RESEARCH ARTICLE

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A Modified Epirubicin and Oxaliplatin Plus Capecitabine (EOX) Regimen as a Second- Line Therapy in Patients with Advanced Gastric Cancer

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Abstract

Objective: We aimed to evaluate the effectiveness of an mEOX (modified epirubicin, oxaliplatin plus capecitabine) regimen as second line therapy after failure of mDCF (modified docetaxel, cisplatin plus fluorouracil). **Methods:** Gastic cancer patients for whom first-line therapy was unsuccessful and who subsequently received mEOX (epirubicin 50 mg/ m^2 on day 1, oxaliplatin 85 mg/m^2 day 1 and capecitabine twice-daily dose of 625 mg/ m^2, p.o. for 2 weeks) every 3 weeks until disease progression or unacceptable toxicity, were retrospectively analyzed. **Results:** The study population comprised 129 cases with a median age of 55 years (range= 27-78), the majority being male (76 %). Most (75.2%) had ≥ 2 sites of metastasis. The median number of chemotherapy courses was five (range= 2–9). Forty-nine achieved a partial response and 33 showed stable disease, resulting in a ORR (overall response rate) of 38% and a DCR (disease control rate) of 63.6%. The most frequent features of grade 3-4 hematological and non-hematological toxicity were neutropenia (8.5%) and nausea/vomiting (5.4%). None of the patients suffered death due to toxicity. The median PFS was 4.7 months (95% CI, 4.1–5.3) and the OS was 7.4 months (95% CI, 6.3–8.5). On multivariate analysis, age ≥ 60 years and ECOG performance status (0-1) were independent prognostic factors affecting PFS and OS. **Conslusions:** In advanced gastric cancer patients, who progress after first line chemotherapy and have an ECOG performance status of 0-1, mEOX is a well tolerated triple regimen associated with a promising OS and PFS.

Keywords: Modified EOX- gastric cancer- modified DCF- second−line therapy

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Introduction

Gastric cancer is the 4th most common cancer and the 3rd most common cause of cancer-related deaths (Torre et al., 2012). More than half of all patients are diagnosed at an advanced stage, and chemotherapy is the most effective treatment for these patients (Siegel et al., 2014). Previous studies have shown that systemic chemotherapy compared to best supportive care prolongs survival time, provides symptom palliation and increases quality of life in patients with metastatic gastric cancer (Wagner et al., 2006; Wagner et al., 2010). According to various studies, combination chemotherapies are related to better response rates and overall survival compared with single agent chemotherapy (Wagner et al., 2006; Wagner et al., 2010). A meta-analysis suggests that triple combination chemotherapies are related to better overall survival rates (Wagner et al.,2006).

In the a randomized phase 3 study, First line therapy for advanced stage gastric carcinoma with docetaxel, cisplatin plus fluorouracil (DCF) compared with cisplatin plus fluorouracil (CF) significantly improved time-to-progression (TTP) (5.6 vs. 3.7 months, p<0.001) and overall survival (9.2 vs. 8.6 months, p= 0.2) (Van Cutsem et al., 2006). Phase 2 and retrospective studies concluded that modified doses of DCF offer similar outcomes (Al-Batran et al., 2008; Meng et al., 2014; Chi et al., 2011). Another randomized phase 3 study compared four triple combination chemotherapy regimens- epirubicin, cisplatin plus uorouracil ECF), epirubicin, cisplatin plus capecitabine (ECX), epirubicin, oxaliplatin plus uorouracil (EOF), and epirubicin, oxaliplatin plus capecitabine (EOX)-on patients with advanced stage eosophagogastric cancer, and EOX proved most effective in terms of longest survival times (Cunningham et al., 2008). For that reason EOX is considered a first line therapy regimen in advanced stage eosophagogastric cancers. However, the preferred treatment regimen varies between centres and regions

