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RESEARCH

Combination Chemotherapy with S-1 and Oxaliplatin (SOX) as First-Line Treatment in Elderly Patients with Advanced Gastric Cancer

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Abstract This study is a retrospective analysis evaluating the efficacy and toxicity of combination chemotherapy with S-1 and oxaliplatin (SOX) as first-line treatment in elderly patients with advanced gastric cancer. One hundred and twenty-nine patients with recurrent or metastatic gastric adenocarcinoma were treated with SOX; S-1 (40–60 mg depending on patient's body surface area) was given orally, twice daily on days 1 to 14 followed by a 7-day rest period, 130 mg/m^2 oxaliplatin was given as an intravenous infusion over 2-hours on day one. The cycle was repeated every three weeks. All of the patients were older than 65 years. Among 129 patients enrolled, nine patients could not be evaluated for responses because of the absence of any measurable lesions or early discontinuation of therapy. Assessment of the response of 120 patients was made. The overall objective response rate was 54.2 % (95 %CI, 45.3–63.1 %), with three complete responses and 62 partial responses. The disease control rate was 80.8 % (95 %CI, 73.8–87.8 %). The median follow-up period was 23 months (range, 5–42 months). The median time to progression was 6.9 months (95 %CI, 5.5–8.3 months) and the median overall survival was 12.8 months (95 %CI, 11.4–14.2 months). The one-year survival rate was 57.5 % (95 %CI, 48.7–66.3 %). In 129 patients assessed safety, grade 3 and 4 toxicities included leucopenia (20.9 %), neutropenia (24.0 %), anemia (10.9 %), thrombocytopenia (10.1 %), anorexia (3.1 %), peripheral neurotoxicity (15.5 %), and fatigue (12.4 %). No treatment-related deaths occurred. Combination chemotherapy with SOX offers an effective, safe and well-tolerated regimen for elderly patients with advanced gastric cancer.

Keywords Advanced gastric cancer · S-1 · Oxaliplatin · Elderly · Combination chemotherapy

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Introduction

Although the incidence and mortality rates of gastric cancer have been decreasing, gastric cancer is currently the fourth most common cancer worldwide [1]. Surgery is the only effective treatment modality for localized resectable cases, but the majority of the patients with gastric cancer are diagnosed at a very advanced stage. The incidence of gastric cancer increases gradually in individuals aged ≥65 years old [2]. These patients have few opportunities for surgery. Providing adequate health care for elderly people is becoming an increasingly important issue in industrialized nations. According to many randomized studies, chemotherapy for advanced (including recurrent or metastatic) gastric cancer (AGC) has been accepted as palliative treatment leading to improvement of survival and quality of life compared to the best supportive care [3]. However, only a few studies have administered

chemotherapeutic regimens to elderly patients. Thus, it is essential to find highly effective and minimally toxic therapeutic approaches for elderly patients with AGC.

S-1 is an orally administered prodrug of 5-fluorouracil (5-FU) that contains tegafur blended with two modulators, gimeracil and potassium oxonate [4]. As a single agent, S-1 has been shown to achieve response rates ranging from 28.9 to 49 % [5, 6]. In addition, several phase I-II studies have demonstrated that S-1 in combination with oxaliplatin (SOX) has a high response rate ranging from 53 to 59 % and an excellent toxicity profile in the treatment of advanced gastric cancer [7–9]. However, the information on the use of a SOX regimen in elderly patients is limited. This study retrospectively analyzed the clinical efficacy and safety of combination chemotherapy with SOX as first-line treatment in elderly patients with AGC.

