

# Reduced Doses of Docetaxel and Cisplatinum Plus 5 Fluorouracil Combination Chemotherapy in Metastatic Esophagogastric Adenocarcinoma: The Impact on Outcomes

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## ABSTRACT

Docetaxel-cisplatin-5-fluorourasil (DCF) protocol is one of the standard regimen at present however it is difficult to administer owing to high toxicity rates. The aim of study was to modify the dose of DCF regimen in order to render it more tolerable and to evaluate the efficacy and tolerability of modified DCF (mDCF) protocol. 267 patients followed in Ankara Numune Hospital were included in the study. All patients were administered mDCF regimen as metastatic first line treatment. Doses in mDCF arm was as follows: docetaxel 60 mg/m<sup>2</sup> 1. day, cisplatin 60 mg/m<sup>2</sup> 1. day and 5-fluorouracil 600 mg/m<sup>2</sup>/day (1-5 days) every three weeks. In the study, files of overall 267 patients who did not previously receive treatment were evaluated retrospectively. Median number of cycles in all patients was 6 (range 2-10). Median age of patients was 55 (range 22-76). Median follow up period was 9 months. Complete response 5 (1.9%) patients, partial response 74 (27.7%) patients and stable disease 95 (35.6%) patient. Median PFS was 6.0 (95%CI, 5.3-6.6) months, and median OS 10.0 (95% CI, 8.8-11.1) months. Parameters effect in univariate analysis were submitted to multivariate analysis results were CEA, grade, ECOG effective on OS. Grade 3-4 neutropenia was found 28.1%, anemia 11.6%, thrombocytopenia 4.1% and Febrile neutropenia 4.9%. Although mDCF regimen seems to be as effective as original DCF regimen, grade 3-4 toxicity rates were found to be lower. mDCF may be preferred as a tolerable and effective regimen in ECOG 0-2 metastatic gastric cancers.

**Keywords:** Metastatic esofagogastric cancer, Modified DCF, mDCF, Efficacy, Toxicity, Progression free survival, Overall survival

## ÖZET

### Metastatik Özofagogastrik Adenokarsinomlarda Modifiye Doz Doksetaksel-Sisplatin-5-Fluorourasil

#### Kombinasyon Tedavisi: Sonuçlara Etkisi

Günümüzde metastatik mide kanserinde Doksetaksel-cisplatin-5-fluorourasil (DCF) standart tedavi rejimlerinden biridir ancak yüksek toksisite oranları nedeniyle uygulaması zordur. Çalışmamızın amacı DCF rejiminin modifiye dozlarda etkinlik ve tolerabilitesinin gösterilmesidir. Çalışmaya Ankara Numune Hastanesinde takipli 267 hasta alındı. Tüm hastalar metastatik birinci basamakta modifiye DCF (mDCF) rejimi aldı. mDCF de ilaç dozları doksetaksel 60 mg/m<sup>2</sup> 1. gün, sisplatin 60 mg/m<sup>2</sup> 1. gün ve 5-fluorourasil 600 mg/m<sup>2</sup>/gün (1-5 günler) üç hastada bir olarak verildi. Çalışmada daha önce tedavi almamış 267 hastanın dosyaları retrospektif olarak incelendi. Hastaların aldığı median kür sayısı 6 (2-10), median yaş 55 (22-76) idi. Median takip süresi 9 ay idi. Tam yanıt 5 (1.9%) hastada, parsiyel yanıt 74 (%27.7) hastada, stabil hastalık 95 (%35.6) hastada tespit edildi. Median PFS 6.0 (%95 CI, 5.3-6.6) ay, median OS 10.0 (%95 CI, 8.8-11.1) ay olarak bulundu. Multivariate analizde OS üzerine etki eden faktörler CEA düzeyi, tümör greydi ve ECOG skoruydu. Grade 3-4 nötropeni %28.1, anemi %11.6, trombositopeni %4.1 olarak bulundu. Febril nötropeni oranı %4.9 idi. mDCF rejimi orijinal DCF rejimi kadar etkilidir, grade 3-4 toksisite oranları daha düşüktür. mDCF, ECOG 0-2 metastatik mide kanserinde etkili ve daha tolerabl bir rejim olarak tercih edilebilir.