Almost all of the patients have progressive disease after first-line therapy. However, patients with a low Eastern Cooperative Oncology Group (ECOG) performance score (0-2) and sufficient organ functions are candidates for second-line therapy. With improving medical care and

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palliative support, more patients now have lower ECOG scores and become eligible for second-line therapy. Salvage chemotherapies using docetaxel or irinotecan compared to best supportive care as second line therapies are shown to improve overall survival significantly for advanced stage gastric cancer, according to randomized phase 3 studies (Kim et al., 2013; Thuss-Patience et al., 2011; Kang et al., 2012). These studies also showed that second line therapies with irinotecan and docetaxel were similar in terms of overall survival times and side effects (Kang et al., 2012). Paclitaxel another agent of the taxane group compared with irinotecan is demonstrated to be similar in terms of overall survival but associated with fewer side effects (Hironaka et al., 2013). The RAINBOW study, which compared paclitaxel with a combination of paclitaxel and ramucirumab (a biological agent also used in second-line therapy) demonstrated that ramucirumab improved progression-free survival (PFS) and overall survival (OS) (Wilke et al., 2014). Although some improvement in OS and PFS can be achieved with single or combined second-line therapies, there is no standard therapeutic approach, and ramucirumab isn't yet available in most of the world's countries. In undeveloped and developing countries, advanced stage gastric cancers are currently treated with single agent or combined chemotherapies for patients with good performance status. Efficiency and side effect profiles for second-line treatment using EOX chemotherapy regimen, which proved to be effective in first-line treatment, are yet to be fully explored. We therefore aimed to assess the efficiency and side effect profile of second-line treatment with a modified EOX (mEOX) regimen on patients with progressive disease after first-line treatment with modified DCF (mDCF).

Materials and Methods

Patients and Methods

In this study, patients with metastatic gastric cancer who were treated in our hospital between November 2009 and August 2016 were evaluated. Our general approach in terms of first-line therapy was mDCF for patients considered suitable. Patients with progressive disease after first-line mDCF chemotherapy received the EOX regimen as second-line treatment and were assessed retrospectively. Inclusion criteria were histopathologically approved diagnosis of gastric or gastroesophageal adenocarcinoma, being aged 18 years or older, ECOG performance status of 0-2 before second-line EOX chemotherapy, no central nervous system metastasis, sufficient bone marrow (neutrophil count greater than 1500, platelet count greater than 100,000), good kidney, liver and cardiac functions, no other primary malignancy, no concomitant uncontrolled disease, and at least two cycles of EOX as second-line therapy. Patient selection consort diagram was shown in Figure 1.

Chemotherapy was infused through a port catheter in right or left subclavian vein or through peripheral veins. First-line mDCF regimen received 60 mg/m^2 docetaxel and cisplatin on Day 1, followed by a 5-fluorouracil 600 mg/m^2/day infusion for 5 days, repeated every 3 weeks. Patients were treated with mEOX consisting of epirubicin at 50 mg/m^2 (intravenous infusion [IV] on day 1), oxaliplatin at 85 mg/m2 (IV on day 1) and capecitabine at a twice-daily dose of 625 mg/m^2 (p.o. for 2 weeks) every 3 weeks until the disease progressed or unacceptable toxicity levels were reached. Dose modifications and treatment delays were conducted according to the extent of hematological and nonhematological toxicities.Toxicity evaluations were performed using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

A physical examination, complete blood counts and blood biochemistry tests were performed before every cycle of the treatment. Computed tomography was used to determine the disease stage and response evaluation after the second or third cycle of treatment. Tumour response was classified according to the Response Evaluation Criteria in Solid Tumours, version 1.1 (Eisenhauer et al., 2015). The survival statuses of the patients were determined from the hospital files and Central Civil Registration System records using the patients Turkish Republic Registration Numbers.

