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Original Article

Continuous oral cyclophosphamide as salvage or maintenance therapy in ovarian, primary peritoneal, and fallopian tube cancers: A retrospective, single institute study

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ABSTRACT

Objective: Most patients with recurrent ovarian cancer are treated with multiple regimens of intravenous salvage chemotherapy. These anticancer agents often cause severe toxicities and offset their therapeutic effects. The present study assessed the experience of a single institute regarding the safety and treatment outcomes of continuous oral cyclophosphamide in patients with ovarian, primary peritoneal, and fallopian tube cancers.

Materials and methods: A retrospective review was conducted on patients who received oral cyclophosphamide as salvage or maintenance therapy. All the patients had received platinum plus paclitaxel as the front line chemotherapy before being enrolled in the study. Oral cyclophosphamide 50 or 100 mg daily was administered. The response rate, progression-free survival, and side effects were evaluated.

Results: Twenty patients were eligible for analysis, and 18 patients (90%) initially had FIGO stage IIIC disease. Most patients were heavily pretreated with the median number of previous chemotherapy regimens being 4 (range 1–8). Seventeen patients received oral cyclophosphamide as salvage therapy. Complete and partial responses were obtained in 3 and 2 patients, respectively. Five patients were classified as having stable disease. The median progression-free survival was 15 weeks (range 5–60 weeks). Three patients received oral cyclophosphamide as maintenance therapy in the remission status. The remission duration was maintained for 18, 28, and 67 weeks. Grade 2–3 myelosuppression was the only side effect.

Conclusion: Continuous oral cyclophosphamide can be used as an alternative salvage therapy in recurrent ovarian cancer with an acceptable response rate and toxicity. Additional clinical trials are required to evaluate its efficacy as maintenance therapy.

Introduction

Epithelial ovarian cancer is the leading cause of death among all gynecological malignancies. Presently, debulking operation followed by postoperative platinum-based chemotherapy remains the standard first-line treatment of this disease. However, approximately 75% of patients with advanced ovarian cancer experience tumor recurrence, and most of them succumb despite salvage chemotherapies. The 5-year survival of patients with stage III disease and suboptimal residual tumor is about 25% [1].The poor outcome of patients with advanced ovarian cancer is mainly because of the lack of effective drugs for relapsed or recurrent diseases, which have developed resistance to current chemotherapeutic agents. Thus, searching for effective drugs with pharmacological mechanisms different from conventional therapeutic agents has become an urgent clinical need. Target therapy, particularly the anti-vascular endothelial growth factors (VEGF), has been added to chemotherapy for treating ovarian cancer in recent years; however, the benefits have been limited [2,3].

Currently, almost all the chemotherapeutic agents used for treating ovarian cancer are administered systemically through the intravenous route. The major side effects of these chemotherapies include myelosuppression and specific organ or tissue toxicities. These side effects are frequently too severe, hampering the scheduled administration of drugs; therefore, their therapeutic effects are suppressed. However, several studies have suggested that some antineoplastic agents can be administered orally for

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treating ovarian cancer [4–8]. Usually oral anticancer drugs exert less severe toxicities and can be feasibly administered, with no need to stay in the hospital. These characters should be more acceptable by patients.

Cyclophosphamide, an alkylating agent, is one of the major drugs used in the intravenous form to treat ovarian cancer in the era before paclitaxel was available. Intravenous cyclophosphamide has fallen out of use presently because the combination of cisplatin and paclitaxel was proven more effective than cisplatin–cyclophosphamide combination [9,10]. However, a few studies have reported that oral cyclophosphamide administered in the metronomic manner to patients who had previously received multiple lines of chemotherapy can still yield benefit in progression-free and overall survival rates [8,11,12]. Therefore, continuous oral cyclophosphamide may be an option for clinicians to treat patients with recurrent or relapsed ovarian cancer.

In this study, we analyzed the efficacy and toxicity of oral cyclophosphamide in our patients with ovarian, primary peritoneal, and fallopian tube cancers.

Patients and methods

A retrospective review was conducted on patients with ovarian, primary peritoneal, and fallopian tube cancers who had been treated at Show Chwan Memorial Hospital in Changhua, Taiwan, between 2008 and 2015. Clinical data were collected from electronic or paper records with the approval of the institutional review board.

All recruited patients had been previously treated with at least one platinum-paclitaxel regimen before oral cyclophosphamide. Recurrent disease was determined through abdomen-pelvic CT scan or CA-125 assay. The patients were prescribed oral cyclophosphamide as either maintenance or salvage therapy at a dosage of 50 or 100 mg daily depending on clinical evaluation, i.e., general performance, bone marrow condition, and tumor response. The treatment duration was determined according to side effects or tumor responses. For response evaluation, serum CA-125 level was checked every two weeks during the drug administration. A modified Gynecologic Cancer Intergroup CA-125 criteria was used to evaluate the response [13]. Briefly, complete response (CR) was normalization of CA-125, and partial response (PR) was a decrease in CA-125 of more than 50% of the pretreatment level. Both CR and PR were required to be maintained for at least 4 weeks. Progressive disease (PD) was an at least 25% increase in CA-125. Stable disease (SD) was defined as a response not meeting these criteria. CR, PR, and SD were recognized as clinical benefit. The toxicity of the therapy was determined according to Common Terminology Criteria for Adverse Events v.4.0 [14].

