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Efficacy and Safety Analysis of Oxaliplatin-based Chemotherapy for Advanced Gastric Cancer

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Abstract. *Background: Significant efficacy of oxaliplatin-based chemotherapy has been demonstrated for advanced gastric cancer (AGC). However, the appropriate dose of oxaliplatin, and the efficacy and toxicity of administration of oxaliplatin subsequent to cisplatin therapy still remain unclear. Patients and Methods: In total, 55 patients with AGC that were scheduled to receive oxaliplatin-based chemotherapy were prospectively examined. Results: The median age was 67 years and oxaliplatin was administered to 39 (71%) patients as first-line and in 16 (29%) patients as second-line therapy. An initial dose of 130 or 100 mg/m^2 of oxaliplatin was administered to 11 and 36 patients, respectively. The overall response rates (ORR) and median progression free survival (mPFS) were 86 and 33%, and 7.2 and 7.8 months, respectively. Compared to 100 mg/m^2, the relative dose intensity was significantly lower and severe toxicity tended to increase with oxaliplatin at 130 mg/m^2. A total of 10 patients (18%) had a prior cisplatin-based therapy. The ORR of the patients pretreated with cisplatin was 14% and the mPFS was 6.1 months. Conclusion: An initial oxaliplatin dose of 130 mg/m^2 resulted in a good response, but tended to increase the risk of toxicity. Subsequent oxaliplatin-based therapy after cisplatin exhibited modest efficacy, especially in cases with cisplatin intolerance.*

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Gastric cancer (GC) is the fourth most frequent malignant tumor and the second most common cause of tumor death in the world (1). Recurrent GC after curative resection and initially unresectable metastatic GC (advanced GC; AGC) are treated with systemic chemotherapy (CT), that can prolong survival and maintain quality of life. For the initial CT, combination consisting of fluorouracil or fluoropyrimidine and platinum has been demonstrated to be effective. The triplet regimen including fluoropyrimidine, platinum and epirubicin is often used in European countries (2). Effectiveness of a triplet of docetaxel, cisplatin and fluorouracil has been shown in the United States (3). The standard therapy for patients with AGC in Japan has been a combination of the oral fluoropyrimidine S-1 and cisplatin (SP) based on the results of the phase 3 SPIRITS study (4). Another fluoropyrimidine, capecitabine, has also been shown to be effective for AGC in combination with cisplatin (5).

Oxaliplatin has also been employed for systemic CT for AGC in combination with fluorouracil or fluoropyrimidine

(2, 5, 6). Non-inferiority of oxaliplatin over cisplatin in terms of overall survival (OS) was demonstrated in the randomized phase III REAL-2 study, in which the dosage of oxaliplatin was 130 mg/m^2 (2). A phase II study that examined a combination CT of S-1 plus oxaliplatin (SOX) exhibited efficacy for AGC (7). Subsequently, a phase III G-SOX study aimed at confirming the effectiveness of SOX for Japanese patients with AGC demonstrated similar progression-free survival (PFS) and OS by using a dose of oxaliplatin of 100 mg/m^2. This lower dose of oxaliplatin was used because of frequent thrombocytopenia induced by oxaliplatin in the previous phase II study (7, 8). Therefore, different doses of oxaliplatin have been used in individual regimens in Japanese clinical practice; however, it remains to be clarified which of these doses are the most effective and the safest.

Both cisplatin and oxaliplatin are forms of platinum and can inhibit DNA-duplication by cross-linking double-stranded DNA. Cross-resistance between the two drugs is thought to be unlikely because of the different repair mechanisms for the DNA damage induced by each drug (9-15). Several clinical studies have been conducted to address the efficacy of oxaliplatin-based CT against cisplatin-resistant cancer (16-18). A phase I study that examined a combination of fluorouracil, leucovorin, mitomycin C and oxaliplatin for cisplatin-resistant AGC demonstrated a response rate (RR) of 35%, PFS of 4.1 months and OS of 8 months (17). A phase II study that employed FOLFOX4 (fluorouracil, leucovorin and oxaliplatin) showed an RR of 26% and a median OS of 7.3 months (18). Although these studies suggested efficacy of oxaliplatin-based CT against cisplatin-resistant AGC, sequential usage of cisplatin- and oxaliplatin-based CTs has not been well determined, especially in prospective studies.

