pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2013;45(1):40-47

http://dx.doi.org/10.4143/crt.2013.45.1.40

Original Article

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Feasibility of Oxaliplatin, Leucovorin, and 5-Fluorouracil (FOLFOX-4) Chemotherapy in Heavily Pretreated Patients with Recurrent Epithelial Ovarian Cancer

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Received November 7, 2012
Accepted January 18, 2013

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Purpose
The purpose of this study is to evaluate the efficacy and toxicity of oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-4) chemotherapy in heavily pretreated patients with recurrent epithelial ovarian cancer (EOC).

Materials and Methods
Clinical data were reviewed in 28 patients who received FOLFOX-4 as more than the second-line chemotherapy, consisting of 85 mg/m^2 of oxaliplatin as a 2-hour infusion, 200 mg/m^2 of leucovorin as a 2-hour infusion, and bolus 400 mg/m^2 on day 1, followed by a 22-hour infusion of 600 mg/m^2 of 5-fluorouracil for two consecutive days every three weeks. In addition, its efficacy and toxicity were compared with those reported in in three previous relevant studies.

Results
A total of 128 cycles of FOLFOX-4 were administered with the median number of five cycles (range, 1 to 10 cycles). In nine patients with measurable disease, complete response (CR) and partial response (PR) were observed in 0 (0%) and two (22.2%) patients, whereas in 19 patients with non-measurable disease, CR and PR were observed in 0 (0%) and five (26.3%) patients. Among all patients, grade 3 anemia, neutropenia, and thrombocytopenia were observed in two (7.1%), three (10.7%), and one (3.6%) patient, and grade 3 fatigue, nausea and vomiting, and peripheral neuropathy were observed in one (3.6%), two (7.1%), and three (10.7%) patients. In addition, median values of time to progressive disease and chemotherapy-specific survival were three months (range, 0 to 10 months) and nine months (range, 4 to 24 months).

Conclusion
FOLFOX-4 is feasible as salvage chemotherapy with acceptable toxicity for heavily pretreated patients with recurrent EOC.

Key words
Oxaliplatin, Leucovorin, Fluorouracil, Ovarian neoplasms

Introduction

Epithelial ovarian cancer (EOC) is the second most common malignancy of the female genital tract [1]. Because of rare specific symptoms and lack of feasible screening methods, more than two-thirds of patients with EOC are diagnosed at advanced-stage disease, which leads to poor prognosis. The standard treatment consists of a staging operation, including maximal cytoreduction and adjuvant chemotherapy. In particular, taxane- and platinum-based chemotherapy after surgery has been established as the first-line treatment by previous randomized controlled trials, which have reported an overall response rate of 60% to 80% in advanced-stage disease [1,2]. However, a majority of patients ultimately show disease recurrence.

When EOC recurs after primary treatment, the second-line chemotherapy is different between platinum-sensitive and platinum-resistant diseases. Patients with platinum-sensitive disease, who relapse later than six months after primary

treatment, can be treated again with taxane- and platinum-based chemotherapy, whereas different cytotoxic drugs, including topotecan, gemcitabine, and pegylated liposomal doxorubicin are administered to those with platinum-resistant disease, which are known to show a relatively low response rate of 15% to 35% [3,4]. Thus, up to now, effective combination drugs have been investigated for salvage chemotherapy.

When compared with carboplatin and cisplatin, oxaliplatin, a diaminocyclohexane, platinum derivative, has different cytotoxic effects and various intracellular targets [5]. Preclinical and clinically relevant studies have shown minimal cross-resistance of oxaliplatin with carboplatin or cisplatin in ovarian cancer [6]. In addition, the efficacy of leucovorin (LV)/5-fluorouracil (5-FU) through inhibition of thymidylate synthase has been documented in EOC [7,8]. Thus, the combination of oxaliplatin, LV, and 5-FU (FOLFOX -4) may be expected to have a synergy to overcome chemoresistance [9].

FOLFOX-4 is currently one of the most efficient chemotherapeutic regimens for treatment of colon and breast cancers [10,11]. However, few relevant studies have been reported, resulting in a lack of evidence for its efficacy in recurrent EOC [12-14]. Thus, we reviewed our experience with FOLFOX-4, and compared our results with those reported in previous studies in order to evaluate the efficacy and toxicity of FOLFOX-4 as salvage chemotherapy in heavily pretreated patients with recurrent EOC.

