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Efficacy of Conversion Surgery Following S-1 plus Cisplatin or Oxaliplatin Chemotherapy for Unresectable Gastric Cancer

MINORU FUKUCHI, ERITO MOCHIKI, TORU ISHIGURO, TOSHIRO OGURA, JUN SOBAJIMA, YOUICHI KUMAGAI, KEIICHIRO ISHIBASHI and HIDEYUKI ISHIDA

Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

Abstract. *Background/Aim: To evaluate the efficacy of conversion surgery following S-1 plus cisplatin (CS) or oxaliplatin (SOX) chemotherapy. Patients and Methods: We retrospectively analyzed clinicopathological and survival data of 74 patients with unresectable gastric cancer receiving CS or SOX. Results: Fifty-five and nineteen patients received CS and SOX, respectively. Conversion surgery (odds ratio (OR), 0.17; 95% confidence interval (CI), 0.04-0.64; p=0.01) was the only significant independent predictor of longer survival in multivariate Cox regression analysis. Patients (median age, 74 years) receiving SOX were significantly older than those receiving CS (median age=67 years) (p<0.01), although the rates of response, severe toxicity or conversion surgery did not differ significantly between the two treatment groups. Conclusion: Conversion surgery after a response to CS or SOX chemotherapy may have survival benefit in selected unresectable gastric cancer patients, for both non-elderly and elderly patients responding to SOX.*

Gastric cancer is the third leading cause of cancer death worldwide and the second leading cause of cancer death in Japan (1). It is generally diagnosed in the late stages, and exhibits a high frequency of invasion or metastasis. The prognosis of patients with unresectable gastric cancer characterized by invasion or metastasis is usually poor. These patients are currently not considered candidates for surgery and are usually offered chemotherapy. However, several novel combined chemotherapy regimens occasionally allow conversion of initially unresectable gastric cancer to resectable cancer. Additional (conversion) surgery after response to chemotherapy results in long-term survival in selected patients (2-7). We have previously reported that patients with unresectable gastric cancer obtained survival benefit from S-1-based chemotherapy, and subsequent conversion surgery (8).

In Japan, the SPIRITS trial, a phase III study, established S-1 plus cisplatin (CS) as a standard first-line treatment for unresectable gastric cancer (9). The G-SOX trial, a phase III study of patients with unresectable gastric cancer, has recently shown that S-1 plus oxaliplatin (SOX) therapy is not inferior to CS therapy (10). Japanese guidelines indicate that SOX therapy has become an option for first-line treatment and is tentatively rated as recommendation category 2 (11). In the sub-analysis of the G-SOX trial, SOX demonstrated favorable efficacy and feasibility compared with CS in elderly patients with unresectable gastric cancer (12).

Recent advances in chemotherapy for gastric cancer encouraged us to perform conversion surgery following a response to chemotherapy for patients with initially unresectable gastric cancer. Although the efficacy of SOX is shown to be equivalent to that of CS for unresectable gastric cancer, candidacy for conversion surgery following SOX remains unclear. In this study, we retrospectively investigated the efficacy and feasibility of SOX therapy and conversion surgery compared with CS therapy for patients with initially unresectable gastric cancer, especially focusing on patients aged 70 years or older.

Patients and Methods

Patients. We retrospectively reviewed a database of 74 patients with unresectable gastric cancer who underwent first-line chemotherapy with SC or SOX at the Saitama Medical Center of Saitama Medical University from May 2005 to November 2016. The study was approved by the Local Ethics Committee of Saitama Medical Center of Saitama Medical University (No. 613-II).

Tumor staging was performed according to the Union for International Cancer Control pTNM staging guidelines, 7th edition

Correspondence to: Minoru Fukuchi, MD, Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan. Tel: +81 492283619, Fax: +81 492228865, e-mail: mfukuchi@saitama-med.ac.jp

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(13). Terminology defined by the Japanese Gastric Cancer Association was used to avoid unnecessary confusion (14). In addition, eligible patients were required to have an Eastern Cooperative Oncology Group performance status (PS) of 0-2. Patients with unresectable gastric cancer were considered if they had at least one initially proven lesion with any noncurative factor, such as tumor invasion of adjacent structures (T4b), peritoneal (P1), hepatic (H1) and distant (M1) metastasis or positive peritoneal cytology (CY1). The main indication for conversion surgery was anticipation of curative resection based on the response to chemotherapy (8).