The use of oxaliplatin for AGC was approved in Japan in 2015. Some patients with cisplatin-resistant AGC have been treated with oxaliplatin-based CT, and patients intolerant to cisplatin have continued their platinum-based CT by switching from cisplatin to oxaliplatin in clinical practice in Japan. However, the efficacy and safety of administration of oxaliplatin subsequent to cisplatin therapy are poorly understood. In addition, clinical studies of pre-operative SP therapy were recently conducted (19, 20). Conservation of the efficacy and safety of oxaliplatin-based CT in patients who were treated with perioperative cisplatin-based CT in cases of recurrence is an important issue. This study prospectively examined the efficacy and safety of oxaliplatin-based CT in Japanese clinical practice, especially in terms of differences in doses of oxaliplatin and the subsequent use of oxaliplatin after cisplatin therapy.

Patients and Methods

Patients. Patients who started treatment between October 2014 and February 2016 at any of six institutions participating in the Kyushu Medical Oncology Group with written informed consent were assessed. The eligibility criteria were: 20 years or older, histologically proven metastatic or recurrent gastric adenocarcinoma or esophagogastric junction adenocarcinoma, patients who were planned to receive oxaliplatin-based chemotherapy at any treatment line. This study was approved by the Ethics Committee of Kyushu University Hospital (Approval No. 27-80) and was performed according to the guidelines for biomedical research specified in the Declaration of Helsinki.

Treatment. All patients were treated with systemic CT consisting of a combination of SOX, oxaliplatin plus capecitabine (CapeOX), SOX plus trastuzumab, or oxaliplatin, S-1 plus leucovorin. In the SOX regimen, 40-60 mg of S-1 was orally administered twice-daily on days 1-14, depending on the patient's body surface area, and 100 mg/m^2 or 130 mg/m^2 oxaliplatin was administered intravenously on day 1 every 3 weeks. In the CapeOX regimen, 1,000 mg/m^2 capecitabine was orally administered twice-daily on days 1-14 and 100 mg/m^2 or 130 mg/m^2 oxaliplatin was administered intravenously on day 1 every 3 weeks. Trastuzumab was administered at a dose of 8 mg/kg for the initial course and at a dose of 6 mg/kg from the second course on day 1 every 3 weeks. In the combination regimen of oxaliplatin, S-1 plus leucovorin, 85 mg/m^2 of oxaliplatin was administered on day 1 every 2 weeks, and 60 mg S-1 and 25 mg leucovorin were administered twice daily on days 1-7 every 2 weeks. These treatments were continued until disease progression, unacceptable toxicity or the decision to discontinue by the patient or the investigator. Dose reduction and treatment delay were performed basically following the dose modification and interruption protocol of the G-SOX study (8).

Assessments. Assessment of tumor lesions was basically performed by computed tomographic scan. Gastrointestinal endoscopy, magnetic resonance imaging and positron-emission tomography were also utilized for examination of lesions if necessary. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (21). PFS was defined as the period from the initiation of oxaliplatin-based CT to the day of tumor progression or the day of death from any cause. Additionally, for patients who had first-line cisplatin therapy and were then administered oxaliplatin-based therapy as a second line, the period from the initiation of cisplatin therapy to the termination of oxaliplatin-based CT was also examined, which was defined as whole-platinum PFS. All adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (22). The most severe grades of AE in the period of chemotherapy were recorded.

Statistics. PFS was estimated using the Kaplan–Meier method. Comparison of tumor responses and the survival of patient groups according to the dose of oxaliplatin was performed using Fisher's exact test and the log-rank test, respectively. Comparison of baseline characteristics before the initiation of oxaliplatin-based CT was performed using Student's *t*-test. Values of $p<0.05$ were considered statistically significant. All statistical analyses were carried out using JMP software (SAS Institute Japan, Tokyo, Japan).

