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Docetaxel and Cisplatin Plus Fluorouracil Compared With Modified Docetaxel, Cisplatin, and 5-Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Retrospective Analysis of Single Institution

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Gastric cancer is the second most common among cancer-related deaths in the world. Systemic chemotherapy for patients with gastric cancer has limited impact on overall survival. We performed a retrospective analysis of the efficacy and side effects of Docetaxel and Cisplatin Plus Fluorouracil (DCF) versus Modified-Dose Docetaxel, Cisplatin, and 5-Fluorouracil (mDCF) in the metastatic gastric cancer with first-line chemotherapy treated patients.

Retrospectively were reviewed 107 locally advanced or metastatic gastric cancer patients who were treated DCF or mDCF as first-line treatment from June 2007 to August 2011 in Dicle University Hospital, Department of Medical Oncology.

The DCF protocol included 75 mg/m^2 docetaxel and cisplatin on day 1 and 750 mg/m2/day 5-FU infusion for 5 days, repeated every 3 weeks. The mDCF protocol included 60 mg/m^2 docetaxel and cisplatin on day 1 and 600 mg/m^2 5-Fluorouracil continuous infusion per day on days 1–5, every 3 weeks.

Patients were treated using DCF arm 85 (M: 56, F: 29), the mDCF arm 22 (M: 13, F: 9) After treatment toxicities were: Grade III-IV neutropenia (48.2% vs 13.6% p=0.003), anemia (21.2% vs 4.5% p=0.06), nausea (44.7% vs 13.6% p=0.008) and vomiting (31.8% vs 4.5%, p=0.01) was higher in the DCF arm. Other toxicities profile was similar in both groups (p>0.05). The rate of response was similar in both arm. Among patients with the DCF and mDCF arm rate complete response (10.3% vs 6.7%, p>0.05), partial response (35.3% vs 40.0%, p>0.05), stable disease (32.4% vs 33.3%, p>0.05), progressive disease (22.1% vs 20.0%, p>0.05) and overal response (45.6% vs 46.7%, p>0.05) did not have a statistically difference (p>0.05). Progression-free survival (PFS) and overall survival (OS) were more favorable in the DCF arm than mDCF arm, but the difference was not significant statistically (9.9 vs 8.6, 7.4 vs 6.5 p>0.05)

In conclusion, the response rate, median PFS and median OS are similar in both arms, while the mDCF regimen are more favorable than the DCF for toxicity profile regimen in advanced gastric cancer patients who were undergoing first-line palliative treatment. Therefore, a prospective and larger clinical trials are needed.

Key words: advanced gastric cancer, docetaxel, cisplatin, fluorouracil

Despite the reduced incidence during the second half of the 20th century, gastric cancer is still the second most common among cancer-related deaths in the world. In two-third of patients with gastric cancer is diagnosed for metastatic disease (1,2). Without effective treatment, the median survival for metastatic disease is 3 to 5 months, however it may be extended to 8-12 months with the platinum and taxane-containing regimens (3-6).

Several randomized studies have shown that systemic chemotherapy resulted in significant survival benefits when compared with best supportive care (7–10). The meta-analysis by Wagner et al. in patients with advanced gastric cancer suggest that the combination chemotherapy response rates prevail over monotherapy alone (11). This systematic review have found that this survival benefit is approximately 1 month in pooled median survival time for combination chemotherapy.

In the Tax 325 study, two regimens were compared;75 mg/m^2 docetaxel and cisplatin on day 1 and 750 mg/m^2 5-Fluorouracil continuous infusion per day on days 1–5, every 3 weeks (DCF) versus cisplatin 100 mg/m^2 on day 1 and 1000 mg/m^2 5-Fluorouracil continuous infusion per day on days 1–5, every 4 weeks (CF). The DCF arm response rates (37% vs 25%) and OS (median survival, 9.2 v 8.6 months, respectively; P=0.02) were higher than CF arm, while the toxicities of grade 3 to 4 was higher in the DCF arm. On the other hand, because of drug toxicity with the

standard DCF regimen, 41% of patients required dose reduction, 64% cycle delays occurred, and 2.7% died (4).