Statistical analysis

The Statistical Package for the Social Sciences Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A p value of <0.05 was deemed to indicate statistical significance. Categorical variables were analyzed using the chi-squared or Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method. Possible factors identified with univariate analyses were entered into the Cox regression analysis, using backward selection to determine independent predictors of survival. Progression-free survival (PFS) was defined as the time interval from the first day of mEOX protocol to the date of disease progression or death, whichever occurred first. Overall Survival (OS) was defined as the time interval from the first day of mEOX protocol to the date of death or last follow-up visit.

Results

Patient characteristics

129 patients were included in the study. The demographic and clinicopathological characteristics of the patients are presented in Table 1. The median age of the patients was 55 (ranging between 27 and 78 years) and the majority (76%) of them were male. The most common histopathologic type was poorly differentiated adenocarcinoma/signet-ring cell (72.1%). Primary tumor location was most commonly the cardia-fundus (45.7%). 21 patients had undergone previous curative surgery and 15 of them had received adjuvant chemotherapy or chemoradiotherapy. The majority of patients had an ECOG performance score of 0 or 1 (72.9%). Most common metastasis locations were the intraabdominal distant lymph node (55.8%), the liver (45.7%) or the periton (39.5%), and 75.2% of those had two or more metastasis regions.

All patients received mDCF chemotherapy regimen as a first-line therapy. Overall response rate (ORR)

Table 1. Demographic Characteristics of the Patients

Characteristics	N	%
Age (median, years)	55 (27-78)	
Gender		
Female	31	24
Male	98	76
Smoking		
Active smoker	49	38
Ex-smoker	34	26.4
No	46	35.6
ECOG		
0	29	22.5
1	65	50.4
2	35	27.1
Weight loss*		
Yes	83	64.3
No	46	35.7
Comorbidity		
Yes	48	37.2
No	81	62.8
Histological Type		24
Well/Moderately dif	31	62
Poorly dif/signet-ring cell	80	14
Unknown	18	
Tumor location		
Fundus-Cardia	59	45.7
Corpus	46	35.6
Antrum	24	8.7
CEA*		
Normal	62	48
High	67	52
CA19-9 (U/mL)*		55.8
Normal	72	44.2
High	57	
Hemoglobin (g/dL)		
≤10	11	26.2
>10	31	73.8
Albumin (mg/dL)		42.6
<35	55	57.4
≥35	74	
The number of metastatic sites		
1	29	22.5
2	68	52.7
>2	32	24.8
Site of metastasis		
Liver	59	45.7
Peritoneum	51	39.5
İntra-abdominal distant LAP	72	55.8
Lung	19	14.7
Mediastinal lymphadenopathy	18	14
Bone	19	14.7
Others	29	22.7

* Before second-line therapy; CA 19-9, Carbohydrate antigen 19-9; CEA, Carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; LAP, Lymphadenopathy

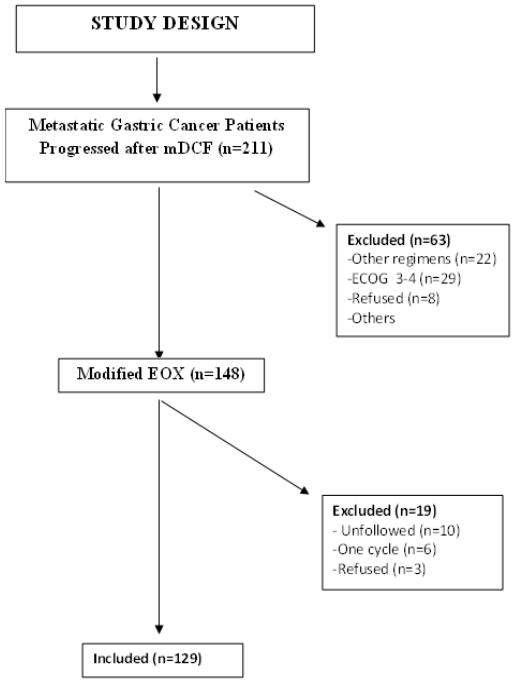

Figure 1. Patient Selection Consort Diagram

and disease control rate (DCR) were 48.8% and 86% respectively and median PFS was 7.0 months (95% CI, 6.3–7.8) for first-line therapy.