Results

Patient characteristics. In total, 60 patients with AGC who were treated with oxaliplatin-based CT were registered, of

Table I. *Patient characteristics (n=55).*

Characteristic	No.	%
Median age (range), years	67 (31-83)	-
Gender		
Male	35	64
Female	20	36
PS		
0	29	53
1	24	44
2	1	2
3	1	2
Disease status		
Advanced	48	87
Recurrent	7	13
Histology		
Well/moderately differentiated adenocarcinoma	26	47
Poorly differentiated adenocarcinoma/ signet-ring cell carcinoma	28	51
Mucinous adenocarcinoma	1	2
HER2 status		
Positive	3	5
Negative	47	85
Not measured	5	10
Site of metastasis		
Lymph node	31	56
Peritoneum	28	51
Liver	15	27
Lung	4	7
Bone	3	5
No. of organs with metastases		
0	1	2
1	32	58
2 or more	22	40
Previous therapy for cancer		
Surgery	16	29
Adjuvant CT	8	15
No. of prior CT regimens		
0	39	71
1	16	29
Drug administered in prior CT	n=16	
Cisplatin	10	63
S-1	16	100
Capecitabine	0	0
Trastuzumab	2	13
Number of cycles of prior cisplatin, median (range)	3 (1-6)	-
Reasons for cisplatin discontinuation		
Adverse event	8	80
Progressive disease	2	20

PS: Eastern Cooperative Oncology Group performance status, CT: chemotherapy, HER2: human epidermal growth factor receptor 2.

whom 55 who were treated with oxaliplatin-based CT as first- or second-line therapy were analyzed (Table I). Severe comorbidities prior to CT were observed in 18 patients (33%), including renal dysfunction (creatinine clearance <50 ml/min) in 10 (18%), pulmonary disease in two (4%), poorly controlled diabetes mellitus (hemoglobin-A1c level >7.0%) in two (4%) and moderate to severe ascites in three (5%). At the initiation of oxaliplatin-based CT, poorly controlled hypertension, and hepatic and bone marrow dysfunctions of CTC-AE grade 3 or more were noted in one patient (2%).

Table II. *Details of the oxaliplatin-based chemotherapy (CT) as first-line and second-line (n=55).*

	No.	%
Regimen		
S-1 plus oxaliplatin	50	91
Capecitabine plus oxaliplatin	3	5
Trastuzumab, S-1 and oxaliplatin	2	4
Initial dose of oxaliplatin		
130 mg/m^2	11	20
100 mg/m^2	36	65
<100 mg/m^2	8	15
Initial dose reduction of S-1 or capecitabine		
Yes	21	38
	Median	**Range**
Number of cycles of oxaliplatin-based CT	7	1-22
Number of cycles of oxaliplatin	5	1-17
RDI of oxaliplatin (%)	69	17-100
RDI of capecitabine/S-1 (%)	79	27-100

RDI: Relative dose intensity.

Treatments and their efficacy for the whole patient group. An oxaliplatin-based CT regimen was performed in the 55 patients (Table II). Most patients (65%) were treated with an initial dose of oxaliplatin of 100 mg/m^2. One patient received 85 mg/m^2 of oxaliplatin every 2 weeks and this was considered as the equivalent of a dose of 130 mg/m^2 every 3 weeks. In the 55 patients, the median number of cycles and the median relative dose intensity (RDI) of oxaliplatin-based CT were shown in Table II.

Reasons for discontinuation of oxaliplatin-based CT included progressive disease in 32 patients (58%), AEs in three (5%), patient's wish in two (4%), complete response (CR) in one (2%), complete resection in one (2%), and one patient lost due to transfer to another hospital (2%). Fifteen patients (27%) continued to receive oxaliplatin-based CT.

The best response of the oxaliplatin-based CT is shown in Table III. The ORR was 46% and the disease control rate (DCR; CR, partial response (PR), stable disease (SD) and non-CR/non-progressive disease (PD)) was 85% (Table III). The median follow-up period was 13.1 months. The median PFS was 7.8 months (95% confidence interval (CI)=6.1-10.2 months) (Figure 1A). For patients who received oxaliplatin-based CT as first-line therapy, the ORR was 60% and DCR was 92%; the median PFS was 9.8 months (95% CI=7.2-12.3 months) (Figure 1B).