Patients and Methods

Eligibility Criteria

One hundred and twenty-nine patients were enrolled in the investigation after being histologically-proven to have AGC. Inclusion criteria were as follows: initially diagnosed disease which was locally-advanced (unresectable) or metastatic disease or recurrent disease, ECOG performance status ≤2, measurable disease by imaging, age greater than 65 years old, life expectancy >3 months, and no prior chemotherapy except those who had completed postoperative adjuvant therapy at least 6 months before enrollment. Patients were also required to have adequate hematologic, renal and hepatic function, defined by an absolute neutrophil count ≥1000/μL, hemoglobin ≥8.0 g/dL, platelets ≥80,000/μL, bilirubin less than 2 mg/dL, estimated creatinine clearance of more than 50 mL/min or creatinine concentration less than twice the upper limit of normal, and AST, ALT, and alkaline phosphatase levels less than two times the upper limit of normal. Patients were excluded if they had active bleeding or had chemotherapy in the three months before entering the study or if they had any history of clinically significant cardiac disease or pre-existing peripheral neuropathy or brain metastasis. In addition, patients with any other active carcinoma or history of major neuropsychiatric disease or active infection were excluded. Consent was obtained from all the patients prior to entry into the study.

Treatment Program

The treatment program adopted consisted of oxaliplatin at a dose of 130 mg/m^2 given in 250 ml of 5 % dextrose as an intravenous infusion over 2-hours on day one. This was followed by S-1 that was administered orally twice daily for 14 days (from the evening on day 1 until the morning on day 15), followed by a 7-day rest period. Dosages were assigned according to the patient body surface area; <1.25 m^2 received 40 mg/day, 1.25–1.5 m^2 received 50 mg/day, and ≥1.5 m^2 received 60 mg/day. The cycle was repeated every three weeks. Management continued for up to 6 cycles until intolerable toxicity or disease progression occurred or until treatment withdrawal. A median of four cycles of treatment (range, 1-6cycles) was administered to all patients. Granulocyte colony-stimulating factor (G-CSF) could be administered if needed. The dose could be modified or the rest between cycles increased if adverse effects developed.

Evaluation of Response and Toxicity

The pretreatment assessment included relevant medical history, physical examinations, laboratory tests (including complete blood count and biochemical tests), pathology, ECG, and radiology. Pretreatment staging was by computed tomography (CT) scans of the chest, abdomen and pelvis. A radiologic evaluation was completed within two weeks prior to treatment. During treatment, patients were evaluated weekly by a complete blood count. Physical examination, performance status, and serum chemistry were recorded prior to each subsequent cycle. Radiologic studies, including CT scans were repeated every two cycles.

The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Patients were considered assessable for response if they had early disease progression or received a minimum of two cycles of treatment with at least one tumor measurement. If a patient was documented as having a complete (CR) or a partial response (PR), the response was confirmed at least four weeks after the first evident response. At the end of two cycles, patients were evaluated for response then observed at 3-month intervals over the first year, and observed for survival thereafter. Time to progression (TTP) was measured from study entry until documented progression, relapse, or death from any cause; patients in remission who received further therapy were censored. Overall survival (OS) was measured from study entry until death from any cause. No patient was excluded from survival analyses. Toxicity was assessed during the period of treatment of each cycle via the National Cancer Institute common toxicity criteria (NCI-CTC) version 3.0 toxicity scale.

Statistical Analysis

Descriptive statistics were used to describe the patient population, treatment outcome, and incidence of toxicity. Continuous variables were summarized by displaying descriptive statistics. TTP and OS analyses were all estimated using the Kaplan-Meier method. The statistical data were obtained using an SPSS software package (SPSS 16.0 Inc., Chicago,

IL, USA). Multivariate analyses using the Cox proportion-hazard regression mode were performed to assess the impact of the following variables on TTP and OS; sex, ECOG score, metastatic site, disease status, number of metastases, histological differentiated, and location of primary tumor. Differences were considered significant at $P<0.05$.

Results

Patient Characteristics and Clinical Data

All patients who were evaluated and treated from January 2008 to September 2013 at the Fujian Medical Union Hospital were included in the current retrospective analysis. The characteristics of 129 enrolled patients with gastric cancer are listed in Table 1. The median age of the patients was 69 years old (range, 65–78 years old), there were 82 males and 47 females. One hundred and two (79.1 %) of the patients had metastatic disease, whereas twenty-seven (21.9 %) patients had recurrent disease after surgery and/or adjuvant chemotherapy. Only seven patients received prior adjuvant chemotherapy (six cycles of 5-FU and cisplatin) who had completed post-operative adjuvant therapy at least 6 months before enrollment. Lymph nodes, peritoneum and liver were the most common metastatic sites.