Treatment and toxicity

590 courses of chemotherapy were administered. The median number of chemotherapy courses was five (ranging= 2-9). The rate of patients who underwent at least three courses of chemotherapy was 92.2% , and 48.1% of the patients completed the six courses of mEOX.

Grade 3-4 hematologic or non-hematologic toxicities are shown in Table 2. Most common among these were neutropenia (8.5%) and nausea/vomiting (5.4%). Five patients (3.9%) developed febrile neutropenia. Six patients were administered secondary granulocyte colony-stimulating factor prophylaxis because of grade 3 to 4 neutropenia. One patient developed the pre-renal type of acute renal failure due to grade 3 to 4 nausea and vomiting, and was hospitalized. Course delay was performed for 14 patients (10.8%), and dose reduction was performed for 17 patients (13.2%) due to toxicity levels.

Table 2. Grade III-IV Adverse Effects in the Patients

Adverse events	n (%)
Dose reduction	17 (13.2)
Course delay	14 (10.8)
Grade 3-4 toxicity	
Neutropenia	11(8.5)
Anemia	5 (3.9)
Thrombocytopenia	2 (1.6)
Nausea and vomiting	7 (5.4)
Mucositis	1 (0.8)
Diarrhea	1 (0.8)
Febril neutropenia	5 (3.9)

Table 3. Univariate and Multivariate Analysis for Overall Survival

Characteristics	Number of patients N (%)	Univariate analysis for OS	P value (univariate)	Multivariate analysis
Age (mean, years)				
<60	84 (65.1)	5.9		p=0.03, HR: 1.5, %95 CI: 1.027-2.251
≥60	45 (34.9)	9.2	0.05	
Gender				
Female	31 (24.0)	8.1		
Male	98 (76.0)	7.2	0.23	
ECOG				
0-1	94 (72.9)	8.9		p<0.001, HR: 2.2, %95 CI: 1.450-3.459
2	35 (28.1)	4.9	<0.001	
Weight loss				
Yes	46 (35.6)	5.9		
No	83 (64.4)	7.6	0.29	
Histological Type				
Well/Moderately dif.	31 (27.9)	9		
Poorly dif/signet-ring cell	80 (72.1)	6.2	0.24	
Smoking				
Yes	83 (64.3)	7.2		
No	46 (35.7)	7.8	0.43	
Comorbidity				
Yes	48 (37.2)	8.9		
No	81 (62.8)	6.8	0.69	
Tumor location				
Fundus-Cardia	59 (45.7)	9.2		p=0.058, HR:1.2, %95 CI: 0.992-1.581
Corpus	46 (35.6)	5.4		
Antrum	24 (18.7)	7.4	0.002	
CEA				
Normal	62 (48.0)	8.5		p=0.001, HR: 1.9, %95 CI: 1.320-2.892
High	67 (52.0)	6.9	0.006	
CA19-9				
Normal	72 (55.8)	8.9		p=0.12, HR: 1.3, %95 CI: 0.912-2.084
High	57 (44.2)	6.7	0.003	
Hemoglobin (g/dL)				
≤10	28 (21.7)	5.4		p=0.42, HR:1.2, %95 CI: 0.754-1.951
>10	101 (78.3)	7.6	0.1	
Albumin (mg/dL)				p=0.11, HR:1.3, %95 CI: 0.925-2.077
<35	55 (42.6)	5.8	0.13	
≥35	74 (57.4)	8.1		
The number of met. sites				
≤2	97 (75.2)	7.4		
>2	32 (24.8)	7.4	0.2	
Response to first-line chemotherapy				
Yes	63 (48.8)	7.8	0.83	
No	66 (51.2)	7.3		

CA 19-9, Carbohydrate antigen 19-9; CEA, Carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group

There were no treatment-related deaths.

