RESEARCH ARTICLE

Phase II Clinical Study on the GEMOX Regimen as Second-line Therapy for Advanced Ovarian Cancer

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Abstract

Aim: To investigate the effectiveness and adverse effects of gemcitabine by fixed-dose rate infusion plus oxaliplatin (GEMOX regimen) as second-line therapy for advanced ovarian cancer. Methods: 64 patients with advanced ovarian cancer were divided into an experimental group (44 cases) and a control group (20 cases). The experimental group was treated with continuous intravenous infusion of gemcitabine at 1000 mg/m^2 with a fixed-dose rate of 10 mg/m^2/min, on days 1 and 8 and oxaliplatin at 100 mg/m^2 on day 1, IVGTT, repeated every 3 weeks. The control group was treated with intravenous infusion of gemcitabine at 1000 mg/m^2 within 30 min on days 1 and and oxaliplatin at 100 mg/m^2 on day 1, IVGTT, again repeated every 3 weeks. CT scans or MRI were used for review every 1-2 cycles. Results: The effective rate in the experimental group was significantly high than control group (43.2% vs 35.0%; $P < 0.05$), with no obvious difference of hematologic or non-hematologic toxicity between the two groups ($P > 0.05$). Conclusion: GEMOX regimen is very effective to treat advanced ovarian cancer, with low toxicity, good tolerance and improved life quality in patients.

Keywords: Ovarian cancer - gemcitabine - oxaliplatin

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Introduction

Ovarian cancer is a kind of common gynecologic tumor that features the onset of a hidden process which is hardly discovered, but is easily transferred and often there is poor prognosis. Seventy percent of cases are already in an advanced stage when they are diagnosed. The main treatment method is to carry out platinum-based chemotherapy after cytoreductive surgery (Deraco et al., 2012; Hanker et al., 2012). Ovarian cancer is sensitive to chemotherapy. The clinical remission rate of front-line chemotherapy is 80 percent postoperatively. Despite the platinum-based treatment that often has positive short-term effects; some patients will ultimately relapse with recurrent ovarian cancer. There also are 20 to 30% of the patients with no response to front-line chemotherapy, which is then called "refractory ovarian cancer" (Sherman-Baust et al., 2011; Kim et al., 2012; Meier et al., 2012). These patients need second-line chemotherapy. The effective rate based on paclitaxel as second-line treatment was only 13-15%. Therefore there is a need for a new effective anti-tumor medicine for ovarian cancer recurrences (Miyoshi et al., 2011; A Boere and EL van der Burg, 2012).

In recent years, paclitaxel has been used for recurrent ovarian cancer and front-line therapy for advanced ovarian cancer further has improved the efficiency and extended survival time. The American Society of Gynecologic Oncologists has proposed using paclitaxel plus carboplatin as the front-line chemotherapy for advanced ovarian cancer. With this method the success rate has been 73 to 77% with a median progression-free time of 16-18 months and a median survival time of 35-38 months. Despite this increase in success, there still were quite a few patients who had relapse (Meier et al., 2012; Sorbe et al., 2012). Choosing proper chemotherapy is an important part of the entire treatment for recurrent advanced ovarian cancer. For this reason many scholars are immersed in research for newer and more effective second-line methods. It has been confirmed that a new anti-cancer drug gemcitabine has a positive effect on refractory ovarian cancer. The FDA has approved the drug for the treatment of ovarian cancer. We chose the infusion of gemcitabine at a fixed dose rate plus oxaliplatin (GEMOX regimen) as second-line method to treat 44 cases of advanced ovarian cancer, and achieved good clinical outcomes. The drug is well tolerated and has very good effect on patients.

