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ORIGINAL ARTICLE

A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy

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Abstract
Purpose Fluoropyrimidine (F) and platinum (P) combination chemotherapy has been widely used as a first-line treatment of advanced gastric cancer (AGC). Docetaxel has shown promising activity against this disease. In this study, we explored the efficacy and safety of docetaxel monotherapy as salvage chemotherapy in AGC after F and P combination chemotherapy failed.
Materials and methods From October 2004 to October 2005, 49 eligible patients were enrolled in this study. The median treatment-free interval was 28.0 days, and 81.6% of patients had suffered cancer progression within 4 months after the withdrawal of first-line chemotherapy. Docetaxel was given IV at a dose of 75 mg/m^2 every 3 weeks, together with dexamethasone prophylaxis.
Results A total of 182 cycles of docetaxel were administered with a median of 3 (range 1–9) cycles. From an intention-to-treat analysis, eight patients achieved objective response with a response rate of 16.3% (95% CI, 6.0–26.6). The median response duration was 4.7 months. A total of 20 patients showed stable disease, but 17 patients suffered disease progression. At a median follow-up duration of 11.3 months for surviving patients (range 6.3–18.8 months), the median time to disease progression was 2.5 months (95% CI, 2.3–2.7) and the median overall survival time since the start of docetaxel monotherapy was 8.3 months (95% CI, 6.7–9.8). Grade 3/4 neutropenia and febrile neutropenia occurred in 18.4% of patients and in 5.4% of cycles. The incidence of non-hematologic toxicities of grade 3 or worse was asthenia 32.7%, diarrhea 10.2% and peripheral sensory neuropathy 8.2%.
Conclusion Docetaxel at 75 mg/m^2 is active against AGC as second-line chemotherapy after prior exposure to F and P combination chemotherapy. The toxicity profile is moderate.

Keywords Gastric cancer · Docetaxel · Salvage therapy · Chemotherapy

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Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of death from cancer worldwide [19]. The Korean Cancer Registry reported that gastric cancer was the most common cancer (24.0%) and also the second leading cause of cancer death (18.7%) in South Korea in 2002 [22]. Although improvements in early diagnosis have increased the number of curative resections (the main curative treatment), many patients present with locally advanced unresectable disease or have a distant metastasis when first diagnosed. Even after complete resection, local and distant relapses are common. In such patients, palliative chemotherapy improves the duration and

quality of life to extents greater than those achievable with high-quality supportive care alone [7, 18, 20].

The drugs 5-fluorouracil (5-FU) and cisplatin have been widely used in advanced gastric cancer (AGC) patients, in different combinations, such as ECF (epirubicin, cisplatin, and 5-FU) and FUP (5-FU and cisplatin). In prospective randomized studies, AGC patients on ECF showed significant response rates and survived longer than patients given FAMTX (5-FU, adriamycin and high-dose methotrexate) chemotherapy [28, 29]. Several non-randomized studies demonstrated that superior response rates (up to 70%) were achieved by combining cisplatin with 5-FU in various schedules, with only moderate increases in toxicity. In randomized phase III trials, FUP caused improved response rates compared with FAM (5-FU, doxorubicin and mitomycin) or 5-FU single-agent therapy [11], and FUP tended to yield higher response rates than those obtained with FAMTX or ELF (etoposide, leucovorin and bolus 5-FU) [26]. As a result, FUP is now widely used as the first-line treatment of AGC. Oral 5-FU pro-drugs such as capecitabine [9, 13] and S-1 [14] have recently been developed and are used in clinical practice to obviate the inconvenience associated with intravenous infusion of 5-FU and to improve the safety of therapy.

Unfortunately, about half of the patients receiving chemotherapy are unresponsive and the majority of the patients who do respond eventually suffer disease progression. Second-line chemotherapy treatments used to date have been unsatisfactory. There is thus an urgent need for novel, active and less toxic regimens for AGC patients who fail the first line of chemotherapy using fluoropyrimidine (F) and platinum (P).