Response and survival

Forty-nine patient achieved a partial response and 33 patients showed stable disease, resulting in a ORR of 38% and a DCR of 63.6%. All patients had progressive disease at the time of analysis and 90.7% (n=117) of the patients had died. The median follow-up period was 7.3 months (range=1.8-30.7 months). The median PFS was 4.7 months (95% confidence interval [CI], 4.1–5.3), and

Table 4. Univariate and Multivariate Analysis for Progression Free Survival

Characteristics	Number of patients N (%)	Univariate analysis for PFS	P value (univariate)	Multivariate analysis
Age (mean, years)				
<60	84 (65.1)	4.3		p=0.029, HR: 1.7, %95 CI: 1.057-2.734
≥60	45 (34.9)	5.6	0.008	
Gender				
Female	31 (24.0)	4.8		
Male	98 (76.0)	4.6	0.7	
ECOG				
0-1	94 (72.9)	5.4		p=0.002, HR: 2.0, %95 CI: 1.311-3.311
2	35 (28.1)	3.4	0.006	
Weight loss				
Yes	46 (35.6)	5		
No	83 (64.4)	4.4	0.94	
Histological Type				
Well/Moderately dif.	31 (27.9)	5		p=0.29, HR:1.2, %95 CI: 0.807-2.007
Poorly dif/signet-ring cell	80 (72.1)	3.9	0.18	
Smoking				
Yes	83 (64.3)	4.6		
No	46 (35.7)	4.8	0.25	
Comorbidity				P=0.08, HR:1.4, %95 CI: 0.943-2.328
Yes	48 (37.2)	5.2		
No	81 (62.8)	4.3	0.13	
Tumor location				
Fundus-Cardia	59 (45.7)	5.2		p=0.24, HR:1.1, %95 CI: 0.901-1.516
Corpus	46 (35.6)	3.9		
Antrum	24 (18.7)	4.3	0.07	
CEA				
Normal	62 (48.0)	5		p=0.31, HR: 1.2, %95 CI: 0.813-1.909
High	67 (52.0)	4.4	0.05	
CA19-9				
Normal	72 (55.8)	5		p=0.059, HR:1.4, %95 CI: 0.984-2.263
High	57 (44.2)	4.4	0.09	
Hemoglobin (g/dL)				
≤10	28 (21.7)	3.9		p=0.96, HR:1.0, %95 CI: 0.605-1.688
>10	101 (78.3)	5	0.12	
Albumin (mg/dL)				p=1.3, HR:1.0, %95 CI: 0.865-1.983
<35	55 (42.6)	3.9	0.2	
≥35	74 (57.4)	5		
The number of met. sites				
≤2	97 (75.2)	4.9		
>2	32 (24.8)	4.3	0.4	
Response to first-line chemotherapy				
Yes	63 (48.8)	4.8	0.31	
No	66 (51.2)	4.6		

CA 19-9,Carbohydrate antigen 19-9; CEA, Carcinoembriyonic antigen; ECOG, Eastern Cooperative Oncology Group

the median OS was 7.4 months (95% CI, 6.3–8.5). The survival curves are shown in Figures 2 and 3.

Prognostic factors

Univariate and multivariate analyses of factors affecting PFS were performed. Univariate analysis revealed that age ≥60, an ECOG performance score of 0-1 and normal pre-mEOX treatment serum CEA (carcinoembryonic antigen) levels were significant factors in PFS. The Age ≥60 and an ECOG performance score