Materials and Methods

General information

64 cases with advanced ovarian cancer aged from 35

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to 77 years (median age: 55 years) were treated in our department from January 2008 to January 2011. There were 36 cases of serous carcinoma, 16 cases of mucinous carcinoma, 9 cases of endometrioid carcinoma and 3 cases of clear cell carcinoma. After previous treatment, 31 cases made progress by using TP (paclitaxel plus carboplatin or cisplatin), 15 cases made progress by using CAP (cyclophosphamide plus doxorubicin plus cisplatin), 11 cases progressed by using docetaxel plus cisplatin and 7 cases progressed by using irinotecan plus cisplatin. There were 36 cases with platinum-sensitive (remission for > 6 months) and 28 cases that were platinum-resistant (remission within 6 months) (Table 1). All Patients met the following eligibility criteria: (1) each patient was diagnosed with epithelial ovarian cancer confirmed by histopathology; (2) those with KPS score of 60 or more had an expected survival rate of 3 months or more; (3) all patients were treated with primary maximum cytoreductive surgery. After surgery, an examination or imaging diagnosis suggested there was at least one measurable lesion, in which 27 cases had pulmonary metastases, 23 cases had hepatic metastases, 11 cases had supraclavicular lymph node metastases and 8 cases had abdominal and/or pelvic lymph node metastases; (4) blood tests showed that there was no significant abnormal symptom in the heart, liver, or kidney; (5) patients received no radiation therapy, chemotherapy, hormones or other treatments within 4 weeks.

Treatment methods

All patients were systematically treated with a combination of chemotherapy of gemcitabine plus oxaliplatin. They were divided into experimental group (44 cases) and control group (20 cases). The specific chemotherapy schemes were as follows: (1) experimental group, continuous intravenous infusion of gemcitabine at 1000 mg/m^2 with rate of 10 mg/m^2/min on day 1 and 8 and oxaliplatin at 100 mg/m^2 on day 1, IVGTT, repeated every 3 weeks; (2) control group, intravenous infusion of gemcitabine at 1000 mg/m^2 within 30 min on day 1 and 8 and oxaliplatin at 100 mg/m^2 on day 1, IVGTT, repeated every 3 weeks. All the while conventional antiemetic and symptomatic treatment was given to patients. Blood, hepatic and the renal function as well as CAl25 were periodically reviewed. CT scan or MRI was used to review every 1-2 cycles. Each patient received at least 2 cycles of chemotherapy drugs. Efficacy and adverse effects were evaluated after every 2 cycles.

Evaluation of efficacy and adverse effects

Evaluation standard After 2 cycles, patients were reviewed with a CT (including Abdominal, pelvic and chest) to evaluate measurable tumor lesions and confirm the efficacy of treatment. In accordance with RECIST (Response Evaluation Criteria in Solid Tumors), the evaluation could be divided into several parts: complete remission (CR), partial remission (PR), no change (NC) and progressive disease (PD). Response rate (RR) was defined as the sum of patients with CR and PR (Therasse et al., 2000).

Survival time Progression-free survival time (PFS) is the length of time by using GEMOX methods on a tumor and that shows progress. Overall survival (OS) is the length of time from using GEMOX methods to a patient's death (Suprasert et al., 2012).

Quality of life KPS score change was observed before and after chemotherapy. It was meaningful under the condition that scored an increase of 10 points. This could be judged as an improvement on the quality of life.

Toxic effects In accordance with the U.S. NCI chemotherapy drug toxicity grading criteria. Assessment is divided into four degrees.

Statistic analysis

SPSS 13.0 software was adapted for use in this research. The Kaplan-Meier curve method was used in the survival analysis. *P* less than 0.05 were considered statistically different.

