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Original Article

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Outcomes of Third-Line Docetaxel-Based Chemotherapy in Advanced Gastric Cancer Who Failed Previous Oxaliplatin-Based and Irinotecan-Based Chemotherapies

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Purpose

Little is known about outcomes in the use of third-line chemotherapy in cases of advanced gastric cancer (AGC). The primary aim of this retrospective study was to evaluate outcomes of docetaxel-based chemotherapy in patients with AGC that progressed after both oxaliplatin-based and irinotecan-based regimens.

Materials and Methods

Eligible patients were those with AGC who had previous chemotherapy including fluoropyrimidine and oxaliplatin as well as fluoropyrimidine and irinotecan and who received subsequent docetaxel-based chemotherapy. Thirty-five patients were retrospectively recruited from 5 medical centers in Korea. Patients received either weekly or 3 weekly with docetaxel +/- cisplatin.

Results

Thirty-one out of 35 patients were evaluated for treatment response. A total of 94 cycles of chemotherapy (median, 2; range, 1 to 7) were administered. The overall response rate was 14.3%, and the disease control rate was 45.7%. The median progression-free survival (PFS) was 1.9 months (95% confidence interval [CI], 1.1 to 2.7 months). The median overall survival (OS) was 3.6 months (95% CI, 2.8 to 4.4 months). PFS and OS were significantly prolonged in patients of the Eastern Cooperative Oncology Group, with performance status of 0 or 1 in multivariate analysis (PFS: hazard ratio[HR], 0.411; 95% CI, 0.195 to 0.868; p=0.020 and OS: HR, 0.390; 95% CI, 0.184 to 0.826; p=0.014, respectively). Four of the 35 patients enrolled in the study died due to infection associated with neutropenia.

Conclusion

Our findings suggest that salvage docetaxel-based chemotherapy is a feasible treatment option for AGC patients with good performance status (PS), whereas chemotherapy for patients with poor PS (PS≤2) should be undertaken with caution for those who previously failed oxaliplatin- and irinotecan-based regimens.

Key words
Stomach neoplasms, Docetaxel, Oxaliplatin, Irinotecan

Introduction

Gastric cancer ranks fourth in incidence and second in cancer mortality worldwide [1]. In Korea, it is the most common malignancy and second-most common cause of cancer mortality [2]. Although gastric cancer is now detected earlier due to implementation of gastroduodenoscopy as a screening test in Korea, more than 20% of gastric cancer patients are still diagnosed with metastatic or advanced stage disease [3].

Systemic chemotherapy can provide significant palliation of symptoms and survival benefits to patients with advanced gastric cancer (AGC) [4-6]. First-line chemotherapy regimens for AGC patients generally confer a response rate of less than 50% and prolong survival by several months [7]. Second-line chemotherapy regimens may also be helpful for patients that are refractory to first-line treatment. We recently showed that there was a survival benefit of second-line chemotherapy over best supportive care in AGC patients who had failed first-line therapy [8]. Little is known, however, about the clinical outcomes of third-line or sequenced chemotherapy in AGC patients.

Although various chemotherapeutic agents are used in the treatment of AGC, no clear standard chemotherapy regimen has been established. Several studies have suggested that combination chemotherapy provides better response rates and favorable survival benefits compared with a single agent [6,9,10]. Based on these data, combination chemotherapeutic regimens containing fluoropyrimidine and platinum agents or irinotecan are commonly adopted as first-line treatment for AGC in Korea, regardless of the sequence in which the agents are administered [11-14].