Table 1 Patients' characteristics ($n=129$)

Characteristics	Number of patients
Gender	
Male	82 (63.6)
Female	47 (36.4)
Age (years)	
Median (range)	69 (65~83)
ECOG performance status	
0	15 (11.6)
1	47 (36.4)
2	67 (51.9)
Location of primary tumor	
Gastro-esophageal junction	36 (27.9)
gastric	93 (72.1)
Histology (adenocarcinoma)	
Well differentiated	6 (4.7)
Moderately differentiated	42 (32.6)
Poorly differentiated	64 (49.6)
Unspecified	17 (13.2)
Disease status	
Metastatic	102 (79.1)
Recurrent	27 (21.9)
Surgery only	20 (15.5)
Surgery with adjuvant chemotherapy	7 (5.4)
FP	7
Metastatic site	
Peritoneal seeding	67 (51.9)
Liver	20 (15.5)
Lymph node	56 (43.4)
Lung	12 (9.3)
Bone	3 (2.3)
Others (ovary, pancreas)	9 (6.9)
Number of metastases	
1	29 (22.5)
2	85 (65.9)
≥3	15 (11.6)

Figures in parentheses are percentages; FP, 5-FU and cisplatin

Treatment Outcomes and Impact Factors

Of a total of 129 patients, 9 could not be evaluated for responses because of the absence of any measurable lesions or early discontinuation of therapy. The responses of 120 patients are listed in Table 2. The median follow-up period was 23 months (range, 5–42 months). The overall objective response rate was 54.2 % (95 %CI, 45.3–63.1 %), with three CR (2.5 %) and 62 PR (51.6 %). Thirty-two cases of stable disease and 23 cases of progressive disease were observed in the remaining patients. The one-year survival rate was 57.5 % (95 %CI, 48.7–66.3 %). The number of metastases had a significant impact on the response rate to chemotherapy with SOX ($P=0.012$). The median time to progression was 6.9 months (95 %CI, 5.5–8.3 months) and the median overall survival was 12.8 months (95 %CI, 11.4–14.2 months) (Fig. 1). Therefore, the overall disease control rate was 80.8 %. Most of the patients had a documented improvement of tumor-related symptoms, such as reduced pain or dysphagia. Patients with peritoneal seeding, lymph node metastatic sites, and fewer than two metastatic tumors benefited from SOX.

Table 3 shows the univariate and multivariate analysis of variables for OS and TTP. Among the clinical factors in the univariate analysis, disease status, the number of metastases, and the histological differentiation had a significant prognostic impact. A multivariate analysis with a Cox regression model was performed to determine which clinical variables were associated with OS. There were three independent prognostic indicators; disease status (HR 1.614 and $P=0.004$), number of metastases (HR 1.871 and $P=0.002$), and histological differentiation (HR 1.135 and $P=0.018$). The multivariate analysis of TTP identified the following four relevant factors; metastatic site (HR 1.128 and $P=0.025$), disease status (HR 1.669 and $P=0.005$), number of metastases (HR 2.219 and $P=0.001$), and histological differentiation (HR 1.066 and $P=0.040$). Three of them were common with factors of OS, but metastatic site only predicted TTP.

