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ORIGINAL ARTICLE

Treatment outcomes of oxaliplatin, 5-FU, and leucovorin as salvage therapy for patients with advanced or metastatic gastric cancer: a retrospective analysis

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Abstract
Purpose We performed a single-institution retrospective study to evaluate the efficacy and toxicities of oxaliplatin, 5-fluorouracil (5-FU), leucovorin (LV) combination chemotherapy as salvage treatment in patients with metastatic or advanced gastric cancer.
Methods Sixty-two patients with advanced gastric cancer previously treated were eligible for the study. Patients received oxaliplatin 100 mg/m^2 and LV 100 mg/m^2 (2-h intravenous infusion) followed by 5-FU 2,400 mg/m^2 (46-h continuous infusion) every 2 weeks, and responses were assessed after every three cycles.
Results Fifty-nine out of 62 patients were assessable for response. Among them, 46 patients had previously been treated with cisplatin based chemotherapy. Patients had a median age of 57 years (range 32–76 years), 72.6% had an Eastern Cooperative Oncology Group performance status of 0 or 1. Total 296 courses of chemotherapy were administered as second-line (67.7%) or third-line (27.4%), and the median courses per patient was three cycles. Out of 59 evaluable patients, 14 partial responses were observed (overall response rate, 22.6%). Stable disease was observed in 22 patients (35.5%), and progressive disease in 23 patients (37.1%). The median response duration, time to progression, and overall survival were 2.3, 3.0, and 8.0 months, respectively. The major toxicities were neutropenia, mucositis, and peripheral neuropathy. Grade 3 or 4 hematologic toxicities included neutropenia in nine patients (14.5%) and thrombocytopenia in one patient (1.6%). Other grade 3 or 4 toxicities included mucositis in one patient (1.6%) and vomiting in two patients (3.2%). Grade 1 or 2 peripheral neuropathy were observed in 18 patients (29.0%), however there were no cases of grade 3 or 4 peripheral neuropathy and no treatment-related deaths.
Conclusion The combination of oxaliplatin, 5-FU and LV was effective and safe salvage chemotherapy in advanced gastric cancer patients.

Keywords Oxaliplatin · 5-Fluorouracil · Salvage therapy · Gastric cancer

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Introduction

Gastric cancers in locally advanced or metastatic stages are the second leading cause of cancer death in Korea [1], and the prognosis is extremely poor: The overall response rate of chemotherapy in advanced gastric cancer is 30–50% [2, 3]. Furthermore, complete response is rare and the time to progression is short, thus necessitating the need for development of effective second or third-line chemotherapy regimen. Oxaliplatin (*cis*-[oxaloto(trans-l-1,2-diaminocyclohexane) platinum(II)]) is a third generation platinum compound that has known to be effective in various type of tumors [4, 5]. Compared with cisplatin, oxaliplatin appears to have a better safety profile and has higher anticancer activities [6], and the dose-limiting toxicity is a cumulative sensory peripheral neuropathy [7]. It has been approved for the treatment of advanced colorectal cancer and has also shown activity in several other malignancies, such as lung, ovary,

head and neck, and pancreatic cancer [4, 8–10]. In addition, synergism between oxaliplatin and 5-fluorouracil (5-FU) has been demonstrated in vitro and in vivo [11, 12], and the combination of oxaliplatin, 5-FU, and leucovorin (LV) has been proven to be effective as first-line chemotherapy in metastatic gastric cancer with fewer side effects than other agents [13–17], thus suggesting its usefulness as salvage chemotherapy. Therefore the present study was undertaken to investigate the efficacy and safety of an oxaliplatin, 5-FU, and LV combination in previously treated patients with advanced or metastatic gastric cancer.

Patients and methods

Patients

Eligibility

Patients were eligible with histologically confirmed inoperable or metastatic adenocarcinoma of the stomach; at least one measurable lesion, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, age >18 years, life expectancy $\geq$12 weeks, no concurrent uncontrolled medical illness, no other malignancies, and adequate hepatic, renal and bone marrow function (leukocytes, 4,000–12,000 cells/mm^3; platelets, $\geq$100,000/mm^3; hemoglobin concentration, $\geq$9.0 g/dl; aminotransferases $\leq$2.5 times the upper limit of normal; and total bilirubin and creatinine, <1.5 times the upper limit of normal in the respective center). Patients were excluded from the study if they had peripheral neuropathy of National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade $\geq$2, were pregnant or breast-feeding, showed clinical evidence of major organ failure, had central nervous system metastases; had neurologic or mental disease, or active infection. Signed informed consent was obtained from all patients.

