOC)?

Knowledge Generated

A combination of pazopanib and oral cyclophosphamide is associated with significant improvement in objective response rate (partial response rate, 45%) and progression-free survival (median, 5.5 months) in a heavily pretreated patient population. It is a well-tolerated regimen and has the advantage of oral administration.

Relevance

Pazopanib and oral cyclophosphamide combination may be considered as one of the options in patients with platinum-resistant or -refractory EOC.

However, there was no improvement in OS, as shown in the updated analysis of this trial.[11] Moreover, in a subgroup of East Asian patients, pazopanib maintenance had a detrimental effect on PFS versus placebo (n = 354; 17.9 *v* 21.5 months, respectively; hazard ratio [HR], 1.114; 95% CI, 0.818 to 1.518; $P = .4928$).[12]

The efficacy and safety of metronomic oral cyclophosphamide were evaluated in patients with heavily treated, relapsed ovarian cancer. The objective response rate was 20.4%, and median PFS was 4 months, which seems to be in the range obtained with intravenously administered cytotoxic drugs.[13] Furthermore, in experimental models, the combined use of metronomic chemotherapy with antiangiogenic therapies demonstrates marked inhibition of tumor growth.[14,15] Bevacizumab and metronomic oral cyclophosphamide have shown encouraging activity in recurrent ovarian cancer.[16,17] The impressive results with metronomic cyclophosphamide and anti-VEGF therapy could be a result of synergy in their antiangiogenic effect; metronomic cyclophosphamide decreases CD133+/CD44+/CD24+ cancer stem cells and the T regulatory cells.[18] Vessel normalization induced by anti-VEGF therapy could also facilitate the effector T-cell homing, leading to the activation of antitumor immunity.[18]

A phase I/II study of pazopanib and cyclophosphamide in patients with recurrent, pretreated ovarian cancer has shown promising activity in these patients, with a median PFS of 8.5 months.[19,20] On the basis of the activity of metronomic cyclophosphamide and anti-VEGF therapy in recurrent ovarian cancer as described earlier, we treated women with recurrent, platinum-resistant or -refractory EOC with this regimen. We present here the retrospective analysis of patients treated at our institution with this oral regimen to evaluate the efficacy of pazopanib and cyclophosphamide combination in a real-world setting.

PATIENT AND METHODS

Patient Population

A prospectively maintained database was used to identify patients who received pazopanib and cyclophosphamide after failure of platinum-based therapy with or without prior bevacizumab for recurrent ovarian cancer. This was a retrospective study of these patients. The institutional ethics committee of our center approved this study. Only patients with platinum-resistant or -refractory disease were included. Platinum resistance was defined as disease progression within 6 months of completion of last platinum-based therapy, and platinum-refractory disease was defined as progression while on platinum-containing therapy or within 1 month of completion of platinum-based therapy. The definition of platinum-resistant or -refractory disease refers to the most recent platinum regimen used in the patient, which could be first-line or subsequent therapy.

Data Collection and Treatment

The electronic medical record of each patient who had a histologically or cytologically confirmed diagnosis of EOC or peritoneal cancer and had received pazopanib and cyclophosphamide (after failure of available standard chemotherapies) was reviewed manually. The standard therapies that had been administered to our patient population (with platinum-resistant disease) were as follows: liposomal doxorubicin, irinotecan, gemcitabine, or weekly paclitaxel, with or without bevacizumab. After treatment failure with these therapies, the oral regimen of cyclophosphamide and pazopanib was prescribed to patients who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1-2, had no clinical evidence of intestinal obstruction, were able to take tablets orally, and had no major cardiac comorbidities. This regimen was also considered for patients who had rapidly filling ascites. Patients who had previously received bevacizumab were also treated with this regimen. Thus, this regimen was used when patients had experienced treatment failure with standard single-agent treatment of platinum-resistant or -refractory disease. To our knowledge, this regimen is not approved for ovarian cancer, and its use in our patients was off label.