Materials and Methods

1. Study design

The current study is a retrospective review, which enrolled patients who received FOLFOX-4 as salvage chemotherapy for treatment of recurrent EOC. Approval by the Institutional Review Board of Seoul National University Hospital was obtained in advance. Because this study was a retrospective review of medical records, informed consent was waived.

All data were acquired from a database of heavily pretreated patients with recurrent EOC between January 2002 and February 2011. The eligibility criteria were as follows: patients with histological confirmation of EOC; those with Eastern Cooperative Oncology Group performance status of 0 to 1; those who underwent cytoreductive surgery followed by taxane- and platinum-based chemotherapy as primary treatment; those who received FOLFOX-4 for treatment of recurrent disease as more than the second-line chemotherapy; those without other combined malignancies; those with adequate hepatic, renal, and bone marrow functions.

2. Chemotherapy

FOLFOX-4 consisted of 85 mg/m^2 of oxaliplatin as a 2-hour infusion on day 1, 200 mg/m^2 of LV as a 2-hour infusion on day 1, and bolus 400 mg/m^2 of 5-FU on day 1, followed by a 22-hour infusion of 600 mg/m^2 of 5-FU for two consecutive days every three weeks. Chemotherapy was terminated when progressive disease (PD) developed, chemotherapy-induced toxicities were uncontrolled by conservative treatment such as granulocyte colony stimulating factor, or the treatment schedule was delayed by more than two weeks.

3. Efficacy and toxicity

Tumor response was assessed every three cycles by repeating baseline assessments using imaging studies (computed tomography, magnetic resonance imaging) according to the Response Evaluation Criteria in Solid Tumors (RECIST) for patients with measurable disease [15]. Complete response (CR) was defined as the disappearance of all lesions for at least four weeks. Partial response (PR) and PD were defined as a reduction of more than 30% and an increase of more than 20% in the sum of the perpendicular diameters of lesions, respectively. In addition, tumor response for patients with non-measurable disease was also assessed according to the validated cancer antigen 125 (CA-125) criteria proposed by Rustin [16]. According to the criteria, CR was defined as a return of CA-125 levels to the normal range for at least four weeks. PR and PD were defined as a reduction of more than 50% and an increase of more than 25% in CA-125 levels, compared to prior levels, for at least four weeks. Stable disease (SD) was defined when tumor response could not satisfy the criteria for CR, PR, and PD. Adverse events were checked at each visit and graded according to the Common Terminology Criteria for Adverse Events ver. 3.0 [17].

4. Statistical consideration

For survival analysis, time to progressive disease (TTPD) was defined as the time lapse from the beginning of FOLFOX-4 chemotherapy to the date of proven PD. Chemotherapy-specific survival (CSS) was calculated as the time lapse from the beginning of FOLFOX-4 chemotherapy to the date of cancer-related death or the end of the study. Overall survival (OS) was defined as the time lapse from the date of diagnosis to the date of cancer-related death or the end of the study. TTPD, CSS, and OS were evaluated using the Kaplan-

Meier method with the log-rank test. Statistical analyses were performed using SPSS ver. 19.0 (SPSS Inc., Chicago, IL). Finally, we compared the efficacy and toxicity of FOLFOX-4 chemotherapy between the current study and three previous relevant studies [12-14].

Results

1. Patients' characteristics

A total of 28 heavily pretreated patients with recurrent EOC were enrolled in the current study. Their clinicopathologic characteristics are shown in Tables 1 and 2.

Table 1. Characteristics of patients

Characteristic	No. (%)
Median age (range, yr)	61 (46-79)
Menopause	
Yes	21 (75.0)
No	7 (25.0)
ECOG performance status	
0	17 (60.7)
1	11 (39.3)
FIGO stage	
IIB	1 (3.6)
IIC	1 (3.6)
IIIA	1 (3.6)
IIIB	1 (3.6)
IIIC	19 (67.7)
IV	5 (17.9)
Histology	
Serous	21 (75.0)
Non-serous	7 (25.0)
Median follow-up (range, mo)	34 (10-95)
Treatment time for FOLFOX-4	
3rd line	4 (14.3)
4th line	7 (25.0)
5th line	8 (28.6)
6th to 9th line	9 (32.1)
Cycles of FOLFOX-4	
1	2 (7.1)
2	7 (25.0)
3	4 (14.3)
4	3 (10.7)
5-9	12 (42.9)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; FOLFOX-4, oxaliplatin, leucovorin, and 5-fluorouracil.