Chemotherapy

Patients received oxaliplatin 100 mg/m^2 and LV 100 mg/m^2 (2-h intravenous infusion) followed by 5-FU 2,400 mg/m^2 (46-h continuous infusion). Cycles were repeated every 2 weeks, and treatment was continued until disease progression, unacceptable toxicity, patient's refusal, or physician's decision, and assessment of responses was repeated every three cycles.

Evaluation of efficacy, toxicities and dosage modification

Responses were classified according to Response Evaluation Criteria In Solid Tumors (RECIST) guideline [18]. Computed tomography (CT) scans of measurable lesions were carried out within 4 weeks before the start of the treatment and were repeated every three cycles (6 weeks). Responses were confirmed by subsequent CT scans 4–6 weeks after initial response documentation. Toxicity was graded according to NCI-CTC version 3.0 before starting each 2-week cycle. Peripheral sensitive neuropathy was graded according to the following oxaliplatin-specific scale [19]: grade 1, paresthesias/hypoesthesias of short duration with complete recovery before the next cycle; grade 2, paresthesias/hypoesthesias persisting between two cycles without functional impairment; and grade 3, permanent paresthesias/hypoesthesias resulting in functional impairment.

Chemotherapy was delayed until recovery if neutrophils decreased to less than 1.5×10^9/l or platelets decreased to less than 75×10^9/l or for significant persisting nonhematologic toxicity. Oxaliplatin and 5-FU dose reductions were required for grade 3 or 4 neutropenia, thrombocytopenia, or anemia. The 5-FU dose was reduced after NCI-CTC grade $\geq$3 diarrhea, stomatitis, or dermatitis occurred. Oxaliplatin was reduced in cases of persistent ($\geq$14 days) paresthesia or temporary (7–14 days) painful paresthesia or functional impairment.

Statistical methods

This study was primarily a retrospective analysis to evaluate efficacy and safety, therefore, no formal estimation of the sample size was done. Survival times were calculated from the start of the study treatment until death. Progression-free survival was calculated from the first day of the chemotherapy until the date of progression or the date of last follow-up for any other reasons. Progression-free survival and overall survival curves were obtained using the Kaplan–Meier method. Multivariate analysis of prognostic factors was performed by the Cox proportional hazard method to evaluate the influence of prognostic factors on patient survival.

Response duration was calculated from the date of response confirmation to the date of disease progression. The difference in response by previous therapy was evaluated with Fisher exact test and chi-squared test. The statistical significance was established as $P < 0.05$.

Results

Between November 2000 and August 2006, 97 patients at Korea University Medical Centers were treated with this chemotherapy, but 27 patients were treated as first-line chemotherapy, 2 patients had brain metastasis, and 6 patients had no measurable lesion, thus they were excluded. Total 62 patients were enrolled in this study, 59 out of 62 patients were assessable for response. Tumor response was not

assessable in three patients; one patient refused to continue the treatment and two patients were lost for follow-up after one and three cycles, respectively. Among 59 evaluable patients, 42 patients had previously been treated with cisplatin based chemotherapy. Twenty patients (32.3%) had previously been treated with more than two regimens.

Patients had a median age of 57 years (range 32–76 years), and 72.6% had an ECOG performance status of 0 or 1. Patient's characteristics and previous chemotherapeutic regimens are listed in Tables 1 and 2.

Response

The overall response rates are listed in Table 3. Response rates were calculated in the intent-to-treat population. Out of 62 intent-to-treat patients, 14 partial responses were observed, giving an overall best response rate of 22.6% [95% confidence interval, (95% CI), 12.0–33.2%]. Median duration of these responses was 2.3 months. Twenty-two patients (35.5, 95% CI, 23.6–47.7%) showed stable disease (SD), and 23 patients (37.1, 95% CI, 24.8–49.4%) had progressive disease (PD). The difference in response by the number of prior therapy, by the response in prior therapy, by the drug of prior therapy containing cisplatin or 5FU was evaluated, but there was no significant difference in response by these variables (Table 4).