Docetaxel has been shown to be efficacious for treatment of AGC and has been widely used either alone or in combination with other agents. A recent meta-analysis showed that docetaxel-containing regimens resulted in favorable survival benefits, though these effects were not statistically significant [15]. Thus, docetaxel may be a feasible treatment option for AGC patients that are refractory to chemotherapy regimens comprised of fluoropyrimidine and either oxaliplatin or irinotecan, which are commonly referred to as folinic acid, fluorouracil, and oxaplatin (FOLFOX), folinic acid, fluorouracil, and irinotecan (FOLFIRI), capecitabine plus oxliplatin (XELOX), capecitabine plus irinotecan (XELIRI) and S-1/oxaliplatin (SOX). However, no studies have examined outcomes of docetaxel treatment as third-line chemotherapy. The primary aim of this retrospective analysis was to evaluate the outcomes of docetaxel-based chemotherapy as a third-line treatment in AGC patients.

Materials and Methods

1. Eligibility

Databases from 5 medical centers were searched for patients with advanced or relapsed gastric adenocarcinoma who underwent chemotherapy between September 2005 and September 2009. All patients had a histologically confirmed diagnosis of adenocarcinoma of the stomach. Patients were eligible for enrollment if they received docetaxel-containing chemotherapy as third-line treatment and had a history of progression after two prior chemotherapy regimens containing fluoropyrimidine and oxaliplatin as well as fluoropyrimidine and irinotecan. Since this was a retrospective study and no personal patient information was used, approval from the institutional review board was not obtained.

2. Chemotherapy regimens

All eligible patients received one of four chemotherapy regimens as follows: 1) docetaxel 30 mg/m^2 IV (wD) on days 1 and 8; 2) docetaxel 30 mg/m^2 with cisplatin 30 mg/m^2 IV (wDP) on days 1 and 8; 3) docetaxel 60 mg/m^2 IV (3wD) on day 1; or 4) docetaxel 60 mg/m^2 and cisplatin 60 mg/m^2 IV (3wDP) on day 1. All chemotherapeutic cycles were repeated every 3 weeks. Standard pre-medications were administered appropriately prior to treatment depending on the protocol of the specific institution.

Relative dose intensity (RDI) was defined as the actual chemotherapeutic dose administered divided by the total planned dose in a given period.

3. Assessment of efficacy and toxicity

The treatment response in patients with measurable lesions was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [16]. The safety evaluation included all patients who received at least one dose of the study drug, and was based on abnormal laboratory values and adverse clinical events. Information about toxicity was collected and graded according to the Common Terminology Criteria for Adverse Events ver. 3.0 (CTCAE v 3.0).

4. Statistical analysis

Since this study was a retrospective analysis, no formal estimation of the sample size was done. Progression-free survival (PFS) was calculated from the first day of salvage docetaxel chemotherapy until either the date of progression or the date of last follow-up. Overall survival (OS) was calculated from the first day of salvage docetaxel chemotherapy to the date of death by any cause. PFS and OS curves

were obtained using the Kaplan-Meier method and the differences between curves were assessed using a log-rank test. Multivariate analyses of the predictive and prognostic factors for survival were performed using the Cox proportional hazard regression model with 95% confidence intervals (CIs). Statistical significance was established as $p < 0.05$. All analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL).

Results

1. Patient characteristics

A total of 35 eligible patients were enrolled from 5 institutions in South Korea. Patient characteristics are listed in Table 1. The median age was 53 years (range, 21 to 73 years) and 60% of the patients enrolled were men. Eighteen (52%) of 35 patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, and 17 (48%) patients had an ECOG PS of 2-3. All patients had more than one metastatic lesion.

2. Drug delivery

Docetaxel and cisplatin were administered for a total of 94 and 70 cycles, respectively. The median number of chemotherapy cycles received per individual patient was 2 (range, 1 to 7). Dose modification for docetaxel and cisplatin was required in 26 (28%) cycles for 13 (37%) patients and 21 (30%) cycles for nine (37%) patients, respectively. Median dose intensities of docetaxel and cisplatin were 18.43 mg/m^2/wk (range, 10 to 25 mg/m^2/wk) and 16.19 mg/m^2/wk (range, 10 to 20 mg/m^2/wk), respectively. The mean RDI for docetaxel and cisplatin was 0.91 (range, 0.5 to 1) and 0.91 (range, 0.5 to 1), respectively.