**Anahtar Kelimeler:** Metastatik özofagogastrik kanser, Modifiye DCF, mDCF, Etkinlik, Toksikite, Hastaliksız sağ kalım, Genel sağ kalım

## INTRODUCTION

Gastric cancer is a health problem that occurs frequently all over the world and is of significance for public health. According to epidemiological data, in 2011, all over the world, gastric cancer is the fourth most common cancer, following lung, breast and colorectal cancers. Throughout the world 989.600 new cases are diagnosed annually and 738.000 cases die of gastric cancer, which accounts for 10% of all cancer related deaths.<sup>1</sup> Metastatic gastric cancer has an unfavorable prognosis and mean survival is between 3-5 months unless it is treated.<sup>2,3,4</sup> At present, expected survival is quite short despite all current advances and large majority of patients die within one year of metastasis development.

At present, there is no gold standard chemotherapy in the treatment of metastatic gastric cancer. According to results of randomized studies and meta-analyses, in metastatic gastric cancer cases, chemotherapy is more effective than supportive treatment with regard to both quality of life and survival.<sup>5,6</sup> 5-Fluorouracil and platin are most frequently used drugs. Then, it was demonstrated that addition of taxane groups chemotherapeutic drugs to these (docetaxel or paclitaxel) may improve treatment outcomes.<sup>7,8,9,10</sup>

After the efficacy of Docetaxel was shown in gastric cancer monotherapy<sup>11-16</sup>, it started to be combined with other agents.<sup>17-20</sup> Investigators have designed TAX 325 study in order to examine the addition of docetaxel to reference regimen in gastric cancer, i.e. cisplatin-5-FU (CF) combination.<sup>21,22</sup> Although TAX 325 demonstrated that in patients with metastatic gastroesophageal cancer, the addition of docetaxel to CF combination increased disease free survival and overall survival rates, it also had high dose limiting toxicity. Standard dose DCF regimen started to be new reference regimen in metastatic gastroesophageal cancer. However, it was a regimen difficult to administer due to its high toxicity rates. These results led to retrospective and then prospective studies investigating the efficacy and reliability of same combination at modified doses.<sup>23</sup>

In the present study, doses of DCF regimen, whose efficacy was shown in metastatic gastric cancer but

is toxic regimen, were modified. The aim of the present study was to evaluate long term real life data of efficacy and toxicity of mDCF regimen.

## PATIENTS AND METHODS

Patients who were followed in Ankara Numune Research and Education Hospital Medical Oncology clinic with the diagnosis of metastatic gastric cancer between 2005-2015 were included in the study. 267 patients file who had metastasis at the time of diagnosis or at follow up and underwent treatment with mDCF combination as first line treatment were examined retrospectively. All patient data were investigated in terms of demographic characteristics such as age and sex, pathological characteristics, and reliability. Long term vital data of the patients was accessed via Turkish population administrative data in addition to their files.

In the evaluation of patient performance while receiving mDCF, Eastern Cooperative Oncology Group (ECOG) scale and in the evaluation of response to treatment Response Evaluation Criteria in Solid Tumors (RECIST ver.1.1) criteria were used. The evaluation of treatment toxicity was made according to data of National Cancer Institute Common Toxicity Criteria (NCI-CTC ver. 2.0)

### Treatment

All patients were administered docetaxel 60 mg/m<sup>2</sup> 1. day, cisplatin 60 mg/m<sup>2</sup> 1. day, 5-fluorouracil 600 mg/m<sup>2</sup> 1-5 days every three weeks. Prior to treatment, all patients underwent whole blood, kidney function and liver function tests in order to determine whether they were suitable for treatment. All patients receiving mDCF treatment after 2011 were routinely administered Aprepitant as antiemetic.

### Statistics

Data analysis was carried out by SPSS 18.0 for Windows program. Descriptive statistics was expressed with mean-standard deviation or median (lowest-highest values) for continuous numerical variables and number of cases and (%) for categorical variables.