Table III. *Best objective response of patients with first-line and second line (n=55) and subgroup analyses.*

	All patients	Oxaliplatin 130 mg/m^2	Oxaliplatin 100 mg/m^2	*p*-Value	Cisplatin-pretreated
Number of patients	55	11	36	-	10
Efficacy					
CR	3	0	3	-	1
PR	14	6	5	-	0
SD	12	1	10	-	4
PD	5	0	3	-	1
NE	3	0	3	-	1
Non-CR and non-PD	18	4	12	-	3
ORR	46%	86%	33%	0.028	14%
DCR	85%	91%	87%	0.231	80%

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable, ORR: overall response rate. DCR: disease control rate, PFS: progression free survival.

Comparison of characteristics and efficacy of CT according to the dose of oxaliplatin. Tumor response in terms of the initial dose of oxaliplatin of the 55 patients treated with first-line and second-line therapy was examined (Table III). The median age of the patients treated with an oxaliplatin dose of 130 mg/m^2 and 100 mg/m^2 as the first-line and second-line was 63 and 67 years, respectively. Pathohistological diagnosis, distribution of organs with metastasis, number of organs with metastasis, and severe comorbidities including poor PS and organ disorders were similar in both groups.

The number of patients who received oxaliplatin-based CT as second-line therapy was one (9%) at a dose of 130 mg/m^2 and 10 (28%) at 100 mg/m^2. Of patients who received the 130 mg/m^2 dose of oxaliplatin, nine (82%) were treated with the SOX regimen and two (18%) with CapeOX. All 36 patients who received the 100 mg/m^2 dose were treated with the SOX regimen. The median number of cycles of oxaliplatin-based CT at a dose of 130 mg/m^2 and 100 mg/m^2 was 8 and 7, respectively, and the median number of cycles of oxaliplatin was 5 for both doses. The median RDI of oxaliplatin was significantly lower at a dose of 130 mg/m^2 than at a dose of 100 mg/m^2 (48%, range=22-78% and 74%, range=17-100%), respectively; p=0.0024). The median RDI of fluoropyrimidine was similar in both groups, being 80% (range=34-100) at a dose of 130 mg/m^2 and 80% (range=27-100) at 100 mg/m^2. The ORR of patients treated with oxaliplatin was more favorable at a dose of 130 mg/m^2 than 100 mg/m^2 at 86% and 33%, respectively (p=0.028) (Table III). The median PFS of the patients treated with oxaliplatin at a dose of 130 mg/m^2 and 100 mg/m^2 was 7.2 and 7.8 months, respectively (95% CI=5.1 months–not reached and 5.6-10.2 months, respectively; p=0.6417) (Figure 1C).

Characteristics of oxaliplatin-based CT treatment and efficacy for patients who had prior cisplatin therapy. Ten patients who had received cisplatin prior to oxaliplatin-based CT for AGC (cisplatin-pretreated patients) were further analyzed. Their median age was 65 years (range=50-75 years). Pathohistological diagnosis, distribution of organs with metastasis and number of organs with metastasis were similar to those of the total patient group. All 10 patients had received S-1 plus cisplatin regimen as first-line therapy, and no patient had CT containing trastuzumab. The baseline characteristics of cisplatin-pretreated patients were compared to those of patients who were not administered cisplatin before the initiation of oxaliplatin-based CT (cisplatin-untreated patients). Renal dysfunction (creatinine clearance <50 ml/min) was significantly increased in the cisplatin-pretreated patients (five patients, 50%) compared to the cisplatin-untreated patients (five patients, 11%) (p=0.0117). The initial dose of oxaliplatin was 130 mg/m^2 in one patient (10%), 100 mg/m^2 in eight (80%) and less than 100 mg/m^2 in one (10%). Nine patients (90%) were treated with the SOX regimen, and one (10%) with CapeOX. The median number of cycles of oxaliplatin-based CT was 7 (range=1-17) and that of oxaliplatin was 6 (range=1-17). The median RDI of oxaliplatin was 69% (range=17-100%). Reasons for discontinuation of oxaliplatin-based CT were progressive disease in six patients (60%) and AEs in one patient (10%); this therapy continued in three patients (30%). The ORR of the patients was 14%, and the DCR was 80%. The median PFS of oxaliplatin-based CT was 6.1 months (95% CI=0.9 months–not reached) (Figure 1D).