3. Toxicity

Hematologic and non-hematologic toxicities are summarized in Table 2, with hematologic toxicities being the most common. Grade 3 or 4 neutropenia was observed in 12 (34%) patients and febrile neutropenia occurred in 4 (11%) patients. Infection, neuropathy, and fatigue were the most common non-hematologic toxicities. There were 4 (11%) treatment-related deaths caused by infection associated with neutropenia.

4. Treatment outcomes and prognostic factors

Thirty-one patients were evaluated for responses to docetaxel-based chemotherapy. Four patients were not included in the analysis due to refusal of treatment (2 patients), death due to pneumonia (1 patient), and death due to lung toxicity (1 patient). A partial response was achieved in 5 patients (14.3%, confirmed response in all 5 patients), and stable disease was observed in 11 patients (31.4%). The overall disease control rate was 45.7%.

Over the median follow-up duration of 3.6 months (range, 0.3 to 14.3 months), 33 patients exhibited disease progression. Of these 33 patients, 32 patients died. The median PFS and OS were 1.9 months (95% CI, 1.1 to 2.7 months) and 3.6 months (95% CI, 2.8 to 4.4 months), respectively.

Prognostic factors that influenced PFS and OS of AGC patients are shown in Table 3 and Fig. 1. According to prognostic factor analysis, only ECOG PS was a significant independent prognostic factor in PFS (hazard ratio [HR], 0.411; 95% CI, 0.195 to 0.868; p=0.020) and OS (HR, 0.390; 95% CI, 0.184 to 0.826; p=0.014) (Table 4, Fig. 1). There were no significant differences in treatment

Table 1. Patient characteristics

Characteristics (n=35)	No. of patients	%
Gender		
Male	21	60
Female	14	40
Median age (range, yr)	53 (21-73)	
ECOG PS		
0-1	18	52
2	12	34
3	5	14
Histology		
Well differentiated	1	3
Moderate differentiated	12	34
Poorly differentiated	18	49
Unknown	4	14
Disease status		
Initially metastatic	24	69
Recurrent	11	31
Sites of metastases		
Liver	12	34
Lung	3	9
Distant lymph nodes	17	49
Bone	6	17
Peritoneum	13	37
Ovary	4	11
No. of metastatic sites		
1-2	18	52
≥ 3	17	48
Treatment regimen		
Weekly D	4	11
Weekly DP	16	46
3 weekly D	9	26
3 weekly DP	6	17

ECOG PS, Eastern Cooperative Oncology Group performance status; D, docetaxel; DP, docetaxel/cisplatin.

Table 2. Toxicity of third-line docetaxel-based chemotherapy

	Total	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	19 (54)	2 (6)	4 (11)	8 (23)	5 (14)
Neutropenia	20 (57)	1 (3)	7 (20)	4 (11)	8 (23)
Anemia	33 (94)	11 (31)	20 (57)	2 (6)	0 (0)
Thrombocytopenia	10 (29)	6 (17)	4 (11)	0 (0)	0 (0)
Neutropenic fever	4 (11)	-	-	2 (6)	2 (6)
Infection	7 (20)	0 (0)	0 (0)	2 (6)	1 (3)
Neuropathy	7 (20)	2 (6)	2 (6)	3 (9)	0 (0)
Fatigue	6 (17)	1 (3)	3 (9)	2 (6)	0 (0)
Renal insufficiency	1 (3)	0	1 (3)	0 (0)	0 (0)
Mucositis	3 (9)	1 (3)	1 (3)	1 (3)	0 (0)
Pulmonary toxicity	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)

Values are presented as number (%).