**Table 1.** Demographic characteristic of patients

Variables	n	%
Age of diagnosis (median)	55 (22-76)	
Sex		
Male	196	73.4
Female	71	26.6
Tumor location		
Cardia	34	12.7
Fundus	42	15.7
Corpus	120	44.9
Pylor	41	15.4
All gastric	30	11.2
Weight loss at diagnosis		
Weight loss present	173	64.8
Weight loss absent	94	35.2
Anemia at diagnosis		
Anemia present	221	82.8
Anemia absent	46	17.2
Tumor Grade		
I	17	6.4
II	65	24.3
III	152	56.9
Unknown	33	12.4
ECOG		
0	42	15.7
1	174	65.2
2	51	19.1
Metastasis locations		
Visceral	212	79.4
Non-Visceral	55	20.6
Adjuvant treatment		
Adjuvant chemotherapy	43	16.1
Adjuvant chemoradiotherapy	39	14.6

Progression and overall survival rates of all cases were investigated using Kaplan-Meier survival analysis. 3 months, 6 months, 9 months, 1 year, 2 years and 3 years cumulative progression free and overall survival rates along with mean survival were calculated with their 95% confidence intervals. Demographic characteristics of patients were evaluated using descriptive statistical methods. Parameters which were significant in univariate analysis were submitted to Cox regression multivariate analysis.

## RESULTS

### Demographic Characteristics

267 patients were included in the present study. Median age was 55 (range 22-76). One hundred

**Table 2.** Survival rates in patients undergoing mDCF chemotherapy.

Survival rates	Progression free survival	Overall survival
6 months	55%	76%
1 Year	18%	41%
2 Years	5%	14%

ninety-six of cases was (73,4%) male and 71 (26,6%) female. At the moment of diagnosis, there was weight loss in 64.8% of patients and anemia in 82.8% of patients. Primary tumor localization was gastric corpus in nearly half of patients (44.9%), cardia tumor was observed only in 12.7% of patients. About 80% of patients were metastatic at the moment of diagnosis and over 50% was histopathologic grade 3.

In Table 1, demographic characteristics of patients are demonstrated.

### Treatment Characteristics and Efficacy Data

In all patients, median number of mDCF cycles was 6 (range 2-10). When best response rates obtained with mDCF regimen were evaluated, it was observed that complete response was found in 5 (1,9%) patients, partial response in 74 (27.7%) patients, and stable disease in 95 (35.6%) patients. Control rate of disease was found to be 65.2%. In 34.8% of patients progression developed under treatment. During follow up, progression was observed in 92.5% while 7.5% was being followed without progression. Survival rates are shown in Table 2.

Median follow up period was 9 months. Median progression free survival was 6.0 (95% CI, 5.3-6.6) months, while median overall survival was 10.0 (95% CI, 8.8-11.1) months. Overall survival and disease-free survival curves of patients included in the study are depicted in Figure 1 and Figure 2.

In the univariate analysis of factors that can influence survival, weight loss prior to mDCF, ECOG performance of 2, high tumor grade, presence of lymphovascular invasion and high CEA levels were established to exert inverse effect on overall