Docetaxel is a relatively new cytotoxic agent that binds to and stabilizes microtubules, causing cell-cycle arrest and apoptosis. The mechanism of action of docetaxel differs from those of F and P, and docetaxel lacks cross-resistance with F and P. Docetaxel has shown single-agent activity in AGC. When given in doses of 100 mg/m^2 every 3 weeks, both chemotherapy-naïve [5, 23] and treated patients [6, 27] on docetaxel showed response rates of 17–22%. In these studies, hematologic toxicity was often significant and about half of the patients experienced neutropenia of grade 3 or worse, which necessitated prophylactic growth factor support. In Asian studies [3, 24], docetaxel at a dose of 60–75 mg/m^2 every 3 weeks, used as a first-line drug, showed a 16–24% response rate with frequencies of grade 3 hematologic toxicities similar to those seen in Western studies using higher docetaxel doses. Our previous retrospective studies of docetaxel monotherapy, at a dose of 75 mg/m^2, as salvage chemotherapy in patients with AGF failing chemotherapy with F and P, showed promising results. The response rate was 21% with a median overall survival (OS) of 8.4 months [15, 16].

Based on these findings, we conducted a prospective phase II study of a moderate docetaxel dose (75 mg/m^2) given every 3 weeks to patients with AGC, who did not respond adequately to first-line F and P chemotherapy.

Materials and methods

Patients

All patients with advanced, unresectable and histologically confirmed adenocarcinomas of the stomach were eligible if they met the following inclusion criteria: (1) aged 18–70 years; (2) ECOG performance status 0–2; (3) prior exposure to fluoropyrimidine (5-FU) or related drugs (capecitabine, doxifluridine, S1 or UFT) and platinum (cisplatin or oxaliplatin) chemotherapy; (4) measurable lesions by the Response Evaluation Criteria in Solid Tumors Group (RECIST) criteria; (5) no previous radiotherapy; (6) estimated life expectancies of over 3 months; (7) adequate bone marrow function [leukocyte counts $\geq$4,000 per μl, absolute neutrophil counts (ANCs) $\geq$1,500 per μl, hemoglobin $\geq$9.0 g/dl, and platelets $\geq$100,000 per μl]; (8) adequate renal and hepatic functions [serum creatinine levels <1.5 mg/dl, bilirubin level <1.5 mg/dl, and serum transaminases (AST and ALT) less than three times the upper normal limit (UNL) (less than five times the UNL for patients with liver metastases)]; and (9) written informed consents. Patients were excluded if they had brain metastases, significant gastrointestinal bleeding or obstruction, serious comorbid conditions or lacked the ability to comply with the requirements of the protocol. This study was approved by the institutional review board of the Asan Medical Center (Approval No. 2004-0221).

Treatment protocol and dose adjustment

Docetaxel at 75 mg/m^2 was given as a 1 h intravenous infusion in 200 ml of 5% dextrose in water on the first day of every 3-week interval. The prophylaxis for potential docetaxel hypersensitivity was dexamethasone 8 mg p.o. twice daily (or equivalent) for 3 days, commencing prior to docetaxel administration. The chemotherapy cycles were delayed if granulocytes were <1,500 per μl or if platelet counts did not return to a minimum of 100,000 per μl on the day of infusion. Other non-hematologic toxicities (except alopecia) were required to be grade 1 or better prior to cycle initiation. During treatment, docetaxel was reduced by 25% in patients with grade 4 neutropenia lasting more than 7 days, febrile neutropenia, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding that required platelet transfusion, and subjects with grade 3 non-hematologic toxicity other than nausea, vomiting, anorexia and

alopecia. Neither colony stimulating factors (CSFs) (e.g., G-CSF and GM-CSF) nor antibiotics were given prophylactically or to treat uncomplicated neutropenia. The treatment was continued for a maximum of 9 cycles unless disease progression, withdrawal of patient consent or unacceptable toxicity occurred.

Efficacy and safety assessment

Tumor response was evaluated every two treatment cycles according to the RECIST criteria. At each assessment, the same imaging technique was used as was employed at baseline. A patient eligible for tumor assessment was defined as a subject who received at least 2 cycles of chemotherapy; Patients were also considered assessable, however, if they received less than two treatment cycles due to rapid tumor progression (per protocol population). For intention-to-treat analysis, those who failed to return to the clinic for any reason after receiving at least 1 cycle of chemotherapy was included into the denominator for response rate calculation (ITT population). Toxicity was evaluated according to the "NCI-CTCAE" scale, version 3.0.