Additionally, we assessed the therapeutic impact of sequential CT of cisplatin and oxaliplatin. We defined the period from the initiation of S-1 plus cisplatin therapy to the termination of oxaliplatin-based CT as the second-line therapy as whole-platinum PFS. The median whole-platinum PFS in 10 patients was 10.9 months (95% CI=5.1-69.3 months) (Figure 1E).

Safety. Various non-hematological and hematological toxicities were observed in the patients (Table IV). Oxaliplatin-specific peripheral neuropathy appeared in 45 patients (75%). Severe

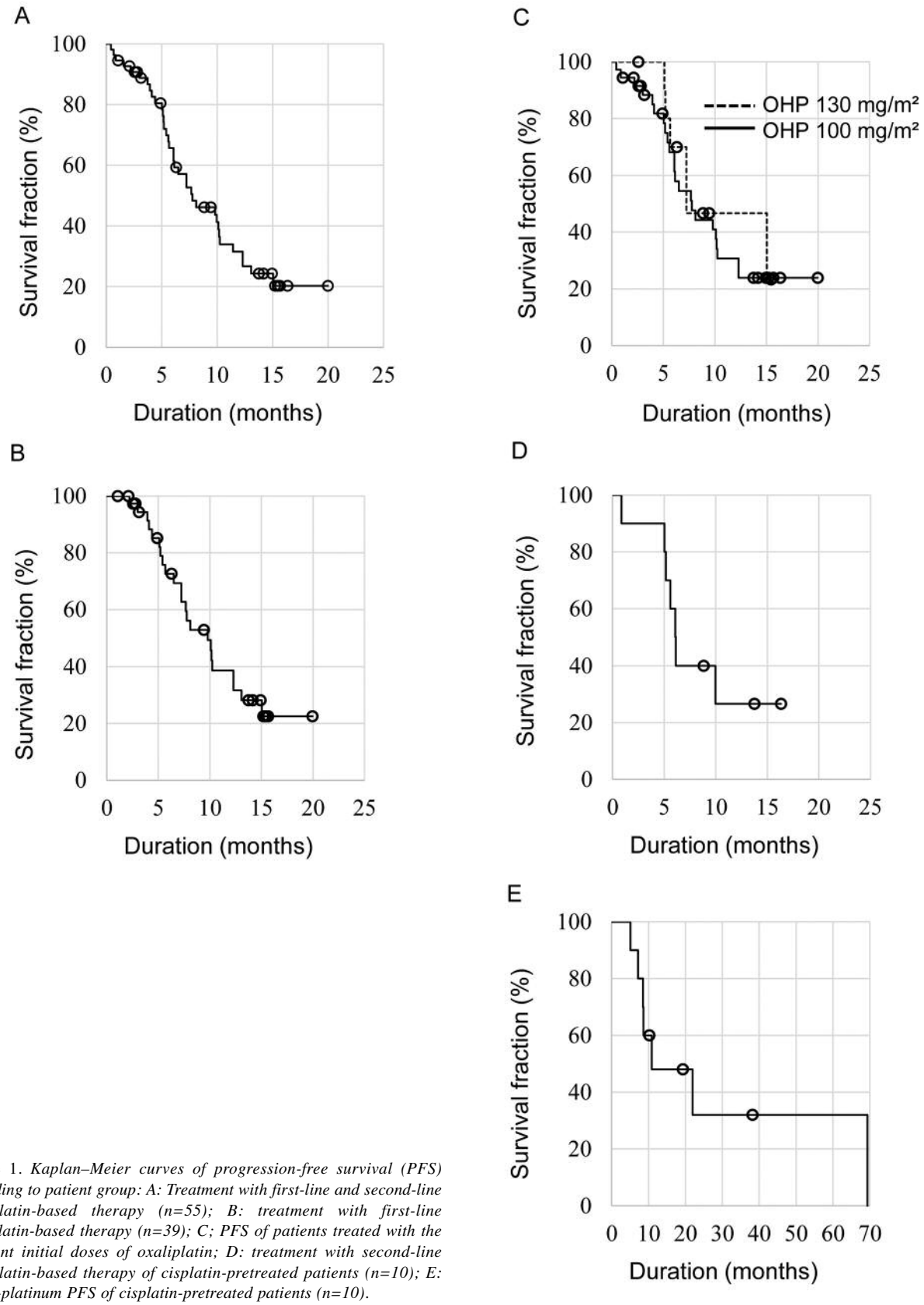

Figure 1. *Kaplan–Meier curves of progression-free survival (PFS) according to patient group: A: Treatment with first-line and second-line oxaliplatin-based therapy (n=55); B: treatment with first-line oxaliplatin-based therapy (n=39); C; PFS of patients treated with the different initial doses of oxaliplatin; D: treatment with second-line oxaliplatin-based therapy of cisplatin-pretreated patients (n=10); E: whole-platinum PFS of cisplatin-pretreated patients (n=10).*

Table IV. *Adverse events of patients with first-line and second line (n=55) and subgroup analyses.*

Adverse event	All patients, n (%) n=55		Oxaliplatin 130 mg/m^2, n (%) n=11		Oxaliplatin 100 mg/m^2, n (%) n=36		Cisplatin-pretreated, n (%) n=10	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Severe non-hematological	-	19 (35)	-	4 (36)	-	7 (19)	-	1 (10)
Nausea	33 (55)	3 (5)	6 (55)	1 (9)	20 (56)	1 (3)	7 (70)	0
Vomiting	10 (17)	0	2 (18)	0	6 (17)	0	2 (20)	0
Anorexia	49 (82)	6 (10)	8 (73)	1 (9)	29 (81)	2 (6)	10 (100)	0
Abdominal pain	7 (12)	1 (2)	0	0	6 (17)	1 (3)	0	0
Fatigue	34 (57)	0	9 (82)	0	17 (47)	0	6 (60)	0
Diarrhea	21 (35)	0	4 (36)	0	11 (31)	0	5 (50)	0
Peripheral neuropathy	45 (75)	1 (2)	8 (73)	1 (9)	28 (78)	0	8 (80)	0
Hand-Foot syndrome	3 (5)	0	1 (9)	0	1 (3)	0	0	0