Patients were treated with pazopanib tablets (600 mg/d orally in 2 divided doses, 400 and 200 mg) and cyclophosphamide (50 mg/d orally for 21 days every 28 days)

until disease progression or unacceptable toxicity. The PACOVAR study used oral cyclophosphamide at a dose of 50 mg daily continuously, whereas we used it at 50 mg/d on days 1 to 21, every 28 days. We used cyclophosphamide in this manner to reduce the incidence of myelosuppression and to reduce the cumulative dose that patients receive in the long term. We used cyclophosphamide at a similar dose in patients with ovarian cancer in an earlier phase II study performed at our institution.[21] Clinical, radiologic, and serologic responses were assessed every 12 weeks. Dose reduction was done for grade 3 or 4 toxicities. The first reduction involved reducing pazopanib to 200 mg twice a day, and the second reduction involved reducing the pazopanib dose to 200 mg once per day. The adverse events that typically required dose reductions were diarrhea, hand-foot syndrome, fatigue, mucositis, and transaminitis.

Statistical Analysis

The data cutoff date for analysis was April 30, 2018. We evaluated PFS, OS, and CBR with this regimen. PFS was defined as time from the first cycle of the oral regimen to the documented radiologic evidence of progressive disease, according to RECIST version 1.1, or death from any cause. OS was defined as time from start of the pazopanib and cyclophosphamide regimen to death from any cause. CBR was defined as the percentage of patients who had achieved complete response, partial response, or stable disease on the pazopanib and cyclophosphamide combination. The Kaplan-Meier method was used to calculate both PFS and OS.

RESULTS

Study Population

Twenty patients were treated with this regimen. All patients had either platinum-resistant or platinum-refractory disease. Most of the patients had an ECOG PS of 2 at the time of start of this oral therapy. The median age of this cohort was 52 years (range, 40-69 years), and the overwhelming majority of patients (95%) had serous histology. Sixty percent of patients had received 4 or more prior lines of chemotherapy, and 3 patients had been previously treated with bevacizumab, suggesting an extensively treated patient population. Detailed baseline patient characteristics are listed in Table 1.

TABLE 1. Baseline Characteristics

Characteristic	No. of Patients (%)
Age at treatment, years	
Median	52
Range	40-60
Performance status (ECOG)	
1	4 (20)
2	16 (80)
Histology	
Serous adenocarcinoma	19 (95)
Clear cell carcinoma	1 (5)
No. of prior chemotherapy regimens	
2	7 (35)
3	1 (5)
≥ 4	12 (60)
Prior antiangiogenic therapy (bevacizumab)	3 (15)
Platinum status	
Resistant	17 (85)
Refractory	3 (15)

NOTE. Values are presented as numbers and percentages, unless otherwise indicated.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Treatment Exposure

The median number of administered cycles was 6 (range, 2-48 cycles), with 6 patients being treated for > 12 months. One patient with platinum-refractory disease continued to be on therapy for 48 months at the time of analysis.

Toxicities and Dose Modifications

Dose reduction as a result of toxicity was required in 14 patients (70%), and no patient stopped treatment as a result of adverse reactions. Common adverse events were fatigue (55%), diarrhea (45%), elevated liver enzymes (50%), mucositis (50%), myelosuppression (35%), hand-foot syndrome (45%), hair depigmentation (15%), and hypertension (5%). Toxicities according to severity are listed in Table 2.

Response and Survival

At the time of analysis, 5 patients were on therapy, 12 had disease progression, and 3 were lost to follow-up. Of the treated patients, 9 (45%) had partial response (including 1 of 3 patients previously treated with bevacizumab), 6 (30%) had stable disease, and 5 (25%) had disease progression as best response. The median PFS time was 5.5 months (Fig 1), and the median OS time was 9.5 months. Treatment exposure and response to treatment are listed in Table 3.