Statistics

The primary end point was an assessment of the overall response rate (ORR). Simon's optimal two-stage design was used to test the null hypothesis $P_0 \leq 0.05$ versus the alternative hypothesis $P_1 \geq 0.2$. The first stage required that at least two patients of 21 had a confirmed response with $\alpha = 0.05$ and $\beta = 0.1$ before the second stage commenced. In the second stage, a further 20 assessable patients were treated and if 5 or more patients achieved a confirmed response, then the primary end point would be met. Time to progression (TTP) was measured from the first day of docetaxel treatment until disease progression was noted, and OS was measured from the first day of docetaxel treatment until death from any cause. Kaplan–Meier estimates were used in the analysis of all time-event variables, and the differences between the curves were analyzed using the log-rank test. The program SPSS for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Patient characteristics

From October 2004 to October 2005, 49 eligible patients were entered in this study. The patient characteristics are listed in Table 1. The median age was 56 years (range 35–70). Seventeen patients had undergone curative gastrectomy and 12 had received adjuvant chemotherapy. The majority of patients had ECOG performance status of one or better and had two or more sites of metastasis. Including 33 patients (67.3%) who had disease progression while receiving F and P combination chemotherapy, 45 patients (91.8%) had disease progression within 6 months after the withdrawal of prior F and P combination chemotherapy. The median TTP since day 1 of the first cycle and day 1 of the last cycle of the previous chemotherapy was 6.2 months

Table 1 Baseline clinicopathologic characteristics of our study patients

	Number of patients	%
Total number	49	100
Age, years (median, range)	56 (35–70)	
Gender		
Male	38	77.6
Female	11	22.4
ECOG performance status		
0	9	18.4
1	36	73.5
2	4	8.2
Histology		
Well/moderately differentiated	20	40.8
Poorly differentiated or signet-ring cell type	26	53.1
Unknown	3	6.1
Metastasis sites		
Liver	32	65.3
Peritoneum	13	26.5
Distant abdominal lymph nodes	34	69.4
Lung	5	10.2
Bone	4	8.2
Number of metastatic sites		
1	14	28.6
2	21	42.9
≥3	14	28.5
Disease status		
Initially metastatic	32	65.3
Recurrent	17	34.7
Prior fluoropyrimidine and platinum combination chemotherapy		
Capecitabine/cisplatin	13	26.5
Capecitabine/oxaliplatin	13	26.5
Doxifluridine/cisplatin	10	20.4
5-FU/cisplatin	7	14.3
S-1/cisplatin	6	12.2
Additional chemotherapy exposure		
Mitomycin C	12	24.4
Adriamycin	1	2.0

(range 1.2–55.4 months) and 21 days (range 6 days–50.6 months), respectively. The median treatment-free interval was 28.0 days (range 21 days–50.8 months).

Drug delivery

The median number of chemotherapy cycles received was three (range 1–9; total 182 cycles). Treatment was delayed in 9 cycles (4.9%) and dose reduction from the initial dose occurred in 21 cycles (11.5%) of ten patients (20.4%). The reasons for dose reduction included febrile neutropenia in five patients, asthenia in four patients and peripheral sensory neuropathy in one patient. The actual median dose intensity per patient was 24.5 mg/m^2/week (range 6.3–25.6) with a relative dose intensity of 98.1% (range 25.0–102.4%).

Efficacy

Eight patients achieved confirmed response including one complete response; The ORR for the ITT population and per-protocol population was 16.3 (95% CI, 6.0–26.6) and 17.7% (95% CI, 6.5–28.9), respectively. The median duration of objective response was 4.7 months (range 2.3–13.4 months). Another 20 patients had stable disease and the overall tumor control rate was 57.1% for the ITT population. Responses were not assessable in four patients; two patients refused treatment, treatment was discontinued early because of neuropathy in one patient and one subject died in a traffic accident. There was no significant correlation between responses to first-line chemotherapy and those to docetaxel monotherapy ($P = 0.887$).

At a median follow-up time of 11.3 months for surviving patients (range 6.3–18.8 months), the median TTP was 2.5 months (95% CI, 2.3–2.7, Fig. 1) and the median OS was 8.3 months (95% CI, 6.7–9.8). The TTP and OS values did not change with patient age (≤56 years vs. >56 years), sex, histologic differentiation, number of metastatic sites, TTP in the first-line setting (≤6.2 months vs. >6.2 months) and treatment-free interval (≤28 days vs. >28 days). The prior response to previous chemotherapy [partial response (PR) or better] was statistically significant in predicting prolonged OS ($P = 0.013$, Fig. 2).