Thromboembolism	2 (4)	1 (2)	1 (9)	1 (9)	1 (3)	0	1 (10)	0
Febrile neutropenia	0	0	0	0	0	0	0	0
Albumin decrease	57 (95)	0	11 (100)	0	33 (92)	0	9 (90)	0
Total bilirubin increase	15 (25)	1 (2)	4 (36)	0	9 (25)	0	1 (10)	0
AST increase	51 (84)	4 (7)	11 (100)	0	29 (81)	2 (6)	9 (90)	0
ALT increase	23 (37)	0	6 (55)	0	13 (36)	0	4 (40)	0
ALP	37 (62)	1 (2)	8 (73)	0	21 (58)	0	7 (70)	0
Cr ratio increase*	17 (28)	1 (2)	2 (18)	0	10 (28)	0	3 (30)	1 (10)
Severe hematological	-	14 (25)	-	4 (36)	-	6 (17)	-	2 (20)
Leukopenia	23 (38)	4 (7)	7 (64)	1 (9)	11 (31)	2 (6)	5 (50)	1 (10)
Neutropenia	39 (65)	8 (13)	11 (100)	2 (18)	24 (67)	4 (11)	5 (50)	1 (10)
Lymphocytopenia	25 (42)	3 (5)	6 (55)	0	11 (31)	1 (3)	4 (40)	0
Anemia	54 (90)	6 (10)	11 (100)	1 (9)	34 (94)	2 (6)	9 (90)	2 (20)
Thrombocytopenia	44 (73)	2 (4)	9 (82)	1 (9)	23 (64)	1 (3)	8 (80)	0

AST: Aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, Cr: creatinine.*From baseline.

non-hematological toxicity of grade 3 or 4 was observed in 19 patients (35%), and severe hematological toxicity was observed in 14 patients (25%). When the groups treated with the different doses of oxaliplatin were compared, severe non-hematological and hematological toxicity of grade 3 or 4 was observed more frequently in patients treated with an oxaliplatin dose of 130 mg/m^2 than in those treated with 100 mg/m^2 (four patients (36%) and seven patients (19%), p=0.2126, four patients (36%) and six patients (17%), p=0.2555, respectively). In the cisplatin-pretreated group, severe toxicity was anemia in two patients (20%). The frequency of severe thrombocytopenia, peripheral neuropathy, and creatinine baseline ratio increase was not increased, but the frequency of severe anemia was tended to increase in this group compared to patients who had no prior chemotherapy of cisplatin (two patients (20%) and one patient (2%), p=0.0818).