Ovarian Cancer Therapies After Discontinuation of Pazopanib and Cyclophosphamide

Of 12 patients with progressive disease, 8 were treated with another line of chemotherapy (weekly paclitaxel, n = 5; liposomal doxorubicin, n = 1; irinotecan, n = 1; and gemcitabine plus carboplatin, n = 1) with or without bevacizumab. Four patients received supportive care without further cancer-directed treatment.

DISCUSSION

This analysis presents a measure of effectiveness of the pazopanib and cyclophosphamide combination in patients with platinum-resistant or -refractory EOC in a real-world setting. Our results suggest that this combination is

TABLE 2. Regimen-Related Adverse Events

Toxicity	No. of Patients (%)	
	Grade 1 or 2	Grade 3 or 4
Fatigue	6 (30)	5 (25)
Transaminitis	9 (45)	1 (5)
Mucositis	8 (40)	2 (10)
Diarrhea	6 (30)	3 (15)
Hand-foot syndrome	7 (35)	2 (10)
Hypertension	—	1 (5)
Hair depigmentation	3 (15)	—

associated with a clinically meaningful objective response, clinical benefit, and PFS benefit in a heavily pretreated patient population. Despite the small sample size, encouraging responses were seen in difficult-to-treat patients (response was observed in 1 patient with clear cell carcinoma, 1 patient with platinum-refractory disease on therapy for 48 months, and 5 patients receiving treatment for at least 12 months).

Many studies have combined pazopanib with chemotherapeutic agents not only in ovarian cancers, but also in other malignancies. In a less heavily treated group of patients who had received up to 2 prior lines of chemotherapy, Pignata et al[22] reported a median PFS time of 6.3 months with the combination of pazopanib and paclitaxel. In a similar phase II randomized placebo-controlled trial by Richardson et al,[23] the combination of pazopanib with weekly paclitaxel was not found to be superior to paclitaxel alone in recurrent EOC. Median PFS was 7.5 months for pazopanib plus paclitaxel compared with 6.2 months for paclitaxel alone, respectively (HR, 0.84; 90% CI, 0.57 to 1.22; $P = .20$).[23] There are a few differences between the Pignata et al[22] MITO-11 trial and the trial by Richardson et al.[23] First, MITO-11 was not placebo controlled; this introduces possible bias into results, particularly regarding PFS and the proportion of patients responding. Second, all patients in MITO-11 had platinum-resistant or platinum-refractory disease, whereas 53% of patients in the study by Richardson et al[23] had platinum-sensitive disease. Third, no patients in MITO-11 had received prior bevacizumab, whereas in the study by Richardson et al,[23] 20% of patients had a history of bevacizumab use. Similarly, the AURELIA trial reported a median PFS of 6.7 months with the combination of bevacizumab and chemotherapy in a group of patients who had received 2 or fewer prior lines of chemotherapy.[5] Our median PFS of 5.5 months in a more heavily treated group (median lines of previous chemotherapy, ≥ 4) compares favorably with these results.

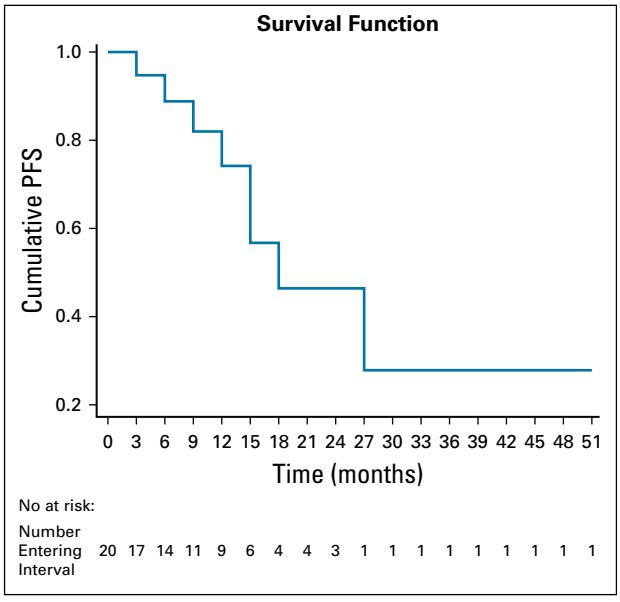

FIG 1. Progression-free survival (PFS) of patients treated with pazopanib and cyclophosphamide.