Table 1 Patient characteristics ($n = 62$)

Characteristics ($n = 62$)	No.	%
Gender		
Female	13	21.0
Male	49	79.0
Age		
Median (range)	57 (32–76)	
Line		
2nd	42	67.7
3rd	17	27.4
4th	2	3.2
5th	1	1.6
Performance status		
0–1	45	72.6
2	17	27.4
Site of metastasis (multiple involved)		
Liver	29	46.8
Lymph nodes	39	62.9
Peritoneum	7	11.3
Lung	4	6.5
Ovary	2	3.2
Pancreas	4	6.5
Adrenal gland	5	8.1

Table 2 Previous chemotherapy

Previous Regimen	No. of patients	%
DPUL[a]	11	17.7
EPUL[b]	3	4.8
Premetexed + cisplatin	7	11.3
Paclitaxel + cisplatin	11	17.7
5-FU + cisplatin	7	11.3
Capecitabine + cisplatin	2	3.2
S-1 + cisplatin	1	1.6
Irinotecan + capecitabine	13	21.0
Docetaxel + S-1	3	4.8
Docetaxel + 5-FU	2	3.2
FAM[c]	1	1.6
Irinotecan + 5-FU	1	1.6
Cisplatin containing CTx	42	67.7
Cisplatin non-containing CTx	20	32.3

[a] DPUL = Docetaxel, Cisplatin, UFT, LV

[b] EPUL = Epirubicin, Cisplatin, UFT, LV

[c] FAM = 5-FU, doxorubicin, and mitomycin

Table 3 Response rate

	No. of patients	%
Not assessable	3	4.8
Complete response	0	0
Partial response	14	22.6
Stable disease	22	35.5
Progressive disease	23	37.1
Response rate (95% CI)	22.6% (12.00–33.22)	
Disease-stabilization rate (95% CI)	58.1% (45.57–70.63)	

Table 4 Difference in response by previous therapy

	No. of responder (CR + PR)	No. of non-responder (SD + PD + NE)	*P* value
Number of prior chemotherapy			
1	9	30	0.723
2	5	14	
3	0	3	
4	0	1	
Previous response			
Yes	12	43	0.651
No	2	5	
Prior therapy containing Cisplatin			
Yes	10	32	0.737
No	4	16	
Prior therapy containing 5-FU			
Yes	0	10	0.099
No	14	38	

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* non-evaluable, *5-FU* 5-fluorouracil

Survival

Sixty-two patients were included in the survival analysis on an intent-to-treat basis. The median duration of follow-up was 6.3 months (range 0.6–46.5 months). Nine patients were followed for longer than 12 months. The median progression-free survival (PFS) was 3.0 months (range 0.5–8.0 months), and the median overall survival (OS) was 8.0 months (range 0.6–34.8 months). PFS and OS were assessed by Kaplan–Meier-Analysis and the result is shown in Fig. 1.

We conducted multivariate analysis of baseline characteristics such as age, gender, ECOG performance status, and the sensitivity to previous chemotherapy regimen in order to evaluate the prognostic factors for survival. As shown in Table 5, good ECOG performance (ECOG 0–1) was found to be significant independent prognostic factors in OS (Hazard ratio 0.252, 95% CI 0.107–0.592, $P = 0.002$).

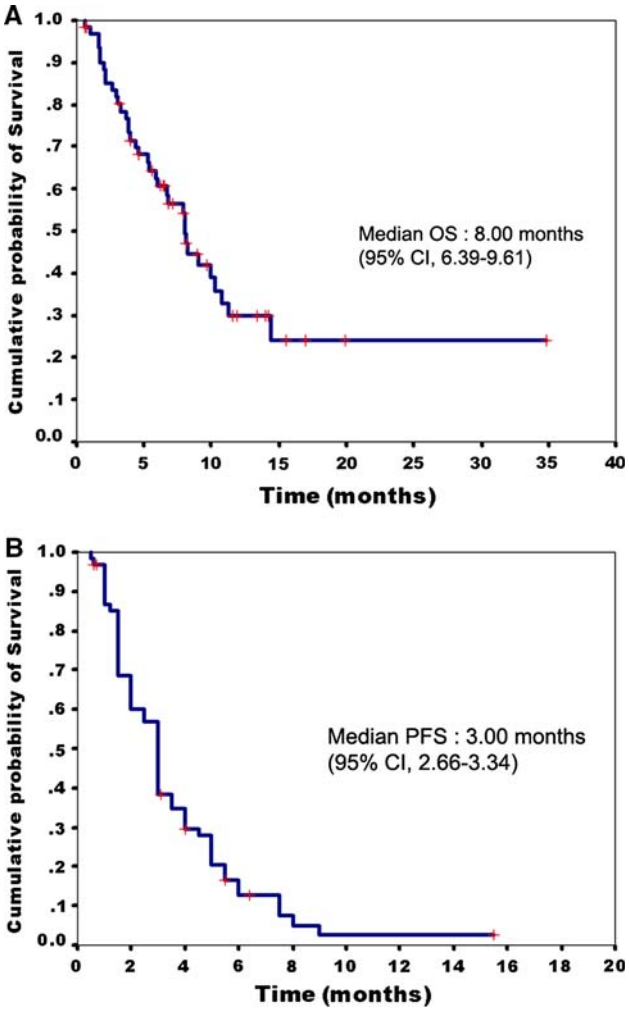

Fig. 1 Overall survival (**a**) and progression-free survival (**b**)