Table 2 Response of gastric cancer (n=120)

Parameter	No.	CR	PR	SD	PD	RR%	P value
Whole study	120	3	62	32	23	54.2	–
Histology (adenocarcinoma)							
Well differentiated	6	0	4	2	0	66.7	0.443
Moderately differentiated	38	2	20	12	4	57.9	
Poorly differentiated	59	1	29	17	12	50.8	
Unspecified	17	0	9	1	7	52.9	
Location of primary tumor							
Gastro-esophageal junction	32	0	14	11	7	43.8	0.618
gastric	88	3	48	21	16	57.9	
Disease status							
Metastatic	97	3	54	20	20	58.8	0.417
Recurrent	23	0	8	12	3	34.8	
Number of metastases							
1	26	3	15	8	0	69.2	0.012
2	83	0	47	21	15	56.6	
≥3	11	0	0	3	8	0	
Gender							
Male	78	2	41	19	16	55.1	0.969
Female	42	1	21	13	7	52.4	
Metastatic site							
Peritoneal seeding	62	1	40	14	7	66.1	0.422
Lymph node	55	2	36	15	2	69.1	
Liver	20	0	2	10	8	10.0	
Lung	12	0	0	4	8	0	
Bone	3	0	0	2	1	0	
Others (ovary, pancreas)	9	0	2	5	2	22.2	

No. Number of patients, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease

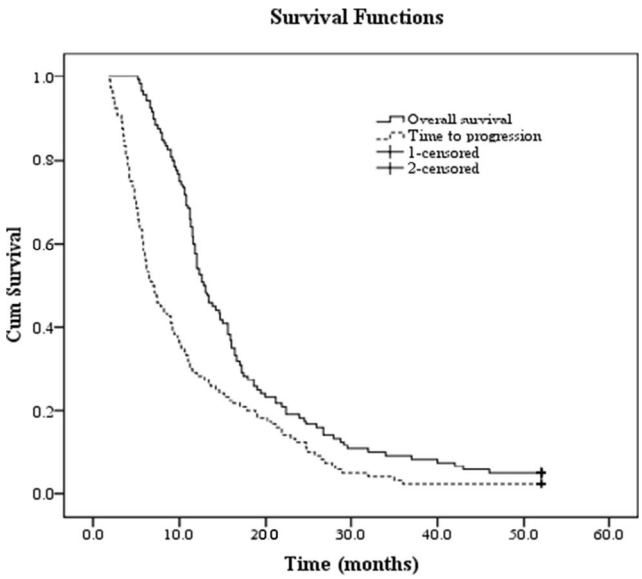

Fig. 1 Overall survival and time to progression in patients (n=120)

Sixteen (13.3 %) patients received second-line treatment; ten paclitaxel plus 5-FU, and six 5-FU/leucovorin plus irinotecan.

Side Effect Analysis

One hundred and twenty-nine patients received a total of 576 cycles of treatment, with a median of four cycles per patient (range, 1–6 cycles). The dose of oxaliplatin was reduced by 25 % for the sixteen patients who developed grade-3 peripheral neurotoxicity.

The toxicity observed in the patients is listed in Table 4. The most common grade-3 and grade-4 hematologic toxicities were neutropenia, thrombocytopenia and anemia, which were reported in 24.0, 10.1 and 10.9 % of patients, respectively. Febrile neutropenia was observed in five patients after one or two cycle, but they recovered without complications. The most common grade-3 and grade-4 non-hematologic toxicities were anorexia, peripheral neurotoxicity and fatigue, which were reported in 3.1, 15.5 and 12.4 % of patients, respectively. No treatment-related deaths occurred.

Discussion

With constant improvement in the quality of life in modern society, people's life span has been prolonged. The incidence of elderly patients with gastric cancer is gradually increasing, and the majority of these patients have advanced disease when they are diagnosed. In AGC, systemic chemotherapy has been considered the choice for palliative treatment, leading to the response of the tumor to therapy, improved quality of life, and survival [3]. AGC is usually treated by combination chemotherapy with fluoropyrimidine derivatives and platinum compounds. Several large-scale phase III studies have shown that the response rate ranges from 25 to 54 %, median PFS from 2.9 to 7 months, and median survival time (MST) from 8.6 to 13 months [10–13]. However, the elderly are less likely to receive the recommended treatment because of their shorter life expectancy, lower immune function, higher incidence of multiple organ dysfunction, and higher risk of complications; all of which lead to reduced tolerance to chemotherapy and increased sensitivity to side effects of these drugs. When chemotherapy is needed, oral chemotherapy may be especially advantageous for elderly patients because of its convenience and the high acceptance rate.