Another phase II trial evaluated the efficacy of cyclophosphamide and bevacizumab in both platinum-sensitive and platinum-resistant ovarian cancer. The median PFS with this regimen was 5.6 months.[16] Despite the inherent limitations of cross-study comparison, our findings suggest that the cyclophosphamide and pazopanib oral regimen has comparable activity to bevacizumab and chemotherapy in patients with platinum-resistant or -refractory ovarian cancer.

The patients included in this retrospective analysis were offered off-label use of pazopanib (with cyclophosphamide) as part of routine clinical practice, and their data were later analyzed. Off-label use includes the use of a drug product in doses, patient populations, indications, or routes of administration that are not reflected in US Food and Drug Administration–approved product labeling.[24] Off-label drug use is common in many clinical scenarios, such as oncology, pediatrics, psychiatry, and intensive care unit.[25,26] It is acceptable practice in India, especially in the setting of relapsed cancers, to use a drug off label, provided that there are some data for its use and the patient is adequately informed of the fact that this is not a labeled indication along with the potential adverse effects and benefits.

Pazopanib and cyclophosphamide combination is less expensive and has the advantage of oral administration compared with other standard treatment options. Most patients in our country are not covered by health insurance and have to pay out of pocket for treatment. The treatment cost of pazopanib and cyclophosphamide is approximately US$285 per cycle, whereas that of bevacizumab-based therapy is approximately US$1,765 per cycle. Therefore, pazopanib plus cyclophosphamide is a more feasible therapeutic option in our patients. Moreover, some patients prefer to be treated with an oral regimen in the platinum-resistant or -refractory setting. Because of these reasons, we treated this patient cohort with off-label pazopanib before bevacizumab.

TABLE 3. Treatment Exposure and Response

Treatment Details	No. of Patients (%)
No. of cyclophosphamide/pazopanib cycles	
Median	6
Range	2-48
Dose reduction (pazopanib)	
Not required	6
Reduction by 33%	11 (55)
Reduction by 66%	3 (15)
Best response	
PR	9 (45)
SD	6 (30)
PD	5 (25)

NOTE. Values are presented as numbers and percentages, unless otherwise indicated.

Abbreviation: PD, progressive disease; PR, partial response; SD, stable disease.

The regimen is fairly well tolerated. Although dose reduction as a result of toxicities was required in 70% of patients, no patient stopped treatment as a result of toxicities. Moreover, the majority of patients (55%) required dose reduction by 33% from the starting dose. The common adverse effects were fatigue, diarrhea, elevated liver enzymes, and hand-foot syndrome. These were managed by supportive care and dose reduction. The dosing schedule of pazopanib in our study was based on the PACOVAR study, in which 600 mg of pazopanib was used instead of 800 mg. The recommended dose of pazopanib (800 mg) is poorly tolerated in our patient population, as shown in studies by Ramaswamy et al[27] and Sharma et al,[28] wherein patients with GI stromal tumors and sarcoma, respectively, were treated with pazopanib.

The current study has limitations because of its retrospective nature, small sample size, potential biases in patient selection, and ascertainment of response and toxicity. Therefore, the results should be interpreted cautiously and cannot be considered definitive

The combination of pazopanib and oral cyclophosphamide is a well-tolerated regimen with clinically relevant benefit in patients with platinum-resistant or platinum-refractory EOC. It may be considered as one of the options in heavily pretreated patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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