Thus, antibiotics with granulocyte colony-stimulating factor (G-CSF) support were commonly permitted in standard DCF that is an effective, while being expensive regimen due to its toxicity and side effects.

Ozdemir et al.(12) have found that mDCF have comparable efficacy with classical DFC, with better toxicity profile.

We performed a retrospective analysis of the efficacy and side effects of DCF versus mDCF in the metastatic gastric cancer patients after first-line chemotherapy treatment .

Patients and methods

Patient Population. We retrospectively reviewed 107 locally advanced or metastatic gastric cancer patients who were treated DCF or mDCF as first-line treatment from June 2007 to August 2011 in Dicle University, School of Medicine, Department of Medical Oncology.

All had advanced gastric cancer. Patients who had received prior treatment were excluded.

Treatment and Assessment. The DCF protocol included 75 mg/m^2 docetaxel and cisplatin on day 1 and 750 mg/m2/day 5-FU infusion for 5 days, repeated every 3 weeks. The mDCF protocol included 60 mg/m^2 docetaxel and cisplatin on day 1 and 600 mg/m^2 5-Fluorouracil continuous infusion per day on days 1–5, every 3 weeks. Imaging studies were documented by computed tomography at baseline and every three cycles for patients.

Table 1. The general characteristics of the patients

Characteristic	DCF	mDCF	p
Enrolled patients.	*85*	22	
Sex			
Male	56	13	
Female	29	9	
Median age,years	52 (23-75)	56 (25-76)	P>0.05
Performance status (%)			
0-1	73.8	71.4	P>0.05
2-3	26.2	28.6	
The number of cycles (median)	4	3	P>0.05
Stage (%)			
Locally advanced	14.1	13.6	P>0.05
Metastatic	85.9	86.4	P>0.05
Location of primary tumor (%)			
Gastroesophageal junction	16.5	9.1	
Fundus	3.5	4.5	
Body	17.6	22.7	P>0.05
Antrum	34.1	27.3	
Total	5.9	13.7	
Unknown	22.4	22.7	
Histology (%)			
Adenocarcinoma	69	59.1	
Mucinous adenocarcinoma	4.8	4.5	P>0.05
Signet ring cell carcinoma	26.2	36.4	
Dose reduction (%)	12.9	4.5	P>0.05
Second-line chemotherapy (%)	34.8	31.3	P>0.05

The responses to chemotherapy were measured according to Response Evaluation Criteria in Solid Tumors (RECIST).

Statistical Analysis. All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for windows). The differences of the clinical characteristics between the two groups were analyzed by chi-square test and student t test. Overall survival was calculated with the log-rank test. The Kaplan–Meier method was for used survival curves. Differences were assumed to be significant when p value was less than 0.05.

Results

Patient Characteristics. We retrospectively reviewed 107 locally advanced or metastatic gastric cancer patients who were treated DCF or mDCF as first-line treatment from June 2007 to August 2011 in Dicle University Hospital, Department of Medical Oncology.

The patients' baseline characteristics are listed in Table 1. DCF arm 85 (M: 56, F: 29), the mDCF arm 22 (M: 13, F: 9) are patients. mDCF arm patients older than the DCF arm (median 56 vs 52 p>0.05). Patients with the DCF arm had a higher dose reduction (12.9% vs 4.5%, p>0.05). Among patients with the DCF and mDCF arm gender, performance status, stage, the number of cycles, second-line chemotherapy did not have a difference statistically (p>0.05).

Safety Results. Neutropenia was the most common significant hematologic toxicity and nausea- vomiting was the most common nonhematologic toxicity in both arms. Grade III-IV neutropenia (48.2% vs 13.6% p=0.003), anemia (21.2% vs 4.5% p=0.06), nausea (44.7% vs 13.6% p=0.008) and vomiting (31.8% vs 4.5%, p=0.01) were higher in the DCF arm. Other toxicities profile was similar in both groups (p>0.05).