Toxicity

For each form of toxicity, the patient distribution of the highest observed grade and the incidence of adverse events per chemotherapy cycle are listed in Table 2. The most common hematologic toxicity was mild or moderate anemia. Granulocytopenia of grade 3 or worse occurred in nine patients (18.4%), all of whom also showed febrile neutropenia, which was treated successfully with antibiotics and G-CSF. Febrile neutropenia never recurred after adequate docetaxel dose modification. There were no episodes of thrombocytopenia of grade 3 or worse. Although grade 3 bleedings were observed in two patients, they were gastric cancer bleedings associated not with thrombocytopenia, but with disease progression. When non-hematologic toxicities of grade 2 or worse are considered, asthenia was seen most frequently (73.5%) followed by stomatitis (34.7%), peripheral neuropathy (26.5%), diarrhea (20.4%), nail toxicity (20.4%), and myalgia (20.4%). With the exception of asthenia, however, clinically relevant non-hematologic adverse events of grade 3 or worse were not frequently observed and were limited to diarrhea (10.2%), peripheral neuropathy (8.2%) and edema (4.1%). There were no treatment-related deaths directly attributable to docetaxel chemotherapy.

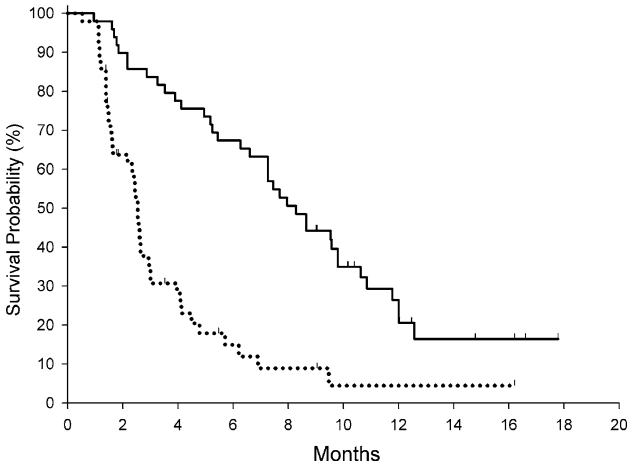

Fig. 1 Time to progression (*dotted line*) and overall survival (*solid line*) in the 49 patients with advanced gastric cancer treated with docetaxel monotherapy after the failure of fluoropyrimidine and platinum combination chemotherapy

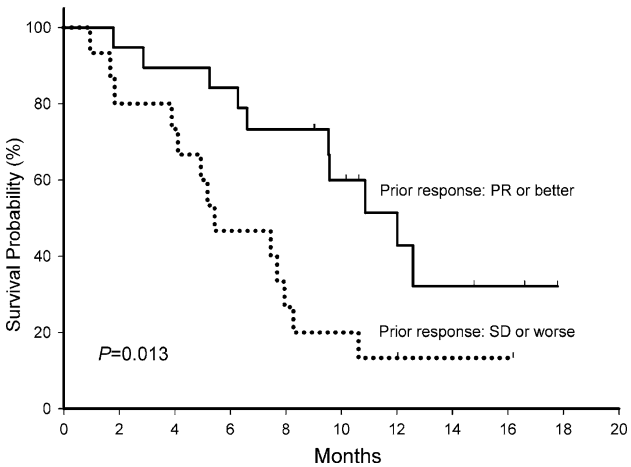

Fig. 2 Overall survival after docetaxel salvage treatment according to responses achieved with prior fluoropyrimidine and platinum combination chemotherapy