Histologically, 21 (75.0%) patients were diagnosed with serous carcinoma and seven (25.0%) patients with non-serous carcinoma (Table 1). Prior to administration of FOLFOX-4, 671 cycles of prior chemotherapy had been administered to all patients with a median number of 24.0 cycles (range, 11 to 53 cycles), which consisted of 233 (34.7%) cycles of paclitaxel/carboplatin, 147 (21.9%) cycles of topotecan with or without cisplatin, 106 (15.8%) cycles of gemcitabine/carboplatin or cisplatin, 63 (9.4%) cycles of docetaxel /carboplatin or cisplatin, and 122 (18.2%) cycles of others. Thereafter, a total of 128 cycles of FOLFOX-4 were administered to all patients with the median number of five cycles (range, 1 to 10 cycles) and median number of prior chemotherapy before administration of FOLFOX-4 was five (range, 2 to 8) (Tables 2 and 3).

2. Efficacy

In evaluation of tumor response according to the RECIST criteria for nine patients with measurable disease, CR, PR, SD, and PD were observed in 0 (0%), two (22.2%), two (22.2%), and five (55.6%) patients, respectively. In 19 patients with non-measurable disease, 0 (0%), five (26.3%), four (21.1%), and 10 (52.6%) patients showed CR, PR, SD, and PD (Table 4). In regard to survival, median values of TTPD and CSS were 3 months (range, 0 to 10 months) and 9 months (range, 4 to 24 months) (Table 3). The median value of OS was 40 months (range, 11 to 95 months) (Fig. 1).

3. Toxicity

In regard to hematological toxicity, two (7.1%), three (10.7%), and one (3.6%) patients showed grade 3 anemia, neutropenia, and thrombocytopenia. In addition, grade 3 fatigue, nausea and vomiting, and peripheral neuropathy were observed as non-hematological toxicity in one (3.6%), two (7.1%), and three (10.7%) patients, respectively (Table 3). All toxicities were controlled by supportive care without occurrence of treatment-related death.

Discussion

The efficacy of FOLFOX-4 has been investigated as salvage chemotherapy in previous studies [12-14], however its use in treatment of recurrent EOC has been uncommon, when compared with other solid tumors, including colon cancer. The main reason is a lack of evidence for the efficacy and toxicity of FOLFOX-4 in treatment of EOC. Thus, we revi-

Table 2. Efficacy of FOLFOX-4 chemotherapy in 28 heavily pretreated patients with recurrent epithelial ovarian cancer

No.	Age (yr)	FIGO stage	Histology	Prior chemotherapy	Treatment time for FOLFOX-4 (mo)	Cycles of FOLFOX-4	Tumor response[a]
1	69	IV	Serous	T/C×9 → T/C×9 → D/C×7 → WT×5 → To/P×3 → G/C×4 → WI×6	8	5	Partial response
2	62	IIIC	Serous	T/C×6 → To×6 → G/P×6 → PLD×4 → D/C×6	6	2	Progressive disease
3	48	IIIC	Serous	T/C×6 → D/P×6 → To/P×6 → G×4	5	2	Progressive disease
4	65	IIIC	Serous	T/C×9 → To/P×9 → G×1	4	10	Partial response
5	46	IIIC	Serous	T/C×9 → G/C×9 → D/P×3 → To×4	5	3	Progressive disease
6	48	IV	Mucinous	T/C×9 → G/C×2	3	3	Progressive disease
7	63	IIIC	Serous	T/C×9 → T/C×6 → G/C×3 → To×2	5	4	Partial response
8	57	IIIC	Serous	T/C×9 → G/C×4 → To×3	4	4	Stable disease
9	53	IIIC	Undifferentiated	T/C×9 → G/P×6 → To×3	4	10	Stable disease
10	69	IIB	Serous	T/C×6 → T/C×6 → G/P×6 → D×6→ To/P×9	6	1	Progressive disease
11	60	IIIA	Endometrioid	T/C×6 → G/P×6	3	7	Stable disease
12	63	IIIC	Serous	T/C×6 → D/C×6 → G/C×6 → To×6 → E×6 → To/P×6 → WT×17	8	7	Stable disease
13	78	IIIC	Mucinous	T/C×9 → G/P×4	3	1	Progressive disease
14	47	IV	Serous	T/C×3 → D/C×6 → G×4 → To×3 → G/P×3 → PLD×6 → Cy/P×6 → WT×3	9	2	Progressive disease
15	56	IV	Serous	T/C×7 → G/P×7 → To×3	4	7	Partial response
16	64	IIIC	Serous	T/C×9 → G/P×6 → To/P×3 → To/C×9	5	2	Progressive disease
17	69	IV	Serous	T/C×9 → To/P×6 → D/C×4 → G/C×2	5	4	Progressive disease
18	50	IIIC	Serous	T/C×6 → T×6 → D/P×3 → To×2 → G/C×6 → To×4 → Cy/Do/P×9 → WI×1	9	4	Progressive disease
19	60	IIIC	Endometrioid	T/C×3 → To/P×3 → Cy/P×1 → G/P×6 → D×1	6	9	Partial response
20	67	IIIC	Serous	T/C×9 → To×6 → G/C×6 → To×12 → D×2 → WI×2 → WT×5	8	7	Stable disease
21	54	IIIC	Endometrioid	T/C×7 → Do/P×4 → G/P×1	4	3	Progressive disease
22	60	IIIC	Endometrioid	T/C×6 → G/C×6→ To/P×6 → WT×3 → Cy/P×6 → D×2	7	7	Stable disease
23	59	IIIC	Serous	T/C×9 → D/P×6 → To/P×6 → G×3	5	5	Progressive disease
24	69	IIIC	Serous	T/C×9 → To/P×9	3	2	Progressive disease