Efficacy. Treatment efficacy was shown in Tables3. The rate of response was similar in both arms. Among patients with the DCF and mDCF arm rate of complete response (10.3% vs 6.7%, p>0.05), partial response (35.3% vs 40.0%, p>0.05), stable disease (32.4% vs 33.3%, p>0.05), progressive disease (22.1% vs 20.0%, p>0.05) and overal response (45.6% vs 46.7%, p>0.05) did not have a difference statistically (p>0.05).

Table 2. Toxicity profile of grade 3 to 4

Characteristic	**DCF (%)**	**mDCF (%)**	**p**
Hematologic toxicity :			
Neutropenia	48.2	13.6	P=0.003
Febrile neutropenia	19.0	4.5	P>0.05
Thrombocytopenia	25.9	9.1	P>0.05
Anemia	21.2	4.5	P=0.06
Nonhematologic toxicity :			
Nausea	44.7	13.6	P=0.008
Vomiting	31.8	4.5	P=0.01
Diarrhea	9.4	4.5	P>0.05
Oral mucositis	4.7	4.5	P>0.05

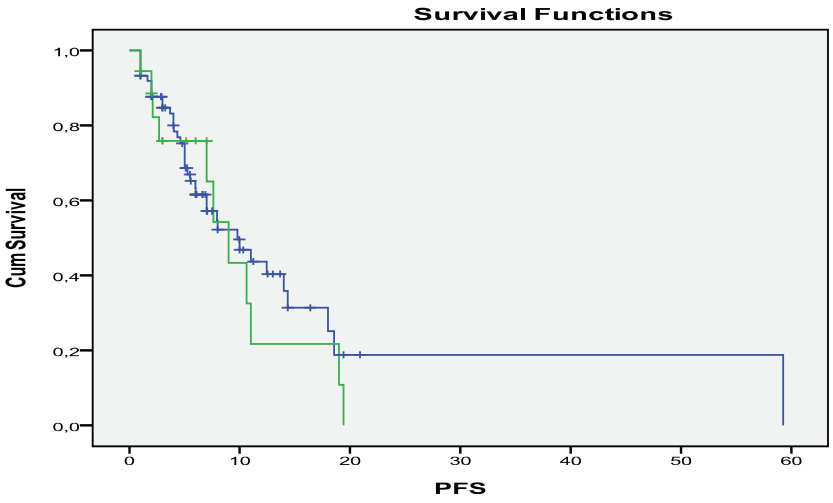

Fig 1. Progression-free survival of the DCF and mDCF groups (p=0.54)

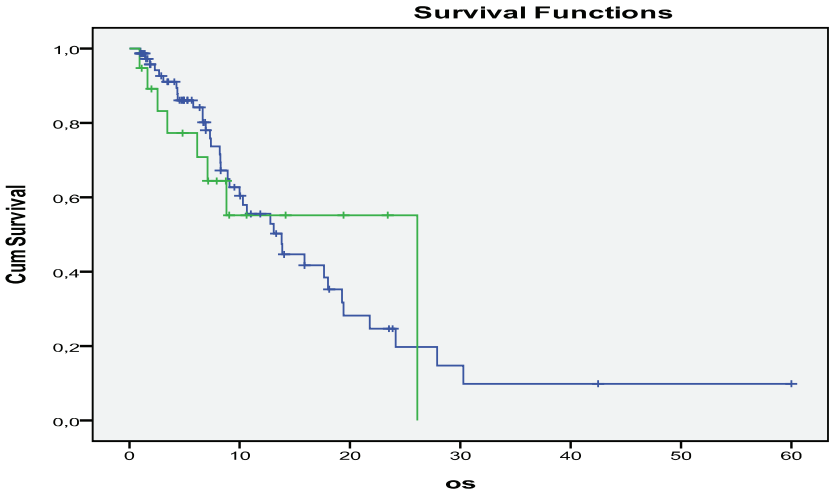

Fig 2. Overall survival of the DCF and mDCF groups (p=0.96)

Median Progression-free survival (PFS) was more favorable in the DCF arm than mDCF arm, but the difference was not statistically significant (7.4 vs 6.5 months, p=0.54) (Fig.1). Median OS was not significantly superior in the DCF arm (9.9 vs 8.6 months, p=0.96) (Fig. 2).