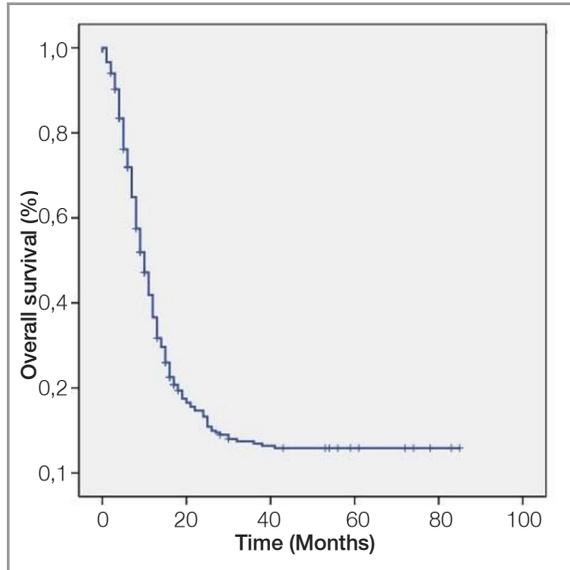


Figure 1. Overall survival graphic

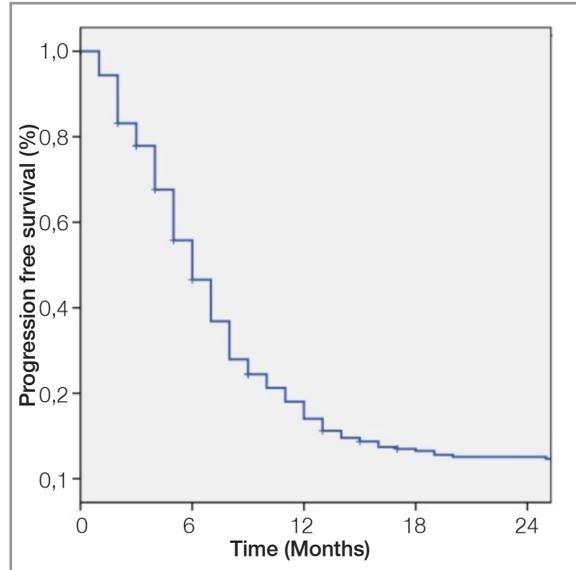


Figure 2. Progression free survival graphic

survival. When parameters with significant effect in univariate analysis were submitted to multivariate analysis the results were as follows: CEA, grade, ECOG performance status still remained significantly effective on OS.

In Table 3a and 3b, univariate and multivariate analysis results are shown.

### Toxicity Data

The most commonly occurring grade 3-4 side effects after mDCF chemotherapy were hematological. Grade 3 and 4 neutropenia rates were respectively 15% and 13%. Neutropenic fever was observed in 4.9% of patients after mDCF chemotherapy and inpatient treatment was required in all of these patients.

Due to toxicity development cure was delayed in 15.4% of patients. The most frequent cause of cure delays was neutropenia at a rate of 9.4%. Due to toxicity in 14.6% of patients dose modification was required. The most common cause of modification was again neutropenia at 10.9% during treatment, toxic death occurred in two patients.

When patients were evaluated for non-hematological toxicities, grade 3 nausea was seen in five patients (1.9%) grade 3 vomiting in three patients, (1.1%) grade 3-4 diarrhea in five patients (1.9%),

grade 3-4 nephrotoxicity in two patients (0.8%) and grade 3 hepatotoxicity in three patients (1.1%).

Hematological and non-hematological toxicity rates are demonstrated in Table 4.

### DISCUSSION

Today, the treatment of metastatic gastric cancer is systemic chemotherapy. In Phase 3 randomized TOGA study, in which clinical efficacy of trastuzumab an antiHER-2 agent, was investigated, particularly in HER-2 positive patients, trastuzumab combination prolonged survival significantly.<sup>24</sup> The overall survival benefit of these agents in bevacizumab and cetuximab studies has not been demonstrated.<sup>25,26</sup> In our daily practice, standard approach in first line treatment of patients with metastatic gastric cancer whose HER-2 status is unknown or negative is systemic combination treatment. Nevertheless, there is no chemotherapy combination regimen that can be considered as gold standard. After the publication of TAX 325 study results, mDCF combination regimen has become one of the first line treatment regimen in our clinic. Our data have been collected retrospectively, but high number of patients and their being real life data may make our study worthwhile.

**Table 3a.** Univariate analysis of parameters effect in overall survival

	Univariate analysis		
	OS	CI (%95)	p value
Weight loss			0.031
Present	9	7.8-10.1	
Absent	11	9.1-12.8	
Tumor Grade			0.01
High Grade	9	7.9-10	
Low Grade	12	9.9-14	
Lymphovascular invasion			0.022
Present	12	10.4-13.5	
Absent	14	7.6-20.3	
CEA value			0.014
High	8	6.4-9.5	
Normal	12	10.5-13.4	
ECOG value			0.02
ECOG 2	7	5.2-8.7	
ECOG 0-1	11	9.7-12.2	

Study of Van Cutsem et al. (TAX 325 study), on which our practice is based, DCF regimen was administered as docetaxel 75 mg/m<sup>2</sup> 1. day, cisplatin 75 mg/m<sup>2</sup> 1. day and 5-FU 750 mg/m<sup>2</sup>/day (1-5. days) every three weeks and in mDCF regimen, doses were administered in the same manner after being modified at 20%. In the recently published phase 3 randomized studies of Jinwan Wang et al, mDCF regimen, with similar dose and administration pattern with our study, was compared with CF regimen and mDCF regimen was established to yield significantly higher PFS and OS compared to CF regimen.<sup>27</sup>