S-1 is a novel oral fluoropyrimidine drug that combines tegafur with 5-chloro-2, 4-dihydropyrimidine (CDHP) and potassium oxonate in a molar ratio of 1:0.4:1. CDHP reversibly inhibits the activity of dihydropyrimidine dehydrogenase (DPD), the rate limiting enzyme for the degradation of fluorouracil, which results in higher concentrations of fluorouracil sustained for prolonged periods in serum and tumors.

Table 3 Cox proportional hazards model evaluating multi-factors on OS and TTP

Variable	OS				TTP			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P
Sex	1.016 (0.722–1.326)	0.851			1.021 (0.885–1.392)	0.725		
ECOG	0.941 (0.756–1.073)	0.119			0.894 (0.772–1.086)	0.115		
Metastatic site	0.965 (0.853–1.012)	0.061			1.087 (1.007–1.136)	0.035	1.128 (1.025–1.231)	0.025
Disease status	1.606 (1.323–1.889)	0.004	1.614 (1.417–1.782)	0.004	1.588 (1.343–1.823)	0.006	1.669 (1.427–1.911)	0.005
Number of metastases	1.986 (1.515–2.455)	0.001	1.871 (1.383–2.359)	0.002	2.447 (1.356–3.479)	0.001	2.219 (1.254–3.251)	0.001
Histological differentiated	1.364 (1.292–1.435)	0.014	1.135 (1.054–1.216)	0.018	1.126 (0.873–1.326)	0.023	1.066 (0.825–1.287)	0.040
Location of primary tumor	0.889 (0.875–1.015)	0.105			1.011 (0.792–1.311)	0.102		
Adjuvant chemotherapy	0.982 (0.823–1.212)	0.638			0.976 (0.796–1.198)	0.587		

Figures in parentheses are 95 %CIs; OS, Overall survival; TTP, Time to progression

Potassium oxonate blocks the phosphorylation of fluorouracil in the gastrointestinal tract, and then reduces the gastrointestinal toxic effects of fluorouracil [14]. Several studies have shown that S-1 as a single agent or S-1 plus cisplatin, produced antitumor activity against AGC [5, 6, 15]. Recently, the JCOG9912 study demonstrated the non-inferiority of S-1 to continuous infusion of 5-FU [16], and the SPIRITS study showed that that treatment outcomes using S-1 plus cisplatin were superior to S-1 alone [15]. In the SPIRITS study, the response rate, median PFS, and MST achieved with S-1 plus cisplatin were 54 %, 6.0 months, and 13.0 months, respectively. However, severe toxic effects were observed in the patients with S-1 plus cisplatin. Thus, it is necessary to develop new therapeutic approaches with improved safety for elderly patients with AGC.

Table 4 Main Toxicity (n=129)

Type of toxicity	Grade[a]				III+IV (%)
	I	II	III	IV	
Hematological toxicity					
Leucopenia	60	26	23	4	27 (20.9)
Neutropenia	69	20	24	7	31 (24.0)
Anemia	49	16	14	0	14 (10.9)
Thrombocytopenia	23	17	13	0	13 (10.1)
Non-hematological toxicity					
Nausea/vomiting	20	6	0	0	0
Diarrhea	12	2	0	0	0
Stomatitis	8	5	0	0	0
Anorexia	12	8	4	0	4 (3.1)
Fatigue	49	18	16	0	16 (12.4)
Peripheral neurotoxicity	17	25	20	0	20 (15.5)
Hypertransaminasemia	20	2	0	0	0
Renal impairment	4	3	0	0	0
Myocardial ischemia	3	0	0	0	0
Anaphylaxis	7	2	0	0	0