Table 2. continued

No.	Age (yr)	FIGO stage	Histology	Prior chemotherapy	Treatment time for FOLFOX-4 (mo)	Cycles of FOLFOX-4	Tumor response[a)]
25	79	IIC	Serous	T/C×6 → D/C×9 → To×3 → G/P×4	5	2	Progressive disease
26	50	IIIB	Serous	T/C×9 → To/P×6 → D/C×4	4	7	Partial response
27	70	IIIC	Serous	T/C×9 → D/C×3 → To×9 → To/P×6	5	6	Partial response
28	60	IIIC	Serous	T/C×9 → To/P×3 → G/C×3	4	2	Progressive disease

FOLFOX-4, oxaliplatin, leucovorin, and 5-fluorouracil; FIGO, International Federation of Gynecology and Obstetrics criteria for ovarian cancer; T, paclitaxel; C, carboplatin; D, docetaxel; WT, weekly paclitaxel; To, topotecan; P, cisplatin; G, gemcitabine; WI, weekly irinotecan; PLO, pegylated liposomal doxorubicin; E, etoposide; Cy, cyclophosphamide; Do, doxorubicin. [a)]Tumor response according to the Response Evaluation Criteria in Solid Tumors.

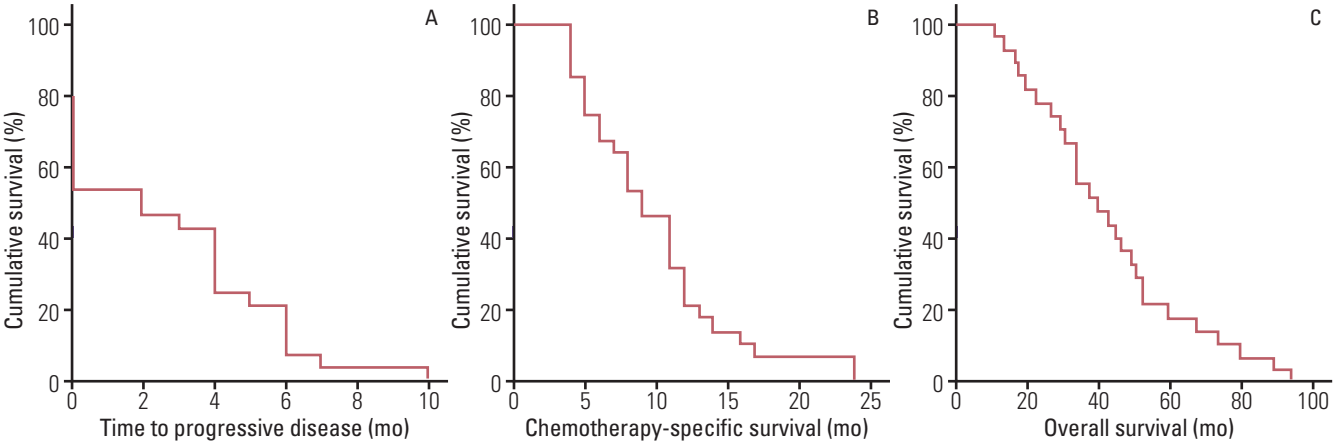

Fig. 1. Kaplan-Meier survival analysis with the log-rank test for (A) time to progressive disease, (B) chemotherapy-specific survival, and (C) overall survival in 28 patients with recurrent epithelial ovarian cancer who received oxaliplatin, leucovorin, and 5-fluoleurouracil (FOLFOX-4) chemotherapy.

ewed our experience, and then compared our results with those reported in three previous studies [12-14].