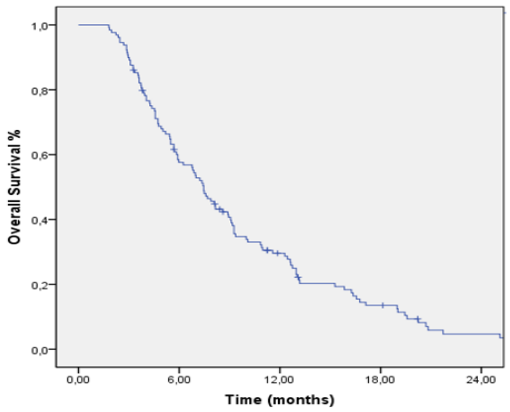

Figure 2. Kaplan Meier Curves for Overall Survival of the Patients

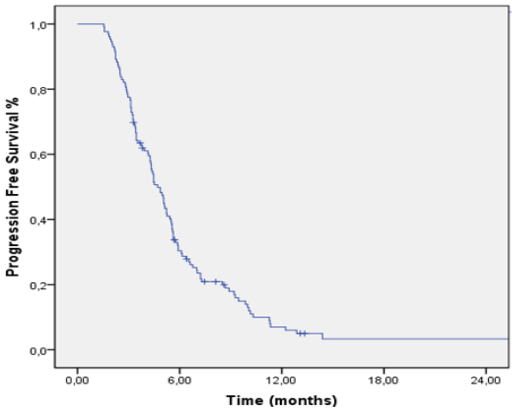

Figure 3. Kaplan Meier Curves for Progression Free Survival of the Patients

0-1 were independent prognostic factors in multivariate analysis (Table 3). Univariate analysis of factors relating to OS revealed that age ≥60, an ECOG performance score of 0-1, having a primary tumour located on the cardia-fundus, normal pre-mEOX treatment serum CEA (Carcinoembryonic antigen) and CA19-9 (carbohydrate antigen 19-9) levels were statistically significant factors. Among these, age ≥60, an ECOG performance score of 0-1 and normal pre-mEOX treatment serum CEA levels were independent factors relating to OS in multivariate analysis (Table 4).

Discussion

The contribution to survival by second-line therapies for metastatic gastric cancer has been demonstrated generally in small groups of patients and mostly with single agent therapies (Kim et al., 2013; Thuss-Patience et al., 2011; Kang et al., 2012). Although recommended as first-line therapy, triple combination chemotherapies are not standard in second-line treatment due to concerns about tolerability and toxicity. Single agent chemotherapy and ramucirumab with or without paclitaxel treatment which has recently proved to be effective are recommended as second-line treatments. In the current study, effectiveness of modified EOX was demonstrated in patients with advanced gastric cancer who were progressed on modified dose DCF as first line chemotherapy regimen proven to be effective in phase 3 trails. Therefore, this finding of our study was important because the sequential usage of modified triple regimens was shown. Additionally, our study is one of the largest studies to evaluate triple chemotherapy regimens as second-line therapy.

The Arbeitsgemeinschaft Internistische Onkologie (AIO) group reported in the first phase 3 study that patients who received irinotecan as second-line therapy had improved the median OS compared to best supportive care (4.0 vs 2.4 months, HR 0.48; 95% CI 0.25–0.92; P = 0.012) (Thuss-Patience et al., 2011). In a Korean study, Kang et al., (2012) verified second-line therapy which demonstrated that patients who received docetaxel or irinotecan as second-line therapy also had improved median OS rates compared to best supportive care (5.3 vs 3.8 months, HR 0.657; 95% CI 0485–0.891; P = 0.007). There was no significant difference between irinotecan and docetaxel in terms of overall survival in this study (P = 0.116). Hironaka et al., (2013) compared weekly paclitaxel and irinotecan (every three weeks) as second-line therapies in a phase 3 study in Japan. In this study, the irinotecan group showed in a median OS of 8.4 months while weekly paclitaxel group achieved 9.5 months (HR 1.13; 95% CI 0.86–1.49; P = 0.38). Median PFS times were 2.3 and 3.6 months for irinotecan and paclitaxel groups respectively (HR, 1.14; 95% CI, 0.88 to 1.49; P = .33). There have been several phase 2, phase 3 and retrospective studies on double combination chemotherapy regimens as second-line therapy, as well as single chemotherapy studies (Higuchi et al., 2014; Park et al., 2005; Rino et al., 2013; Kim et al., 2010; Sym et al., 2013; Maugeri-Sacca et al., 2013). These studies mostly evaluated combinations with irinotecan (e.g. FOLFIRI) and demonstrated ORRs of 15.6-22.8%, PFS rates of 3-3.8 months and OS rates of 5.1-6.8 months (Kim et al., 2010; Sym et al., 2013; Maugeri-Sacca et al., 2013, Jung et al., 2016). In our study, ORR, PFS and OS were better (38%, 4.7 months and 7.4 months respectively) compared to other studies. However Hironaka et al., (2013) demonstrated that median OS for irinotecan group was 8.4 months and 9.5 months for paclitaxel group, which are better than our results . This difference may be due to better population with a higher rate of single-area metastasis (52-57% vs 22%), fewer periton metastasis (25% vs 40%) and a higher majority of patients with ECOG scores of 0-1 (96% vs 73%).