Table 3. Univariateanalysis for survival

Factors		Median PFS (mo)	p-value[a)]	Median OS (mo)	p-value[a)]
Gender	Male	2.2	0.183	4.0	0.241
	Female	1.8		2.9	
Age (yr)	≤53	1.3	0.195	2.9	0.517
	>53	3.0		4.4	
PS	0-1	2.6	0.013	4.0	0.010
	2-3	1.3		2.4	
Grade	MD	2.6	0.180	4.4	0.134
	PD	1.4		3.1	
Presentation	Relapse	2.2	0.594	4.0	0.959
	Initially metastatic	1.8		3.1	
Site of metastases					
Liver	Yes	1.9	0.749	3.0	0.288
	No	1.5		3.7	
Lung	Yes	1.6	0.460	1.6	0.060
	No	1.9		3.6	
Peritoneum	Yes	2.6	0.818	4.4	0.661
	No	1.6		3.1	
Bone	Yes	1.1	0.379	1.6	0.082
	No	2.2		3.7	
Albumin level (g/dL)	<3.0	1.3	0.130	2.4	0.043
	≥3.0	2.4		4.0	
Schedule	Weekly	2.2	0.365	3.7	0.916
	3 weekly	1.5		3.0	
Cisplatin	Yes	2.2	0.115	3.1	0.507
	No	1.3		3.6	

PFS, progression-free survival; OS, overall survival; PS, performance status; MD, moderately differentiated; PD, poorly differentiated.
[a)]Log-rank analysis.

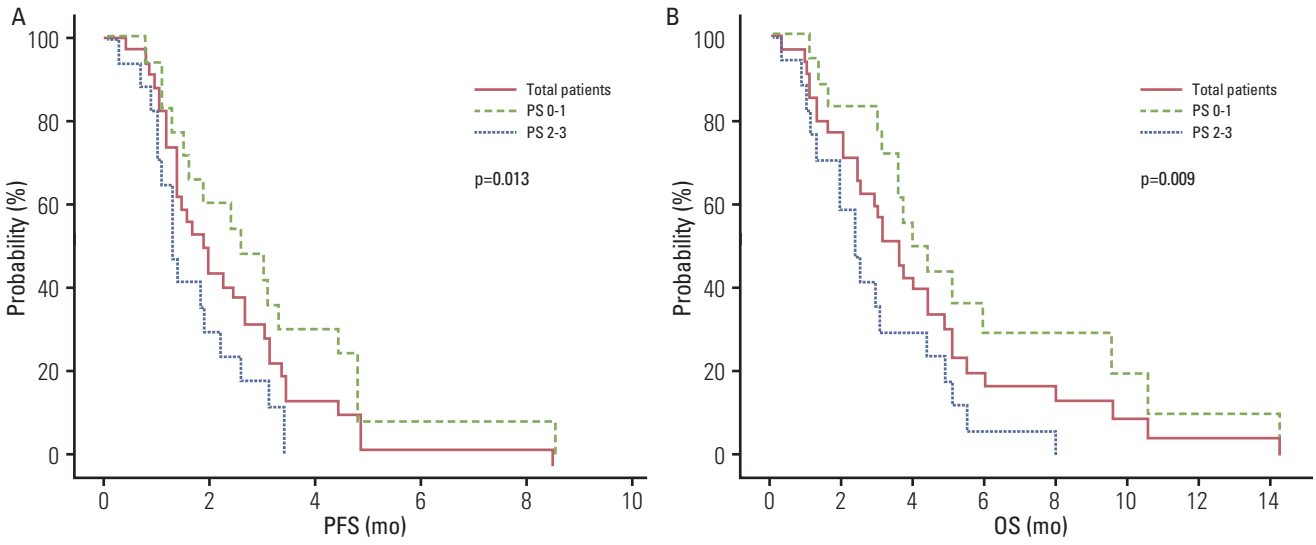

Fig. 1. Progression-free survival (PFS) (A) and overall survival (OS) (B) curves for patients treated with 3rd line docetaxel according to Eastern Cooperative Oncology Group performance status (PS).