Table 5 Prognostic significance of clinical factors according to Cox multivariate analysis

	Hazard ratio	95% CI	*P* value
Gender (female, male)	0.809	0.352–1.862	0.619
Age	0.980	0.950–1.011	0.198
ECOG PS (0–1, 2)	0.252	0.107–0.592	0.002
Responsiveness to prior therapy	2.107	0.802–5.536	0.130

ECOG PS Eastern Cooperative Oncology Group performance status

Toxicities and dose reductions

Sixty-two patients received a total of 296 treatment cycles. The median number of cycles administered was 3 (range 1–12 cycles). Forty-five percent of patients received at least six cycles, and 16% of patients received more than nine cycles.

Toxicities experienced during the treatment are listed in Table 6. The major toxicities were neutropenia and peripheral neuropathy. NCI-CTC grade 3 or 4 hematologic toxicities included neutropenia in nine patients (14.5%) and anemia in two patients (3.2%). Other grade 3 or 4 toxicities included mucositis in one patient (1.6%) and vomiting in two patients (3.2%). Eighteen patients (29.0%) experienced grade 1 or 2 peripheral neuropathy, but there were no cases of grade 3 or 4 peripheral neuropathy. Treatment interruptions or discontinuation for peripheral neuropathy and treatment-related deaths were not reported.

Dosage of oxaliplatin and 5-FU was reduced in 13 patients. The reasons for dose reduction were due to grade 3/4 neutropenia in nine patients (14.5%), grade 3 mucositis in one patient (1.6%), grade 3 fatigue in one patient (1.6%), and grade 3 vomiting in two patients (3.2%). However, percentage of intended dose administered was 97.8% of oxaliplatin and 96.4% of 5-FU and the median cumulative doses were 300 mg/m^2 (range 100–1,175 mg/m^2) for oxaliplatin and 7,200 mg/m^2 (range 2,400–28,200 mg/m^2) for 5-FU.

Discussion

Gastric cancer is the second leading cause of cancer death worldwide [20], and over 80% of all patients are either diagnosed at an advanced stage when the tumor is inoperable, or recur within five years after surgery. Although many chemotherapeutic agents have been studied since 1970, the median survival of patients with metastatic disease remains between 6 and 9 months. Despite being considered to be only slightly chemo-sensitive tumor, combination chemotherapy helps to improve survival and quality of life in

Table 6 Toxicities according NCI-CTC grade

Type of toxicity	Grade of toxicities				% of grade 3 or 4
	1	2	3	4	
Hematologic					
Neutropenia	16 (25.8%)	3 (4.8%)	6 (9.7%)	3 (4.8%)	14.5
Thrombocytopenia	3 (4.8%)	0	1 (1.6%)	0	1.6
Anemia	16 (25.8%)	17 (27.4%)	2 (3.2%)	0	3.2
Non-hematologic					
Mucositis	9 (14.5%)	3 (4.8%)	1 (1.6%)	0	1.6
Neuropathy	14 (22.6%)	4 (6.5%)	0	0	0

Table 7 Comparison of efficacy of salvage regimens in advanced gastric cancer

Study	No. of patients	Response rate (%)	Median TTP (months)	Median OS (months)
Modified FOLFIRI [25][a]	30	10	3.3	14.3
Irinotecan and cisplatin [26][b]	32	28	3.5	9.4
Irinotecan and cisplatin [27][c]	28	25	3.5	5.6
Irinotecan, 5-fluorouracil and leucovorin [28][d]	64	21	2.5	7.6
Docetaxel [29][e]	49	16	2.5	8.3
Oxaliplatin, 5-fluorouracil and leucovorin [22][f]	26	26	4.3	7.3
This report	62	21	3.0	8.0