[a] NCI -CTC version 3.0 toxicity scale

Oxaliplatin is a newer-generation platinum compound which improves tolerability that translates to patient convenience when compared to cisplatin. The REAL-2 study showed that oxaliplatin had a similar effect to cisplatin in patients with previously untreated AGC [12]. A phase III study [13] compared the combination of fluorouracil, leucovorin and oxaliplatin (FLO) with fluorouracil, leucovorin and cisplatin (FLP) in patients with metastatic gastroesophageal adenocarcinoma. The results demonstrated that the median PFS improves with FLO when compared to FLP, 5.8 months to 3.9 months, respectively. However, FLO was associated with significantly fewer serious adverse events than were seen with FLP, 9 and 19 %, respectively. In patients older than 65 years old, this study also showed that the response rate in the FLO group was significantly superior to the FLP group, 41.3 to 16.7 %, and the duration of median PFS 6.0 months to 3.1 months, and OS 13.9 months to 7.2 months, were significantly longer in the FLO group than in the FLP group. Oxaliplatin, when combined with S-1 every three weeks, has demonstrated significant activity in patients with AGC. Koizumi et al. [8] found that the response rate was 59.0 %, and the disease control rate was 84.0 %, the median PFS was 6.5 months, the 1-year survival rate was 71 %, and MST was 16.5 months in a G-SOX study. Park et al. [9] reported an overall objective response of 55.3 %, median time to progression 6.6 months, and median overall survival of 12.5 months. In our experience, combination chemotherapy with SOX for elderly patients achieved a high rate of overall objective response of 54.2 % (95 %CI, 45.3–63.1 %). Pain was alleviated without the need to administer or increase analgesics. The median time to progression was 6.9 months (95 %CI, 5.5–8.3 months) and the median overall survival

calculated from study entry was 12.8 months (95 %CI, 11.4–14.2 months). The results are quite similar to those of the study of Park [9].

A comparison of safety between the SOX regimen and S-1 plus cisplatin that were previously reported indicates a lower incidence of grade 3/4 leucopenia, neutropenia, anemia, anorexia and nausea with the SOX regimen [8, 15]. Comparing the incidence of grades 3 and 4 toxicities following the SOX regimen and a S-1 plus cisplatin regimen found lower incidence of leucopenia, 4 vs. 11 %, neutropenia, 22 vs. 40 %, anemia, 9 vs. 26 %, anorexia, 6 vs. 30 %, and nausea, 2 vs. 11 %. However, the incidence of grade 3/4 thrombocytopenia was higher with the SOX regimen, 13 vs. 5 %. Sensory neuropathy is a characteristic toxicity associated with oxaliplatin, and 89 % of the patients receiving the SOX regimen had neuropathy, but only 4 % had severe grade 3/4 neuropathy. These results indicate that a SOX regimen is more tolerable and tends to be superior to S-1 plus cisplatin in terms of safety. In our study, the most common toxicity associated with combination chemotherapy with SOX was myelosuppression. The most common grade 3 and 4 hematologic toxicities were neutropenia, thrombocytopenia, and anemia were reported in 24.0, 10.1 and 10.9 % of patients, respectively. The most common grade 3 and 4 non-hematologic toxicities were anorexia, peripheral neurotoxicity and fatigue reported in 3.1, 15.5 and 12.4 % of patients, respectively. The results were not highly different from results reported in previous studies of patients with gastric cancer [8, 9]. All the patients with neutropenia, anemia and thrombocytopenia recovered 3–4 weeks after ending treatment on their own or after administration of G-CSF. The toxicity was considered tolerable by the patients.

The prognostic factors including disease status, number of metastases and histological differentiation for OS and TTP were identified in the multivariate analysis in patients with AGC, while only the metastatic site affects TTP. It is important to consider these factors because they provide us with the keys to future improvements.

In conclusion, combination chemotherapy with SOX can achieve a high efficacy with tolerant toxicity in elderly patients with AGC. Moreover, the SOX regimen has the potential to replace current regimens such as S-1 plus cisplatin or 5-FU plus cisplatin because of similar efficacy with less toxicity and more convenient treatment. It may provide an alternative option and prolong survival and improve the patient's quality of life in elderly patients with AGC. However, these were the results of a retrospective study, and this regimen needs to be further assessed, and possibly compared with other regimens in prospective randomized trials.

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