Table 2 Hematologic and non-hematologic toxicities attributable to docetaxel

Category	Grade (number of patients, %)				Grade (number of cycles, %)			
	1	2	3	4	1	2	3	4
Anemia	23 (53.1)	15 (30.6)	7 (14.3)	1 (2.0)	103 (62.0)	43 (25.9)	8 (4.8)	1 (0.6)
Leukopenia	0	1 (2.0)	4 (8.2)	4 (8.2)	0	1 (0.6)	4 (2.4)	4 (2.4)
Granulocytopenia	0	0	3 (6.1)	6 (12.2)	0	0	3 (1.8)	6 (3.6)
Thrombocytopenia	2 (4.1)	1 (2.0)	0	0	2 (1.2)	1 (0.6)	0	0
Bleeding	3 (6.1)	0	2 (4.1)	0	4 (2.4)	0	2 (1.2)	0
Febrile neutropenia	NA	NA	9 (18.4)	0	NA	NA	9 (5.4)	0
Asthenia	10 (20.4)	20 (40.8)	16 (32.7)	0	73 (44.0)	61 (36.7)	18 (10.8)	0
Nausea	19 (38.8)	3 (6.1)	0	0	32 (19.3)	3 (1.8)	0	0
Vomiting	8 (16.3)	2 (4.1)	0	0	12 (7.2)	2 (1.2)	0	0
Stomatitis	15 (30.6)	15 (30.6)	1 (2.0)	1 (2.0)	43 (25.9)	23 (13.9)	2 (1.2)	1 (0.6)
Diarrhea	17 (34.7)	5 (10.2)	5 (10.2)	0	35 (21.1)	9 (5.4)	4 (2.4)	0
Dacryorrhea	2 (4.1)	1 (2.0)	0	0	14 (8.4)	1 (0.6)	0	0
Sensory neuropathy	30 (61.2)	7 (14.3)	4 (8.2)	0	101 (60.8)	17 (10.2)	11 (6.6)	0
Motor neuropathy	17 (34.7)	12 (24.5)	1 (2.0)	0	52 (31.3)	17 (10.2)	3 (1.8)	0
Nail change	21 (42.9)	10 (20.4)	0	0	71 (42.8)	13 (7.8)	0	0
Edema	17 (34.7)	3 (6.1)	2 (4.1)	0	50 (30.1)	3 (1.8)	2 (1.2)	0
Myalgia	24 (49.0)	10 (20.4)	0	0	43 (25.9)	11 (6.6)	0	0
Allergic reaction	1 (2.0)	0	0	0	2 (1.2)	0	0	0

Discussion

Fluoropyrimidine and platinum combination chemotherapy with or without anthracycline is one of the most commonly used first-line treatment regimens for AGC [11, 13, 14, 26, 29]. This chemotherapy produces a response rate of ~30–70%, but most patients eventually experience disease progression irrespective of initial response to first-line chemotherapy. Second-line chemotherapy in these patients, especially in those who have good performance status, remains a challenge. Newer agents, such as docetaxel, irinotecan and oxaliplatin, have been investigated in this context. Based on our previous retrospective analysis [15], we conducted a prospective phase II study of docetaxel monotherapy as a second-line regimen in AGC patients failing to respond to F and P combination chemotherapy.

Docetaxel has shown single-agent activity in AGC. In the second-line setting, Giuliani et al. [6] reported a 17% response rate with single-agent docetaxel at 100 mg/m^2 in 30 patients with AGC refractory to ECF or PELF (cisplatin, epirubicin, leucovorin, and 5-FU). Vanhoefer et al. [27] reported a 20% response rate with docetaxel at 100 mg/m^2 in 25 patients already exposed to first-line FUP. Andre et al. [1] found a 21% response rate when 25 patients pretreated with FUP were given epirubicin at 75 mg/m^2 plus docetaxel at 75 mg/m^2 every 3 weeks. Our results demonstrate that docetaxel given at 3-week intervals, at a dose of 75 mg/m^2, is useful, with moderate activity against F- and P-refractory AGC. A response rate of 16.3%, with a disease control rate of 57.1%, as seen in this study, is largely consistent with previous reports using 100 mg/m^2 of docetaxel [6, 27] or employing a docetaxel plus epirubicin combination regimen as second-line salvage [1]. In addition, the response rate achieved in this study is comparable to those achieved in chemotherapy-naïve patients [3, 5, 23]. Bang et al. [3] reported a 16% response rate with docetaxel at 75 mg/m^2 in 45 chemotherapy-naïve patients. Einzig et al. [5] reported a 17% response rate with docetaxel at 100 mg/m^2 in 41 patients. Sulkes et al. [23] found a 24% response rate when 33 patients were given docetaxel at 100 mg/m^2 every 3 weeks in a first-line setting. The response rate in the current study was also comparable to those reported using weekly irinotecan [4], modified FOLFIRI [2, 12] or modified FOLFOX chemotherapy [10], which required weekly outpatient visits for intravenous 5-FU infusion.

The median TTP was 2.5 months and the median OS was 8.3 months. The TTP and OS values seen in the current study were comparable to or somewhat better than published data from most second-line chemotherapy trials using docetaxel at a higher dosage [6, 27], irinotecan [2, 4, 12] or oxaliplatin [10], where F- and P-refractory AGC patients were included as study subjects. The median TTP was also comparable to that achieved using docetaxel at 75 mg/m^2 in a first-line setting [3]. This may, however, reflect the fact that the proportion of patients with recurrent disease, who might have less tumor burdens and better chances of long-term survival [17], was higher in our study than in previous studies.