Three drugs consisting of FOLFOX-4 have been studied extensively for efficacy in previous studies. Oxaliplatin is known to have relative non-cross-resistance with cisplatin or carboplatin [6], and it has mild to moderate hematological and neurological toxicities [18,19]. Previous studies have reported an overall response rate of 5.6-17% in platinum-resistant EOC when using a single-agent, oxaliplatin [19,20], whereas grade 3 or 4 neutropenia, thrombocytopenia, and anemia were observed in 4%, 2-15%, and 2-3%, and grade 3 gastrointestinal and neurological toxicities were 3-8% and 1-23%. In addition, as reported in previous studies, the combination of LV and 5-FU is also known to be active for treatment of platinum-resistant EOC [7,8,21], where the overall response rate has been reported to be 2.4-23%, and grade 3 or 4 anemia, thrombocytopenia, and gastrointestinal toxicities were reported to be 1.6%, 2%, and 2-14.9%.

Nevertheless, the synergic efficacy and toxicity by the combination of oxaliplatin, LV and 5-FU for treatment of recurrent EOC are still unclear. In the current study, overall response rates were 22.2% (CR, 0; PR, 2) in nine patients with measurable disease, and 26.3% (CR, 0; PR, 5) in 19 patients with non-measurable disease. In addition, clinical benefit rates, including CR, PR, and SD were 44.4% and 47.4% in patients with measurable and non-measurable diseases, respectively. In terms of survival and toxicity, FOLFOX-4 chemotherapy showed an adequate survival benefit (TTPD, 3 months; CSS, 9 months; OS, 40 months), and its toxicity was acceptable (0-10.7%) without treatment-related death. These

Table 3. Comparison of efficacy and toxicity of FOLFOX-4 in recurrent epithelial ovarian cancer

Characteristic	Sundar et al. [12]		Pectasides et al. [13]	Rosa et al. [14]		Current study	
Study design	Prospective		Prospective	Retrospective		Retrospective	
No. of patients	27		38	14		28	
FIGO stage							
I	0 (0)		0 (0)	2 (14.3)		0 (0)	
II	2 (7.4)		14 (36.8)	0 (0)		2 (7.1)	
III	16 (59.3)		18 (47.4)	11 (78.6)		21 (75.0)	
IV	9 (33.3)		3 (7.9)	1 (7.1)		5 (17.9)	
Unknown	0 (0)		3 (7.9)	0 (0)		0 (0)	
Tumor response	WHO criteria (n=20)	Rustin criteria (n=25)	WHO criteiria (n=38)	RECIST criteria (n=14)	Rustin criteria (n=14)	RECIST criteria (n=9)	Rustin criteria (n=19)
CR or 75% response	3 (15.0)	12 (48.0)	3 (7.9)	2 (14.3)	4 (28.6)	0 (0)	0 (0)
PR or 50% response	3 (15.0)	2 (8.0)	8 (21.1)	2 (14.3)	2 (14.3)	2 (22.2)	5 (26.3)
Overall response	6 (30.0)	14 (56.0)	11 (29.0)	4 (28.6)	6 (42.9)	2 (22.2)	5 (26.3)
Median TTPD (mo)	4		4.8	–		3	
Median CSS (mo)	10		10.1	–		9	
Median no. of prior chemotherapy (range)	1 (1-2)		1 (1-3)	5 (3-10)		5 (2-8)	
Median cycles of FOLFOX-4 (range)	7 (2-12)		4 (1-8)	8 (2-11)		5 (1-10)	
Grade 3 or 4 toxicity							
Anemia	1 (3.7)		4 (10.6)	0 (0)		2 (7.1)	
Leukopenia	0 (0)		–	0 (0)		0 (0)	
Neutropenia	4 (14.8)		11 (29.0)	1 (7.1)		3 (10.7)	
Thrombocytopenia	3 (11.1)		8 (20.8)	1 (7.1)		1 (3.6)	
Abdominal discomfort	–		–	0 (0)		0 (0)	
Anorexia	–		3 (7.9)	0 (0)		0 (0)	
Constipation	0 (0)		–	0 (0)		0 (0)	
Diarrhea	1 (3.7)		3 (11.5)	0 (0)		0 (0)	
Fatigue	–		3 (7.9)	0 (0)		1 (3.6)	
Nausea and vomiting	0 (0)		4 (10.5)	0 (0)		2 (7.1)	
Mucositis	–		4 (10.5)	0 (0)		0 (0)	
Peripheral neuropathy	–		6 (15.8)	2 (14.3)		3 (10.7)	
Peripheral edema	–		–	0 (0)		0 (0)	
Hypokalemia	0 (0)		–	0 (0)		0 (0)	