Chemotherapy schedule. For CS therapy, patients received oral S-1 (40 mg/m^2 twice daily) on days 1–21 plus intravenous cisplatin (60 mg/m^2) on day 8 of a 5-week cycle (9). For SOX therapy, patients received oral S-1 (40 mg/m^2 twice daily) on days 1-14 plus intravenous oxaliplatin (100 mg/m^2) on day 1 of a 3-week cycle (10). Treatment was discontinued at the onset of disease progression, development of severe toxic effects, or the patient's request. Disease progression was assessed by physical examination, histological findings, clinical follow-up, and imaging, as described previously (8). Tumor response was objectively assessed after each treatment course according to the Response Evaluation Criteria in Solid Tumors. Adverse events were evaluated by the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis. Continuous variables are expressed as median and range. Patients' characteristics were compared using the χ^2 test, Fisher's exact probability test, and Mann–Whitney *U*-test. We calculated the cumulative overall survival (OS) rates by the Kaplan–Meier method and compared survival curves with the log rank test. OS was estimated from initial chemotherapy to the date of death or the last follow-up visit. Cox proportional hazard regression analysis was used to identify statistically significant independent factors for OS. Factors with a *p*-value <0.05 according to univariate analysis were assessed by multivariate analysis. In the univariate and multivariate analyses, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All statistical analyses were performed with JMP 5.0 software (SAS Institute Inc., Cary, NC, USA), and *p*-values <0.05 were considered statistically significant.

Table I. *Demographics of 74 patients with unresectable gastric cancer who underwent first-line chemotherapy.*

Characteristic	
Median age (range), years	69 (31-82)
Gender, n	
Male/female	59/15
Performance status	
0/1/2	49/20/5
Location, n	
Upper/middle/lower	34/25/15
Macroscopic type	
Type1/2/3/4	3/13/35/23
Histological type, n	
G1/2/3	10/20/44
Tumor depth, n	
T2/3/4a/4b	4/16/41/13
Nodal stage, n	
N0/1/2/3	12/10/19/33
Peritoneal metastasis, n	
P0/1	55/19
Hepatic metastasis, n	
H0/1	46/28
Distant metastasis, n	
M0/1	30/44
Peritoneal cytology, n	
Negative/positive	68/6
Number of noncurative factors, n	
1/2/3	42/27/5
First-line chemotherapy, n	
S-1+cisplatin/S-1+oxaliplatin	55/19
Median number of cycles, (range)	4 (1-12)
Response, n	
CR/PR/SD/PD	1/24/18/31
Toxicity, n	
Grade1/2/3/4	33/13/20/8
Surgery, n	
No/Yes	53/21

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Results

Patients' characteristics. The characteristics of the 74 patients who underwent first-line chemotherapy with CS or SOX are presented in Table I. There were 59 male and 15 female patients with a median age of 69 years (range=31-82 years). Fifty-five patients received CS therapy and nineteen received SOX therapy, which was selected for 12, five and three patients with 70 years or older, renal dysfunction and a request for outpatient treatment, respectively (overlapping). One patient (1%) had a complete response (CR), 24 (32%) had a partial response (PR) and 18 (24%) had stable disease (SD). Twenty-eight patients (38%) had grade 3 or 4 toxicity. Twenty-one patients (28%) were converted to surgery.

Survival. The median OS of all 74 patients was 12 months, with a median follow-up time of 10 months (range=1-93 months). Patients converted to surgery following chemotherapy had significantly longer OS than those treated with chemotherapy alone (median time, 37 months *vs*. 9.7 months, $p<0.01$) (data not shown).