Discussion

The present study was conducted to examine the efficacy and safety of oxaliplatin-based CT for AGC in Japanese clinical practice. Since the efficacy of platinum for AGC has been demonstrated in first-line therapy in pivotal clinical studies, oxaliplatin-based CT was performed in the first-line therapy of 39 patients. Of these patients, S-1 plus oxaliplatin was the most frequently used combination. A previous phase III clinical study that compared S-1 plus cisplatin with SOX (G-SOX study) reported that the median PFS, ORR and DCR of the SOX arm were 5.5 months, 55.7% and 85.2%, respectively (8). The REAL-2 study showed that the PFS and ORR of the combination therapy with epirubicin, oxaliplatin and capecitabine were 7.0 months and 47.9%, respectively (2). In the present study, the ORR of first-line oxaliplatin-based CT was 60% and the median PFS was 9.6 months (95% CI=7.2-12.3 months), which compared favorably with the results of the above pivotal studies. Possible reasons for alteration of the efficacy of oxaliplatin-based CT in the present study might be differences in patient background such as age and comorbidities, disease status including the number of metastatic organs, the pathway of metastasis and histological features. Subgroup analysis of the G-SOX study showed that favorable efficacy of SOX therapy was observed in the patient group with peritoneal dissemination, which consisted of 19% of enrolled patients with AGC (8). Fifty-

one percent of patients in the present study harbored peritoneal dissemination, which might be one reason for the modest efficacy. In terms of AEs, grade 3 or 4 anemia, neutropenia, thrombocytopenia and anorexia were reported in 15.1, 19.5, 10.1 and 15.4% of patients, respectively, in the G-SOX study (8). Consistent with the safety profile of the G-SOX study, the oxaliplatin-based CT employed in the present study was safely administered for the most part, although severe anemia in cisplatin-pretreated patients should be carefully monitored.

When the two different initial doses of oxaliplatin were compared, the RDI of oxaliplatin was significantly lower, and more severe AEs occurred in patients treated with a dose of 130 mg/m^2 than in those treated with 100 mg/m^2. Based on large-scale clinical trials of the combination of SOX, including the G-SOX study, an initial dose of oxaliplatin 100 mg/m^2 has been adopted in Japan. In the present study, the RDI of oxaliplatin at a dose of 130 mg/m^2 was 48%, which was low compared to the median RDI of 100 mg/m^2 in the G-SOX study, which was 79.0%. In addition, all of the patients in the present study that were treated with 130 mg/m^2 underwent dose reduction or oxaliplatin withdrawal due to AEs. Although the ORR was better in the patients treated with 130 mg/m^2 compared to those treated with 100 mg/m^2, and to the results of the G-SOX study, PFS was equivalent, suggesting the possibility that an initial dose of 130 mg/m^2 oxaliplatin is effective in cases where tumor shrinkage is anticipated. However, since no data regarding the effects of a dose of 130 mg/m^2 are available in the literature, a prospective study comparing oxaliplatin doses of 130 mg/m^2 and 100 mg/m^2 for AGC is desired.