Results

Short-term efficacy

64 patients completed a total of 226 chemotherapy cycles, with an average of 3.4 cycles for each patient with a maximum of 8 cycles and a minimum of 2 cycles. According to the RECIST evaluation criteria, the efficacy in two groups could be an objectively evaluated. 44 patients in experimental group and 20 patients in control

Table 1. General Data of 64 Patients with Stage II Advanced Ovarian Cancer

Indexes		Cases	
		Experimental group	Control group
Pathological type	Serous carcinoma	26	10
	Mucinous carcinoma	10	6
	Endometrioid carcinoma	6	3
	Clear cell carcinoma	2	1
Previous treatment	Paclitaxel plus carboplatin or cisplatin	23	8
	Cyclophosphamide plus doxorubicin and cisplatin	9	6
	Docetaxel plus cisplatin	8	3
	Irinotecan plus cisplatin	4	3
Metastatic site	Lung	8	4
	Liver	11	7
	Supraclavicular lymph nodes	8	5
	Celiac and pelvic lymph nodes	32	18
Platinum-resistance	Sensitive	26	12
	Resistant	18	8

Table 2. Comparison of Short-term Efficacy Between Two Groups

Platinum-resistance	Effective rate/case (Experimental/control)			
	CR	PR	NC	PD
Sensitive	2 (4.5%)/0 (0.0%)	13 (29.5%)/3 (25.0%)	9(20.5%)/3 (25.0%)	2(4.5%)/6 (50.0%)
Resistant	0 (0.0%)/0 (0.0%)	4 (9.1%)/1 (12.5%)	9 (20.5%)/2 (25.0%)	5 (11.4%)/0 (62.5.0%)

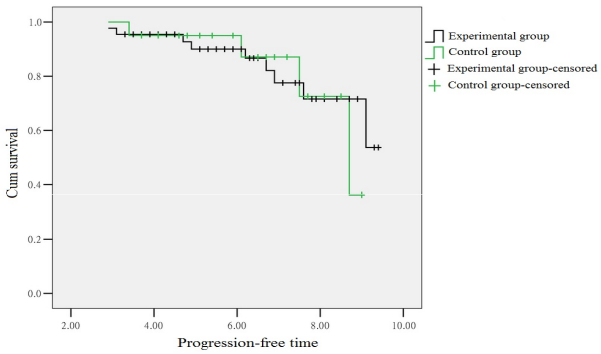

Figure 1. Comparison of Progression-free Time Between Two Groups

group were evaluable for efficacy with an effective rate of 43.2% vs 35.0%, including 2 cases (4.5%) of CR, 17 cases (38.6%) of PR, 18cases (40.9%) of NC and 7 cases (15.9%) of PD vs 7 cases (35.0%) of PR, 7cases (35.0%) of NC and 6 cases (30.0%), respectively. The effective rate of platinum-sensitive patients was 53.8% vs 33.3%, including 2 cases (4.5%) of CR, 13 cases (29.5%) of PR, 9 cases (20.5%) of NC and 2 cases (4.5%) of PD vs 3 cases (33.3%) of PR, 3 cases (33.3%) of NC and 6 cases (66.7%) of PD in experimental group and control group, respectively. The effective rate of platinum-resistant patients was 22.2% vs 12.5%, including 4 cases (9.1%) of PR, 9 cases (20.5%) and 5 cases (11.4%) of PD vs 1 cases (12.5%) of PR, 2 cases (25.0%) of NC and 5 cases (62.5%) of PD, and with no CR record in two groups, respectively (Table 2).

Quality of life

In experimental group, there were 30 cases with KPS scores that had increased, accounting for 68.2%; 5 cases with no improvement, accounting for 11.5%; and 9 cases that had declined, accounting for 20.5%.

Survival analysis

There was a one-year follow-up carried out with a follow-up rate of 100%. The follow-up was January 1, 2012. One year after the last patient was enrolled. The median progression-free time was 6.4 months vs 6.5 months, and median survival time was 20.5 months vs 20.4 months in experimental group and control group, respectively (Figure 1).

Adverse effect

Non-hematologic toxicity Non-hematologic toxicity occurred after chemotherapy with gemcitabine plus oxaliplatin. There were nausea, vomiting, loss of appetite, numbness and hair loss. In experimental and control group, the incidence of nausea and vomiting was 79.5% (35 cases) and 90.0% (18 cases), respectively, though most of them were I/II degree; Numbness was also relatively common, accounting for 59.1% (26 cases) and 70.0% (14 cases), respectively. It appeared after 3 weeks because of the cumulative dose and then, the patient recovered after drug withdrawal which was considered to be related to oxaliplatin. There were 2 and 3 cases respectively in two groups with liver dysfunction showing elevated aminotransferases, respectively. They recovered after liver protection therapy. No patients in two groups had delay or withdrawal phenomena due to non-hematologic toxicity. There was no significant difference in incidence of non-hematologic toxicity between two groups ($P > 0.05$).