Statistical analysis

Mann–Whitney *U* test and Fisher's exact test were used to analyze the distribution of categorical data between the groups.

Results

A total of 20 patients were examined in this study. Table 1 shows the clinical characteristics of these patients. Sixteen patients had ovarian cancer, 3 had primary peritoneal cancer and 1 had fallopian tube cancer. Most patients presented with an initial stage of FIGO IIIC (n = 18, 90%), and 16 patients had serous carcinoma (80%). Oral cyclophosphamide was administered to 17 patients as salvage therapy for recurrent disease and to 3 patients as maintenance therapy after complete remission from previous chemotherapies. Twelve patients were classified as being primarily platinum refractory or resistant, and 8 were platinum sensitive. The median numbers of previous chemotherapy regimens and cycles prior to oral cyclophosphamide was 4 (range 1–8) and 20 (range 6–58), respectively.

Table 1
Demographic characteristics of patients (n:20).

Characteristic	n
Age (yr)	
Median	68
Range	38–91
Cancer type	
Ovary	16
PPC	3
Tube	1
Histology	
Serous	16
Endometrioid	3
CCC	1
Initial stage	
IC	1
IIB	1
IIIC	18
Initial platinum response	
Sensitive	9
Resistant	11
Purpose of treatment	
Salvage	17
Maintenance	3
Previous chemotherapy regimens	
Median	4
Range	1–8
Previous chemotherapy cycles	
Median	20
Range	6–58

PPC = primary peritoneal carcinoma.

Table 2 presents the effects and toxicities of oral cyclophosphamide. The overall response rate in 17 patients who received oral cyclophosphamide as salvage therapy was 29.4%, with CR in 3 patients (17.6%) and PR in 2 patients (11.8%). One patient with stage IIB endometrioid ovarian carcinoma received oral cyclophosphamide

Table 2
Response and toxicity of oral cyclophosphamide.

	n
Salvage therapy	17
Complete response (CR)	3[a]
Partial response (PR)	2[a]
Stable disease (SD)	5
Progressive disease (PD)	8
PFS (CR + PR + SD) (weeks)	
Median	15
Range	5–60
Maintenance therapy	3
After first-line chemotherapy	1
After salvage chemotherapies	2
Duration of complete remission (weeks)	
After first-line chemotherapy	18
After salvage chemotherapies	28
Leukopenia	67
Grade 1	1
Grade 2	2
Grade 3	3
Anemia	
Grade 1	1
Grade 2	2
Grade 3	3
Thrombocytopenia	
Grade 1	1
Grade 2	2

[a] One patient received two times of cyclophosphamide with CR after the first administration and PR after the second administration.

Table 3
Responses to cyclophosphamide by clinical factors.

Clinical factors	CR + PR + SD (n = 9)	PD (n = 8)	Statistics	P
Age (mean ± SD)	63.3 ± 15.9	67.1 ± 7.1	Z = −.626	.531
No. of regimen (mean ± SD)	4.1 ± 3.7	5.0 ± 2.4	Z = −1.167	.243
Pt-sensitivity n (N %)				.131
Yes	5 (55.6%)	1 (12.5%)		
No	4 (44.4%)	7 (87.5%)		

Age and No. of regimen were analyzed by Mann–Whitney *U* tests.
Pt-sensitivity was analyzed by Fisher's exact test.

for two times. In the first recurrence, she was treated with oral cyclophosphamide 50 mg daily for 15 weeks; she experienced CR for 60 weeks. In the second recurrence, the dosage was increased to 100 mg daily. A durable PR was achieved and maintained for 33 weeks. SD was observed in 5 patients (29.4%). Therefore, a total of 58.8% of clinical benefit (CR + PR + SD) was achieved in 9 patients. Eight patients (47%) progressed during treatment. The median progression-free survival was 15 weeks (range 5–60 weeks). Because most of our patients are cases of stage III serous carcinoma, staging and histological type are not fit for response analysis. The other clinical factors including age, number of previous chemotherapy, and the initial platinum sensitivity are assessed. None of these factors is associated with patient response to cyclophosphamide (Table 3). Although the obtained benefit (83.3%) in 5 of the 6 patients with initial platinum-sensitive disease is better than the obtained benefit in 4 of the 11 patients with initial platinum-resistant disease (36.7%), the difference is not significant ($p = 0.13$).

Three patients received oral cyclophosphamide as maintenance therapy. One patient with stage IIIC serous ovarian carcinoma experienced CR for 18 weeks after no evidence of disease from 9 cycles of frontline postoperative carboplatin plus paclitaxel. The other two patients received oral cyclophosphamide on achieving CR from previous 3 lines of salvage chemotherapies for recurrent disease; CR was maintained for 28 and 67 weeks, respectively, before further recurrence.