Values are presented as number (%). FOLFOX-4, oxaliplatin, leucovorin, and 5-fluorouracil; FIGO, International Federation of Gynecology and Obstetrics; WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; TTPD, time to progressive disease; CSS, chemotherapy-specific survival.

findings indicate that FOLFOX-4 chemotherapy is feasible as a salvage treatment for heavily pretreated patients with recurrent EOC.

For clarification of the efficacy and toxicity of FOLFOX-4 chemotherapy in treatment of EOC, we compared our results with those reported in three previous relevant studies (Table 4) [12-14]. The current study showed comparable response to that reported in three previous studies [12-14] in patients with measurable disease (overall response rate, 22.2% vs. 28.6-30.0%). Nonetheless, in the current study, tumor response was lower than that reported in three previous studies [12-14] with non-measurable disease (overall response rate, 26.3% vs. 42.9-56.0%). A possible explanation would be that more heavily pretreated patients were enrolled in the current study, when compared with two previous prospective studies reported by Sundar et al. [12] and Pectasides et al. [13] (median number of prior chemotherapy, 5 vs. 1). However in the current study, tumor response was lower than that reported in a previous retrospective study by Rosa et al. [14] (26.3% vs. 42.9%), in spite

Table 4. Summary of tumor responses

	No. of patients (%)		Total (%)
	Patients with measurable disease (by RECIST criteria)	Patients with non-measurable disease (by Rustin criteria)	
Complete response	0 (0)	0 (0)	0 (0)
Partial response	2 (22.2)	5 (26.3)	7 (25.0)
Stable disease	2 (22.2)	4 (21.1)	6 (21.4)
Partial disease	5 (55.6)	10 (52.6)	15 (53.6)
Total	9 (100)	19 (100)	28 (100)

RECIST, Response Evaluation Criteria in Solid Tumors.

of similar numbers of heavily pretreated patients (median time of prior chemotherapy, 5 vs. 5). Some limitations, including a retrospective design, small number of enrolled patients, and different regimens of prior chemotherapy appeared to show the difference of tumor response between the current study and the previously reported study by Rosa et al. [14].

In addition, we found that the median TTPD and CSS were similar between the current study and the three previous studies (TTPD, 3 months vs. 4-4.8 months; CSS, 9 months vs. approximately 10 months) [12-14]. Furthermore, grade 3 or 4 toxicity of the current study was similar to that reported in the three previous studies [12-14], suggesting that the toxicity of FOLFOX-4 chemotherapy was acceptable (0-29.0%). In particular, grade 3 or 4 anemia (3.7-10.6%), neutropenia (7.1-29.0%), and thrombocytopenia (7.1-20.8%) were the most common, whereas grade 3 or 4 diarrhea (0-11.5%) and nausea/vomiting (0-10.5%), and peripheral neuropathy (10.7-15.8%) were also commonly observed as non-hematological toxicity [12-14].

Conclusion

Through our experience and review of previous relevant studies, we found that FOLFOX-4 chemotherapy was efficient in heavily pretreated patients with EOC. In addition, its toxicity was acceptable, and manageable by supportive care. Thus, FOLFOX-4 chemotherapy should be considered as feasible for treatment of recurrent EOC in patients with heavily pretreated EOC, and its efficacy and toxicity should be approved by relevant clinical trials in the near future.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

This research was supported by a grant (nos. 04-2012-0890; 03-2012-0170) from the Seoul National University Hospital (SNUH) research fund.

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