Table 3. Comparison of Toxic Effects Between Two Groups

Toxic effects	Cases (Experimental/control)			
	I degree	II degree	III degree	IV degree
Leucocytopenia	11/6	11/5	9/6	0/0
Erythrocytopenia	7/3	9/4	2/2	0/0
Thrombocytopenia	9/4	13/4	5/5	0/0
Nausea and vomiting	14/7	15/8	5/3	1/0
Neurotoxicity	12/6	13/7	1/1	0/0
Impaired liver function	1/1	1/1	0/0	0/0

Hematologic toxicity The major adverse effect was bone marrow suppression. In experimental group and control group, patients received 156 vs 70 cycles of chemotherapy, respectively, and there were 31 (70.5%) vs 17 (85.0%) cases with leucocytopenia, 27 (61.4%) vs 13 (65.0%) cases with thrombocytopenia and 18 (40.9%) vs 10 (40.9%) cases with erythrocytopenia, respectively. However, all of them were under the III degree. No IV degree bone marrow appeared. The phenomenon of withdraw due to an adverse event did not appear and patients recovered after receiving G-CSF, IL-II, and EPO treatment. There was no significant difference in incidence of hematologic toxicity between two groups ($P > 0.05$) (Table 3).

Discussion

Combination therapy is required to treat intermediate and advanced ovarian cancers. Platinum-based combination chemotherapy achieves a certain positive effect as an ideal solution for cytoreductive surgery (Kajiyama et al., 2011). For patients with recurrent advanced ovarian cancer, proper chemotherapy is an important part of the entire treatment. Many scholars are involved in research for newer and more effective second-line methods. Gemcitabine is a new anticancer drug which has been much studied recently. It is a new type of synthetic pyrimidine nucleoside analogues, which is a cell cycle specific anticancer drug, mainly killing cells in the S phase. It also blocks the transition process of cell proliferation from Gl to the S phase leading to apoptosis. It has been confirmed that this drug has a positive effect on refractory ovarian cancer. The FDA has approved the drug

in the treatment of ovarian cancer (Murgia et al., 2010; Giuntoli et al., 2011). Oxaliplatin is a third-generation platinum derivative and is a diaminocyclohexane (DACH) platinum analog. Clinical data has shown that it is anticancer in the treatment of ovarian cancer especially effective in patients resistant to DDP or recurrent patients. It is not cross-resistant to cisplatin or carboplatin. It is generally considered that its efficacy is related to mismatch repair deficiency. Deficient mismatch repair often appears in ovarian cancer cells, and the incidence increases after a treatment of cisplatin or carboplatin. Therefore, the application of oxaliplatin can still be effective for patients previously resistant to cisplatin and carboplatin. In terms of a toxicity profile, oxaliplatin differs from cisplatin and carboplatin. Compared to cisplatin, the toxicity of oxaliplatin in kidneys, hearing, gastrointestinal and hematology is lower. Major toxicity is cumulative peripheral neurotoxicity which can be reversed in most patients. Studies have shown that the efficacy rate of oxaliplatin for recurrent ovarian cancer is 16-29% (Frenel et al., 2011; Palma et al., 2011).