Table 3. Treatment efficacy of the patients

Characteristic	DCF (%)	mDCF (%)	p
Response			
Complete response(CR)	10.3	6.7	P>0.05
Partial response(PR)	35.3	40.0	P>0.05
Stable disease(SD)	32.4	33.3	P>0.05
Progressive disease(PD)	22.1	20.0	P>0.05
Overall response	45.6	46.7	P>0.05

Discussion

Systemic chemotherapy for patients with gastric cancer has limited impact on OS not only due to a low response rates, but also because of severe side effects. The meta-analysis by Wagner et al. in patients with advanced gastric cancer suggests that the combination chemotherapy response rates prevail over monotherapy alone (11).

In the Tax 325 study, two regimens were compared. The DCF arm response rates and OS were higher than CF arm, while the toxicities of grade 3 to 4 was higher in the DCF arm (4).

Roth et al. (3) comparing DCF, ECF and DC found that DCF was higher to ECF in response rates. Kos FT et al. (13) suggest that the mDCF chemotherapy was more favorable than the CFF

regimen with an acceptable toxicity profile. In another study Ozdemir et al.(12) have found that mDCF have comparable efficacy with classical DCF, with better toxicity profile.

DCF is commonly used in the metastatic gastric cancer with first-line chemotherapy treated patients, while its tolerability is low owing to toxicity. Patients eligible for combination chemotherapy should be selected carefully. This retrospective study analyzed the efficacy and side effects of DCF versus mDCF in the metastatic gastric cancer with first-line chemotherapy treated patients.

In the Tax 325 study (4), the DCF achieved complete response in 2%, partial response in 35% (overall response rate of 37%), and stable disease in 30% of patients. On the other hand, OS and PFS were 9.2-5.6 months (median). In our study, with DCF regimen, PFS (7.4 months), the rate of complete response (10.3%) and overall response (45.6%) were higher than the Tax 325 study. This result is due to the fact that the rate of patients with locally advanced gastric cancer in our studies was higher than the Tax 325 study. OS and other rates of response were similar.

In the V325 study (4), grade 3–4 toxicity rates were: neutropenia (82%), anemia (18%), thrombocytopenia (8%), febrile neutropenia (29%), nausea (14%), vomiting (17%) and diarrhea (19%). In our study, rate of grade 3–4 toxicities in the DCF arm, neutropenia (48.2%) and febrile neutropenia (19%) were lower than the Tax 325 study, while thrombocytopenia (25.9%), nausea (44.7%) and vomiting (31.8%) were higher than the Tax 325 study.

Ozdemir et al.(12) have found that mDCF have comparable efficacy with classical DFC, with better toxicity profile. These findings were similarly found even in our study. The rate of complete response (10.3% vs 6.7%, p>0.05), partial response (35.3% vs 40.0%), stable disease (32.4% vs 33.3%), progressive disease (22.1% vs 20.0%) and overal response (45.6% vs 46.7%) were similar in both groups (p>0.05). Whereas grade III-IV neutropenia (48.2% vs 13.6% p=0.003), anemia (21.2% vs 4.5% p=0.06), nausea (44.7% vs 13.6% p=0.008) and vomiting (31.8% vs 4.5%, p=0.01) were higher in the DCF arm.

In conclusion, the response rate, median PFS and OS are similar in both arms, while the mDCF regimen was more favorable than the DCF for toxicity profile regimen in advanced gastric cancer patients who were undergoing first-line palliative treatment. For this reason, a prospective and larger clinical trials is needed.

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