Our results showed that toxicity was modest in intensity, with grade 3 asthenia being the leading form of toxicity observed in 32.7% of the patients. The other most common toxicities of grade 3 or worse were diarrhea (10.2%), peripheral sensory neuropathy (8.2%) and edema and stomatitis (4.1%). Febrile neutropenia of grade 3 developed in nine patients (18.3%). This developed without G-CSF prophylaxis and was managed successfully with antibiotics and G-CSF. Febrile neutropenia usually developed within the first two treatment cycles; four patients suffered from this condition in the first cycle of chemotherapy and three during the second cycle. The condition did not recur after adequate dose reduction (5.4% per cycle). Other hematologic toxicities were mild. The incidence of granulocytopenia of grade 3 or worse was the same as that of febrile neutropenia, while severe thrombocytopenia was never observed. There were no treatment-related deaths directly attributable to docetaxel chemotherapy. The incidence of grade 3/4 neutropenia in the current study is somewhat less than that reported by Vanhoefer et al. [27] and comparable to that reported by Giuliani et al. [6], who incorporated prophylactic G-CSF in his protocol. The toxicity profile appears to be more favorable in our study compared to that observed using irinotecan-based chemotherapy [2, 4]. Caution should be exercised, however, when comparing hematologic toxicities between studies, as hematologic monitoring strategies may be different. In the current study, CBC was repeated before each chemotherapy cycle, but was repeated every week for the first 2 cycles in the study of Bang et al. [3]. In their work, neutropenia of grade 3 or worse was reported in 81.8% of patients and 36.1% of cycles, with the same docetaxel dosage.

Although the benefit of second-line chemotherapy in AGC has not been conclusively shown, considering a confirmed survival advantage of docetaxel salvage chemotherapy in non-small cell lung cancer [21], where the salvage chemotherapy showed limited activity in terms of response rate and progression-free survival, salvage chemotherapy may have a beneficial impact on survival in AGC patients whose disease has progressed beyond that controllable with first-line chemotherapy, at least in selected subjects with good performance status. There have been no randomized trials comparing the efficacy and safety of a docetaxel regimen to regimens with irinotecan or oxaliplatin in second-line settings. Based on comparable activity and a favorable safety profile compared with other second-line regimens [2, 4, 6, 10, 12, 27], docetaxel monotherapy at 75 mg/m^2 might be considered as a promising second-line chemotherapy in F- and P-refractory AGC. Further work is needed to define an optimal salvage regimen.

Recently, the TAX325 study group [25] reported that superior response rates, TTP and OS values could be achieved by adding docetaxel to FUP (DCF), compared with FUP combination chemotherapy in a first-line setting. The response rates were 37 (DCF) vs. 25% (FUP) ($P = 0.0106$), and the TTPs were 5.6 and 3.7 months, respectively ($P < 0.01$). However, DCF caused significant hematologic toxicity including neutropenia of grade 3 or worse in 82.3% of patients, and febrile neutropenia in 30.3% of patients, which required the secondary prophylactic use of G-CSF. Although the risk of death was reduced in the DCF group ($P = 0.0201$), with a median OS of 9.2 months vs. 8.6 months in the FUP group, the survival difference does not seem to have clinical significance. Given that docetaxel afforded only a modest survival benefit, showed an increased toxicity profile and did not positively affect the incurable disease status, it is not clear whether docetaxel should be incorporated in the first-line drug cocktail or should be reserved as a second-line regimen after first-line chemotherapy failure. Our group has also reported the efficacy and safety profiles of regimens with capecitabine plus cisplatin (XP) [9, 13] and XP with a docetaxel triplet (DXP) [8]. Treatment outcomes of the XP regimen were comparable to those of the FUP regimen, but with a more favorable toxicity profile. The XP regimen can be conveniently used in the outpatient clinic [9]. In our phase I and II study, the DXP regimen seemed to be more active than the XP regimen. Although the DXP regimen was generally well tolerated, it was, however, more toxic than the XP regimen. Generally, sequential chemotherapy is expected to be more tolerable than concurrent triplet chemotherapy. Moreover, treatment outcomes, especially OS, can be improved by effective second-line chemotherapy. In this study, docetaxel showed good activity as a salvage second-line chemotherapy in AGC, in line with previous reports. Further, well-designed, prospective randomized trials are needed to clarify whether adding docetaxel to FUP or XP will provide superior benefits compared to sequential administration of the same agents (FUP or XP followed by docetaxel) in the treatment of AGC.

In conclusion, docetaxel monotherapy at a dose of 75 mg/m^2 might be valuable for second-line treatment of AGC patients if prior F and P combination chemotherapy has failed. This approach deserves further investigation.

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