We selected the following 11 variables for univariate analysis with regard to OS: age (<69 *vs*. ≥69 years), gender (male *vs*. female), performance status (0 *vs*. 1 or 2), location (upper or middle *vs*. lower), macroscopic type (1, 2 or 3 *vs*. 4), histological type (G1 or 2 *vs*. G3), tumor depth (T2, 3 or 4a *vs*. T4b), nodal stage (N0, 1 or 2 *vs*. N3), P1 (yes *vs*. no), H1 (yes *vs*. no), M1 (yes *vs*. no), CY1 (positive *vs*. negative), number of non-curative factors (1 *vs*. 2 or 3), number of cycles (<5 *vs*. ≥5), first-line chemotherapy (SC *vs*. SOX), response (CR or PR *vs*. SD or progressive disease), toxicity grade (grade 1 or 2 *vs*. grade 3 or 4) and surgery (yes *vs*. no). In univariate

Table II. *Univariate and multivariate analysis in relation to overall survival.*

Variables		Univariate		Multivariate	
	N	Odds ratio (95% CI)	*p*-Value	Odds rate (95% CI)	*p*-Value
Age; years					
<69	37	1			
≥69	37	0.78 (0.43-1.39)	0.40		
Gender					
Male	59	0.77 (0.42-1.50)	0.44		
Female	15	1			
Performance status					
0	49	0.76 (0.56-1.04)	0.09		
1, 2	25	1			
Location					
Upper or middle	59	1			
Lower	15	0.69 (0.44-1.02)	0.07		
Macroscopic type					
Type 1, 2, 3	51	0.80 (0.60-1.08)	0.15		
Type 4	23	1			
Histological type					
G1, 2	30	1			
G3	44	0.83 (0.47-1.51)	0.54		
Tumor depth					
T2, 3, 4a	61	1			
T4b	13	0.58 (0.20-1.34)	0.22		
Nodal stage					
N0, 1, 2	41	0.83 (0.62-1.10)	0.19		
N3	33	1			
Peritoneal metastasis					
P0	55	0.99 (0.73-1.39)	0.95		
P1	19	1			
Hepatic metastasis					
H0	46	0.83 (0.62-1.11)	0.21		
H1	28	1			
Distant metastasis					
M0	30	0.73 (0.54-0.99)	0.04	0.88 (0.62-1.20)	0.42
M1	44	1		1	
Peritoneal cytology					
Negative	68	1			
Positive	6	0.63 (0.19-1.56)	0.35		
No. of noncurative factors					
1	42	0.78 (0.58-1.04)	0.09		
2, 3	32	1			
First-line chemotherapy					
S-1+cisplatin	55	1			
S-1+oxaliplatin	19	0.49 (0.15-1.23)	0.14		
Number of cycles					
<4	36	1		1	
≥4	38	0.52 (0.29-0.95)	0.03	0.57 (0.29-1.08)	0.09
Response					
CR or PR	25	0.23 (0.10-0.46)	<0.01	0.75 (0.21-2.51)	0.65
SD or PD	49	1		1	
Grade 3 or 4 Toxicity					
No	46	0.88 (0.66-1.19)	0.40		
Yes	28	1			
Surgery					
No	53	1		1	
Yes	21	0.13 (0.05-0.31)	<0.01	0.17 (0.04-0.64)	0.01

CI, Confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

analysis, no distant metastasis (p=0.04), number of cycles (p=0.03), response (p<0.01) and surgery (p<0.01) were significantly associated with longer OS. In multivariate Cox regression analysis, only surgery (OR, 0.17; 95% CI, 0.04-0.64; p=0.01) was an independent predictor of longer OS (Table II).

Profile of patients treated with S-1 plus CS or SOX chemotherapy. Assessed characteristics of the study patients included median age, gender, tumor location, macroscopic type, histological type, tumor depth, nodal stage, TNM stage, peritoneal, hepatic and distant metastasis, peritoneal cytology, treatment response, number of treatment cycles, toxicity, and surgery (Table III). Median age (p<0.01) and gender (p=0.01) differed significantly between patients treated with CS and SOX. In addition, median age (p=0.01) also showed a significant difference between patients treated with conversion surgery following CS and SOX (data not shown). Unintentionally, all patients treated with SOX were male. The other baseline characteristics were generally well balanced between the two treatment groups.