[a] Modified FOLFIRI: irinotecan 150 mg/m^2 (day 1), leucovorin 20 mg/m^2, of 5-fluorouracil (bolus) 400 and 600 mg/m^2 (22 h continuous infusion) (days 1–2), every 14 days

[b] The treatment consisted of irinotecan (70 mg/m^2) on day 1 and day 15 and cisplatn (80 mg/m^2) on day 1; repeated every 4 weeks

[c] Salvage chemotherapy with irinotecan and cisplatin in patients with metastatic gastric cancer failing both 5-fluorouracil and taxanes

[d] Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer

[e] Salvage chemotherapy with docetaxel was given IV at a dose of 75 mg/m^2 every 3 weeks

[f] Treatment comprised oxaliplatin (85 mg/m^2 on day 1) as a 2-h infusion followed by bolus 5-FU (400 mg/m^2 on day 1), and 48-h infusion of 5-FU 2.4–3.0 g/m^2 concurrently with LV 150 mg/m^2

comparison to best supportive care [21]. However, the role of medical treatment in advanced gastric cancer still remains palliative, about half of the patients receiving chemotherapy are not responsive and treatment results of second or third-line chemotherapy are unsatisfactory, therefore, there is no standard second or third-line chemotherapeutic regimen for patients with advanced gastric cancer. The combination of oxaliplatin, 5-FU and LV as first-line treatment of advanced gastric cancer was investigated in some phase II studies, however, there are only a few reports on salvage treatment setting until now. The purpose of this retrospective analysis was to evaluate the efficacy and toxicities of oxaliplatin, 5-FU, and LV combination chemotherapy in previously treated patients with advanced gastric cancer. In this study, the overall response rate was 22.6%, median PFS was 3.0 months, and median OS was 8.0 months. The present results are comparable with previously reported oxaliplatin based regimen in second-line setting of advanced gastric cancer that reported a median PFS of 4.3 months and a median OS of 7.3 months [22]. The response rate in our present study was encouraging, because of 22.6% (95% CI 12.0–33.2%) with disease stablization in a further 36% of patients. Recently, other series of studies using different administration schedules of oxaliplatin and 5-FU have also demonstrated good efficacy and tolerable toxicities in gastric cancer. However, other FOLFOX regimen in gastric cancer caused significant peripheral neuropathy and myelosuppression, and therefore, we used biweekly combination therapy with oxaliplatin, 5-FU, and LV without 5-FU bolus in patients with advanced gastric cancer. Compared to FOLFOX6, our protocol consisted of same doses of oxaliplatin (100 mg/m^2) and different doses of 5-FU (2.4 g/m^2 without bolus over 46 h vs. 2.4–3.0 g/m^2 over 48 h plus FU bolus 400 mg/m^2). The most frequent hematologic toxicities in our study were neutropenia and anemia, whereas non-hematologic toxicity was peripheral neuropathy. Grade 1/2 neutoropenia and anemia were observed in 30.5 and 53.2% of patients, respectively, however, grade 3/4 neutropenia occurred in only 14.5% of patients. In other oxaliplatin based phase II studies, grade 1/2 neutropenia and anemia occurred in 12–73 and 51–80% of patients in first-line setting [13, 17, 23], and 16 and 2%

in second-line setting [22], respectively. In the present study, grade 1/2 peripheral neuropathy was found in 29.0% of patients, however, there was no severe grade 3/4 neuropathy and no treatment interruption. It may be due to a relatively low cumulative dose of oxaliplatin (300 mg/m^2) in our study compared to other phase II studies showing different oxaliplatin cumulative dose (451–901 mg/m^2) [13, 17, 24]. Treatment compliance of our regimen appears to be good, because relative dose-intensity for oxaliplatin and 5-FU was 97.8 and 96.4%, respectively. Oxaliplatin is known to have activity against advanced metastatic gastric cancer both in chemotherapy-naive patients and after cisplatin failure. In this study, 42 out of 62 patients had received prior chemotherapy containing cisplatin, and they responded to our protocol, therefore our regimen seems to be effective in second or third-line chemotherapy for patients previously treated with cisplatin. In other salvage chemotherapy, several combination chemotherapy regimens in phase II studies showed overall response rates in the range of 10–28%, while our present study showed comparable response rate and OS (Table 7).

In conclusion, the findings of this retrospective study demonstrate that the combination of oxaliplatin, 5-FU, and LV was an effective salvage regimen (response rate of 22.6%) and toxicity profile was favorable in previously treated patients with advanced gastric cancer. Further prospective studies of this combination chemotherapy in second or third-line setting are warranted.

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