Table 4. Prognostic factors influencing PFS and OS

	Univariate analysis		Multivariate analysis	
	Median PFS (mo)	p-value[a]	HR for PFS (95% CI)	p-value[b]
PFS				
ECOG PS		0.013		0.020
0-1	2.6		0.411	
2-3	1.3		(0.195-0.868)	
OS				
ECOG PS		0.009		0.014
0-1	4.0			
2-3	2.4			
Albumin (g/dL)		0.043	NE	
<3.0	2.4			
≥3.0	4.0			

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not in the equation. [a]Log rank test, [b]Cox proportional hazard analysis.

outcomes including overall response, PFS, and OS according to chemotherapy schedules (weekly vs. every 3 weeks) and regimens (monotherapy vs. combination therapy).

Discussion

This study examined the clinical outcomes of docetaxel-based chemotherapy as a third-line treatment regimen in AGC patients refractory to oxaliplatin- and irinotecan-based combination hemotherapy. The overall response rate (ORR) was 14.3% and the median OS was 3.6 months. Our results were largely consistent with previous reports of third-line chemotherapy outcomes in AGC patients [17-19], in which the ORR had a reported range of 0% to 11%, and the OS ranged from 4.2 to 6.4 months. However, these studies included a variety of third-line chemotherapy regimens. To avoid difficulty in interpreting our results, we limited inclusion criteria to AGC patients who received docetaxel-based chemotherapy as third-line treatment after failure to respond to oxaliplatin- and irinotecan-based sequential chemotherapy.

The relatively short median OS (3.6 months) in our study raises the question of whether the use of third-line chemotherapy is more

efficacious than best supportive treatment in AGC patients. Patients with colorectal cancer who received fluoropyrimidine as well as oxaliplatin and irinotecan have been shown to have a survival benefit over patients who did not receive one of these agents [20]. It is unclear, however, whether a similar approach may be beneficial for gastric cancer patients. Our team recently identified a survival benefit (HR, 0.81) of chemotherapy in patients who had received two or more prior chemotherapy regimens [8]. This finding suggests that third-line chemotherapy may be helpful in prolonging survival.

Since PS is a well-known prognostic factor for AGC [21], decreased survival rates would be expected in patients with a poorer PS. Our data supported this hypothesis, showing that PS was independently associated with patients' survival in multivariate analysis. The proportion of patients with a PS of 3 in our study was higher than in the populations used in two previous studies (14% vs. 0-0.7%) [17,18]. Thus, the shorter survival in our study could be attributed to inclusion of patients with poorer PS.

Clinical trials using docetaxel on a weekly schedule showed less toxicity and comparable efficacy [22]. Most high-risk patients exhibited poor PS, multiple co-morbidities, or reduced bone-marrow reserves due to prior therapy with weekly regimens. Four treatment-related mortalities occurred that were likely attributable to infection associated with neutropenia, despite weekly treatment wDP. All 4 of these patients had poor PS (three with a PS of 2, one with a PS of 3), thus chemotherapy regimens for patients with a poor PS (PS $\leq$ 2) should be considered carefully.

Our study had several notable limitations. In addition to being a retrospective analysis, the size of our patient cohort was small despite recruitment of patients from multiple centers. Difficulty in recruiting patients may have been due to the strictness of the inclusion criteria. The homogeneity of prior and third-line chemotherapeutic regimens received by the patients enrolled, on the other hand, is helpful for interpreting the data and predicting treatment outcomes in similar cases. Limitation in the evaluation of toxicity may exist due to inherent characteristics of the retrospective design.

Conclusion

Our findings suggest that salvage docetaxel-based chemotherapy is a feasible treatment for AGC patients with good PS, whereas chemotherapy for patients with a poor PS (PS $\leq$ 2) should be used cautiously for those with AGC who previously failed oxaliplatin- and irinotecan-based regimens. Further studies are warranted to determine treatment outcomes of various other third-line chemotherapeutic regimens in AGC patients.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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