Control rate of disease was found to be 67% in TAX 325 study and 65.2% in the our study. In

**Table 4.** Hematological and non-hematological toxicity rates in patients undergoing mDCF chemotherapy

	n	%
Dose reduction due to toxicity	39	14.6
Treatment discontinuation due to toxicity	41	15.4
Death due to treatment	2	0.7
Grade 3-4 toxicity		
Neutropenia	75	28.1
Anemia	31	11.6
Thrombocytopenia	11	4.1
Nausea	5	1.9
Vomiting	3	1.1

**Table 3b.** Multivariate analysis of parameters effect in overall survival

	Multivariate analysis		
	HR	CI (%95)	p value
Tumor Grade			0.005
High Grade	1		
Low Grade	0.46	0.26-0.79	
CEA value			0.03
High	1		
Normal	0.60	0.37-0.95	
ECOG value			0.001
ECOG 2	1		
ECOG 0-1	0.35	0.19-0.64	

terms of disease control rates, mDCF seems to reach the efficacy level of original doses. In TAX 325 study, mean time to progression was found to be 5.6 months and mean overall survival 9.2 months. In the study of Jinwan Wang using mDCF regimen, PFS of 7.2 months and OS 10.2 months were obtained while in the our study, PFS obtained was 6.0 months and OS 10.0 months, which are similar to results of above studies. Furthermore, all patients had ECOG status 0-1 in other phase studies, whilst 20% of our study groups consisted of ECOG 2 patients.

In a small randomized study comparing mDCF and standard DCF, modified regimen obtained 18 months OS whereas standard dose yielded 12 months OS. These figures are longer than all previous DCF data. The difference may be attributed to high number of locally advanced patients and to some patients undergoing surgery after tumor size is decreased. In addition, some of these patients underwent surgery after neoadjuvant treatment.<sup>28</sup>

In the study of Inal et al, 107 patients were evaluated retrospectively to compare mDCF and standard DCF regimen and in mDCF arms, modified doses similar to those of our study were administered and OS values were found to be 9.9 months in DCF arm and 8.6 months in mDCF arm. PFS was found to be 7.4 months in DCF arm and 6.5 months in mDCF arm.<sup>29</sup>

TAX 325 study indicated that DCF regimen is one difficult to administer although it is an effective combination. In Standard DCF, grade 3-4 neutro-

penia was observed at the rate of 82%, neutropenic fever 29%, and diarrhea 19%. In the study of Jinwan Wang, in mDCF arm, grade 3-4 neutropenia was found at the rate of 60% and febrile-neutropenia 12%. In our study, grade 3-4 neutropenia was found at the rate of 28%, and febrile-neutropenia around 5%. In the our study, the lower rate of hematological toxicity may be due to the fact that our data was collected retrospectively.

In TAX 325 study, in 64% of patients treatment was delayed and in 41% doses was reduced. Toxic death rate was found to be 2.7%. In our study, treatment delaying occurred at the rate of 15% and dose reduction 14%. Toxic death was occurred only in two patients. As seen, there is significant difference between standard dose and modified dose in terms of both delay in treatment and dose reduction. These delays and dose reductions in standard DCF may be the most important factor limiting its efficacy.

In the study of Inal et al. grade 3-4 neutropenia was found at the rate of 48.2% in standard DCF arm and 13.6% in mDCF arm. In this study, overall survival and progression free survival rates similar to those of our study were obtained and toxicity results were found to be quite lower than original doses.<sup>29</sup>

In conclusion, metastatic gastric cancer has no prospect of survival and main aim of treatment should be palliation or prolongation of survival. However, in a patient group in which cure is not expected, we should take care not to impair quality of life further and not to prolong the duration of hospitalization while trying to improve OS data. In this respect, mDCF is as effective as standard DCF. Furthermore, its tolerability is much better. In the present study, it was demonstrated that modified DCF regimen is an effective and reliable regimen as real-life data.

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