Table III. *Characteristics of 74 gastric cancer patients who underwent chemotherapy with S-1 plus cisplatin or S-1 plus oxaliplatin.*

	S-1+cisplatin (n=55)	S-1+oxaliplatin (n=19)	*p*-Value
Age, years, median (range)	67 (31-79)	74 (44-82)	<0.01
Gender			0.01
Male	40	19	
Female	15	0	
Performance status			0.15
0	39	10	
1, 2	16	9	
Location			0.92
Upper or middle	44	15	
Lower	11	4	
Macroscopic type			0.60
Type 1, 2, 3	37	14	
Type 4	18	5	
Histological type			0.36
G1, 2	24	6	
G3	31	13	
Tumor depth			0.65
T2, 3, 4a	46	15	
T4b	9	4	
Nodal stage			0.43
N0, 1, 2	29	12	
N3	26	7	
Peritoneal metastasis			0.50
No (P0)	42	13	
Yes (P1)	13	6	
Hepatic metastasis			0.92
No (H0)	34	12	
Yes (H1)	21	7	
Distant metastasis			0.87
No (M0)	22	8	
Yes (M1)	33	11	
Peritoneal cytology			0.60
Negative	50	18	
Positive	5	1	
Response			0.15
CR or PR	16	9	
SD or PD	39	10	
No. of cycles, median (range)	3 (1-12)	4 (1-9)	0.57
Grade 3 or 4 toxicity			0.92
No	34	12	
Yes	21	7	
Surgery			0.82
No	39	14	
Yes	16	5	

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Discussion

Patients with initially unresectable gastric cancer usually have a poor prognosis and are initially considered to receive systemic chemotherapy, but not surgery. The exception to this is patients who require palliation of symptoms such as bleeding or obstruction (11). However, according to recent advances in chemotherapy, conversion surgery following a response to chemotherapy is occasionally associated with prolonged survival in selected patients (2-8). Although the efficacy of SOX is equivalent to that of CS for unresectable gastric cancer (10), candidacy for conversion surgery following SOX therapy remains unclear in clinical practice. Our data clearly show that conversion surgery is an independent factor for longer OS among unresectable gastric cancer patients treated with CS or SOX as first-line chemotherapy. Our data also show that response to SOX therapy can be an indication for conversion surgery in non-elderly, as well as elderly patients.

Conversion surgery requires that patients have had a response to chemotherapy (8). In the G-SOX trial, the overall response rate (ORR) and disease control rate (DCR) were 55.7% and 85.2% for SOX, and 52.2% and 81.8% for CS, respectively (10). In the present study, the ORR and DCR were 47% and 74% for SOX and 29% and 53% for CS, respectively. The response in our study was lower than that of the G-SOX trial; probably because of the different patient characteristics. As a result, the rate of conversion surgery was 29% for CS and 26% for SOX. Two recent studies concerning conversion surgery have reported that docetaxel, cisplatin and S-1 (DCS) therapy showed a high ORR of 73.7-81.0% and DCR of 87.7-90% (6, 7). The rates of conversion surgery were 33.0-59.6% in DCS therapy, which seems to be expectedly used for conversion surgery (6, 7). However, it is possible that grade 3 or 4 toxicity is more common in DCS than in CS or SOX (6, 7, 10).

It has been reported that SOX is as effective as CS for unresectable gastric cancer, but grade 3 or worse adverse

events were less frequent in SOX than in CS, except for low incidence of sensory neuropathy, especially in elderly patients (≥70 years) (10, 12). Referring to these studies, we performed SOX therapy selectively in elderly patients with unresectable gastric cancer. In the G-SOX trial, median age of patients receiving CS and SOX was 65 years (10). In the present study, median age of patients treated with CS and SOX was 67 and 74 years, respectively. Patients receiving SOX were older than those receiving CS, although the rates of response, grade 3 or 4 toxicity or conversion surgery did not differ significantly between the two treatment groups. The median age of patients treated with conversion surgery following DCS was 62 years in the recent study (7), although median age of patients treated with conversion surgery following CS and SOX was 63 and 75 years, respectively, in the present study (data not shown). Response to SOX might indicate conversion surgery for nonelderly as well as elderly patients compared with CS or DCS. However, numerous obstacles remain to be overcome regarding the selection of initial combination chemotherapy and the indication or timing of conversion surgery (15).

In conclusion, conversion surgery after a response to CS or SOX may yield survival benefit in selected unresectable gastric cancer patients, indicating it for both non-elderly and elderly patients responding to SOX. Although the current retrospective study was performed at a single center on a small patient population, and was therefore subject to selection bias, our findings should stimulate further inquiry into how to manage initially unresectable gastric cancer. A prospective study with a larger series of cases is needed to evaluate conversion surgery for this type of cancer.

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