Myelosuppression was the major side effect during the treatment period. Grades 2 and 3 anemia occurred in 6 and 2 patients, respectively. Three patients experienced grade 3 neutropenia (15%). All patients with anemia and neutropenia were safely rescued by blood transfusion and/or GCSF administration. Three patients had grade 2 thrombocytopenia with no need for specific treatment. No other significant side effects were observed. Only one of the 20 patients requested for treatment termination because of grade 3 neutropenia and anemia.

Discussion

Metronomic or continuous low dose chemotherapy has been proven an effective strategy for treating cancer. The antitumor mechanism induced by metronomic therapy is attributed to its antiangiogenic effects [15–17]. In a previous animal study, metronomic oral cyclophosphamide was shown to have antitumor activity [18]. This treatment was later reported successful as salvage therapy in a young patient with advanced, platinum resistant, ovarian cancer [19]. Despite the intriguing result, only a few studies have further investigated the effects of oral cyclophosphamide in patients with recurrent ovarian cancer [8,11,12].

In this retrospective study, we presented our experience of metronomic oral cyclophosphamide in patients with ovarian, primary peritoneal, and fallopian tube cancers. Low dose oral cyclophosphamide (50 or 100 mg daily) was administered as salvage therapy to 17 patients who had been heavily treated with multiple lines of chemotherapy. Clinical benefit (CR + PR + SD) was observed in 9 patients, and the median progression-free survival was 15 weeks. Clinical benefit was observed in patients with both initial platinum-sensitive or-resistant diseases. When oral cyclophosphamide was used as maintenance therapy, durable CR was maintained for 28 weeks and 67 weeks in 2 patients on achieving CR after previous salvage chemotherapies.

Regarding toxicities, grade 2–3 myelosuppression was the only observed adverse effect, and only one patient discontinued the treatment because of grade 3 anemia and neutropenia. Therefore, the continuous administration of oral cyclophosphamide at 50–100 mg daily appeared to be tolerable in most patients who had been heavily treated with conventional chemotherapies.

The clinical benefit of oral cyclophosphamide in our study, 58.8%, is between the 40.7% and 88% reported in two other recent studies [11,12], and the 15 weeks of progression-free survival observed in this study is also comparable with these studies (i.e., 4 months) (Table 4). In addition, in patients with remission status after primary or salvage chemotherapy, oral cyclophosphamide may be administered as maintenance therapy to prolong the remission period. However, clinical trials with a large sample size are required to confirm this effect.

Currently, several studies have investigated the effects of metronomic oral cyclophosphamide combined with the intravenous anti-VEGF drug, bevacizumab, in recurrent ovarian cancer [20–23]. All the studies administered bevacizumab 10 mg/kg intravenously every 2 weeks and oral cyclophosphamide 50 mg daily. The response rate (CR + PR) in these studies varied from 24% to 53.3%, and the median progression-free survival was from 3.9 to 7.2 months. Compared with oral cyclophosphamide alone, the addition of bevacizumab seems to yield limited benefits. Moreover, adverse effects related to bevacizumab were observed. Further prospective clinical studies are warranted to evaluate if bevacizumab combined with oral cyclophosphamide is superior to cyclophosphamide alone.

Although conventional intravenous chemotherapies are indispensable in the treatment of ovarian cancer, their toxicities are frequently a major clinical dilemma. Some of the toxicities are so severe that the treatment must be delayed or even discontinued. The therapeutic effects are thus affected and patient outcomes are ominous. Oral chemotherapeutic agents can be administered in outpatient settings and usually have less severe toxicities. In addition to the therapeutic effects, most patients can maintain a tolerable quality of life during treatment. Therefore, this alternative treatment strategy warrants additional clinical trials.

Table 4
Continuous oral cyclophosphamide in the salvage therapy of recurrent ovarian cancers.

Patients (n)	Median no. of prior C/T regimen (range)	Dosage (mg/D)	Benefit (CR + PR + SD)	Median PFS (range)	Authors	Ref.
14	3 (3–5)	100	64.3%	3 (1–13) m	Watanabe et al.	[8]
26	3 (1–6)	50–150	88.0%	4 m	Handolias et al.	[11]
54	4 (1–9)	50	40.7%	4 m	Ferrandina et al.	[12]
17	4 (1–8)	50–100	58.8%	15 (5–60) w	Wong et al.	

In conclusion, we suggest that metronomic oral cyclophosphamide offers an easier and less toxic treatment method for patients with recurrent ovarian cancer. It may provide a chemotherapeutic relief for patients who have experienced side effects of conventional intravenous chemotherapies. In addition, oral cyclophosphamide may be used as maintenance therapy to prolong the remission period following the frontline or salvage chemotherapy.

Conflicts of interest statement

The authors declare that they have no conflict of interest.

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