According to previous reports, gemcitabine plus carboplatin are used in the treatment of patients with epithelial ovarian cancer. The results showed a response rate of 47%. Progression-free survival was 8.6 months. Hematologic toxicity showed neutrophil reduced by 70.3% and platelet reduced by 34.9%. Seliger et al. (Seliger et al., 2009; Gordon et al., 2011) used gemcitabine plus carboplatin to treat 23 cases of platinum-resistant and recurrent patients, and the result showed that CR was 9.5% and PR was 48%. The median progression-free time was 5.5 months and median survival time was 21.6 months, without IV degree hematological toxicity. Raspagliesi et al. (2005) used short-term injection of gemcitabine (30-60 min) combined with oxaliplatin to treat 20 cases of cisplatin-paclitaxel resistant or refractory ovarian cancer. Results found that, the dose-limiting toxicity was thrombocytopenia. 70% of cases were with grade 3/4 thrombocytopenia, in which 2 cases needed platelet transfusion and 8 cases needed corticosteroid therapy. At the same time, 70% of cases were with grade 3/4 of leukocytopenia. The recent effective rate was 26%. Ren et al. (2012) applied the second-line treatment with gemcitabine plus oxaliplatin to treating 21 patients with advanced recurrent ovarian cancer and found that, the total effective rate was 38.1%, with incidence of platinum resistance of 18.5% (5/27), platinum sensitivity of 50% (5/10), nausea and vomiting of 80.9%, neurotoxicity and paresthesia of 61.9%, leucocytopenia of 71.4%, thrombocytopenia of 61.9% and erythrocytopenia of 42.9%. After treatment, the life quality of patients was improved, with 2 cases of treatment-related death. Wang et al. (2009) also used gemcitabine plus oxaliplatin in second-line treatment of 22 cases of recurrent ovarian cancer. There were 2l patients with evaluable treatment efficacy. The clinical benefit rate and total effective rate were 57.1% and 31.8%, respectively. The effective rates in platinum-sensitive patients and platinum resistant patients were 41.7% and 20%, respectively. The main toxicity reactions were myelosuppression and neurotoxicity. The incidence of patients with leucocytopenia, thrombocytopenia, neurotoxicity and paresthesia were 68.2%, 72.7% and 71.4%, respectively. After treatment, the life quality of patient was improved, with no occurrence of treatment-related death. Unfortunately, in later 2 clinical studies, whether gemcitabine was injected with fixed rate was unaccounted.

Previous GEMOX chemotherapy in recurrent advanced ovarian cancer had an inspiring effect, while these treatments of ovarian cancer GEMOX regimen were designed inconsistently in each study (dose intensity of gemcitabine, infusion time, dose intensity of oxaliplatin and the order of use). The GEMOX regimen adapted in this research is more in line with current clinical practice. Results of this study showed that, GEMOX regimen had a very positive effect in the treatment of advanced ovarian cancer. The main toxicity was light, while patient tolerance was good. Among 44 patients in experimental group, 2 cases (4.5%) were CR, 17 cases (38.6%) were PR, and the effective rate was 43.2%, but in control group, no CR case had been obtained, 7 cases (35.0%) of PR, and the effective rate was 35.0%. There was no significance difference of effective rate between two groups ($P < 0.05$). Compared with platinum-resistant patients, platinum-sensitive patients probably had a better effect in two groups. In terms of toxicity, bone marrow suppression was relatively common in GEMOX regimen. In addition, there was still a substantial amount of nausea, vomiting, and neurotoxicity, but most of the patients were under III degree and could recover after systematic treatment. The toxicities in two groups are close to each other ($P > 0.05$), with no occurrence of treatment-related deaths. The results of the effect and toxic tolerance were consistent with what we originally envisaged as well as with a number of similar findings. In addition, we were also aware of having too few cases of patients enrolled in this study. In order to carry out a retrospective study, it is planned that more patients will be enrolled in line with our present study and will undergo forward looking forecasts. The results will be more reliable. According to existing research, we find that this program in experimental group has the following advantages: it is still valid for recurrent patients who have used paclitaxel, irinotecan and pemetrexed. The efficacy in recurrent patients with platinum-resistant is satisfactory and the effective rate is 22.2%.

In conclusion, GEMOX regimen has a positive effect on the treatment of advanced recurrent ovarian cancer with excellent tolerance. It is worthy of promoting as a second-line program.

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