Both oxaliplatin and cisplatin are categorized as forms of platinum that exhibit an inhibitory effect on DNA duplication by forming cross-links in DNA strands. Because the mechanisms by which the DNA damage induced by the cross-linking of oxaliplatin and cisplatin are repaired are different, cross-resistance to the two drugs is thought to be low (9-15). Cisplatin tends to induce tumor cell toxicity by forming intra-strand cross-links. The DNA repair machinery of the tumor cell is believed to ignore the DNA deformation caused by the cross-linking of cisplatin, which links neighboring guanine bases. On the other hand, because the DNA deformation induced by oxaliplatin cross-linking is extensive, the DNA repair enzyme hMutS-alpha cannot access the binding site of the oxaliplatin-DNA strand in order to repair it (9-15). The low possibility of cross-resistance between cisplatin and oxaliplatin suggests that sequential administration of these agents might have favorable efficacy. However, in the treatment of AGC in clinical practice, there are few chances to administer these agents sequentially because a platinum-double regimen is often employed in the initial therapy, and monotherapy or a combination of paclitaxel and ramucirumab are performed in the subsequent therapy (23). Several evaluations of the efficacy of oxaliplatin for cisplatin-resistant AGC have been reported. Al-Batran SE *et al*. reported a phase I study of a combination therapy of fluorouracil, leucovorin, oxaliplatin and mitomycin C (FLOM) for cisplatin-resistant AGC. In total, 20 AGC patients were treated with FLOM therapy; the ORR was 35%, the median PFS was 4.1 months and the OS was 8 months (17). A phase 2 study using a combination of fluorouracil, leucovorin and oxaliplatin (FOLFOX4) for cisplatin-resistant AGC demonstrated a RR of 26% and a median OS of 7.3 months. These reports suggested favorable efficacy of oxaliplatin against cisplatin-resistant AGC; however, no prospective study was performed to determine these sequential CTs.

It may be possible that both platinum agents could be administered to AGC patients in the perioperative CT and recurrent disease. S-1 monotherapy for one year or a combination of capecitabine plus oxaliplatin for 6 months have been standard adjuvant CT for AGC patients who had curative surgery in Japan (24, 25). Since clinical studies assessing adjuvant platinum-based CT have not shown effectiveness in a study of SP plus radiation or in the ARTIST study, they may not be employed in the adjuvant setting. On the other hand, for neoadjuvant chemotherapy, a phase 2 clinical study to assess the effect of a pre-operative CT with S-1, docetaxel and cisplatin is now underway against AGC with extensive lymph node metastasis (JCOG1002) (20). A randomized phase III trial of surgery plus neoadjuvant S-1 plus cisplatin compared with surgery alone for type 4 and large type 3 gastric cancer (JCOG 0501) is also ongoing (19). In cases in which the efficacy of neoadjuvant CTs employing cisplatin are proven, there may be an opportunity to administer oxaliplatin to recurrence cases after the CT and surgery (26-28).

Second-line chemotherapy has been proven to contribute to survival in AGC (29). Clinical studies of such CT compared with best supportive care showed an mPFS of 3.0-4.0 months in the CT group. In a phase 3 randomized study that compared weekly paclitaxel *versus* irinotecan for AGC patients after FU plus platinum therapy, the mPFS was 3.6 *versus* 2.3 months, respectively (30). A combination of ramucirumab plus weekly paclitaxel demonstrated an mPFS of 4.4 months (23). In the present study, the mPFS of oxaliplatin-based CT was 6.1 months and the median whole-platinum PFS was 10.9 months in the cisplatin-pretreated patients, which suggests a relatively favorable survival benefit compared with previous reports. It is interesting that the cisplatin-pretreated group exhibited better survival with subsequent oxaliplatin-based CT than when considered as part of the whole-platinum survival group. No significant difference was seen between the PFS of the first-line oxaliplatin group and that of the whole-platinum cisplatin-pretreated patients. Taking these results

into consideration, the present observation could suggest a survival benefit of oxaliplatin-based CT even after cisplatin-based CT. Although a prospective study that would examine the effect of sequential CT of cisplatin-oxaliplatin for AGC is desired in order to clarify its actual impact on survival, the present findings might be of importance in the present situation.

The present study demonstrated that oxaliplatin-based CT administration to Japanese AGC patients harboring a variety of backgrounds could be effective and safe, especially for patients with a prior treatment with cisplatin-based CT. These findings suggest the possibility of selecting oxaliplatin-based CT for cases of especially cisplatin intolerant patients and patients after cisplatin-containing regimens in neo-adjuvant CT and surgery. An initial oxaliplatin dose of 130 mg/m^2 could be effective in cases where tumor shrinkage is anticipated but tended to increase the risk of toxicity.

Conflicts of Interest

Eishi Baba and Koichi Akashi are conducting research sponsored by Yakult Honsha Co., Ltd. The other Authors declare that they have no conflict of interest.

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