There are two phase 3 studies (REGARD and RAINBOW) concerning ramucirumab as a targeted treatment in second-line therapy for advanced stage gastric cancer patients (Wilke et al., 2014; Fuchs et al., 2014). The REGARD study demonstrated a better OS with ramucirumab compared to placebo (5.2 vs 3.8 months, p=0.047) (Fuchs et al., 2014). The RAINBOW study, which evaluated ramucirumab combined with weekly paclitaxel, reported that paclitaxel plus ramucirumab group had better OS rates (9.6 vs 7.4 months, p=0.017) and PFS rates (4.4 vs 2.9 months, p<0.0001) compared to the paclitaxel only group (Wilke et al., 2014). In light of these results and its tolerable side-effect profile, ramucirumab ± paclitaxel has been approved as a standard second-line therapy (National 2017; Smyth et al., 2016; Japanese

2017). There are also various studies on nivolumab and pembrolizumab as immunotherapies in advanced stage gastric cancer patients. However these were phase 1-2 studies which reported OS and PFS rates of 5-11.4 months and 1.9 month respectively (Muro et al., 2016; Le et al., 2016). Our results are similar to these studies in terms of survival and tolerable side effect rates. Considering the difficulty of accessing these medicines in many countries and the cost of targeted treatments and immunotherapies, easily accessible chemotherapy combinations such as mEOX may be an applicable second-line therapy in many countries.

Patients with progressive disease after first-line therapy are more susceptible to treatment-related toxicities by second-line therapies due to previous chemotherapy. For that reason, treatment-related toxicities should be considered before initiating any form of therapy. Treatment related grade 3-4 hematologic or non-hematologic toxicity rates have been reported variable results due to different chemotherapy agents, doses and the number of agents combined in second-line treatment. The most commonly observed grade 3-4 hematologic side effects were neutropenia and anemia (8.6-39.1% and 2.9-32% respectively) while non-hematologic side effects were most frequently fatigue (10-26%) and diarrhea (3-14.5%) according to studies on second-line therapies for advanced gastric cancer (Kang et al., 2012; Hironaka et al., 2013; Maugeri-Sacca et al., 2013; Jung et al., 2016). In our study, mEOX therapy was well tolerated and showed a similar side effect profile. Observing similar side effects despite using a triple combination regimen may be associated with a well selected population and modified treatment doses.

Serum CEA level is an indicator of curability in patients who underwent gastrectomies, and offers prognostic information for patients with potentially resectable gastric cancer (Kochi et al., 200; Tachibana et al., 1998). It was reported that high serum CEA levels of metastatic gastric cancer patients receiving first or second-line chemotherapy was a poor prognostic factor on OS rates (Louvet et al., 2003; Catalano et al., 2008). In our study, a high serum CEA level was also related with a poorer OS rate. ECOG performance status is the most important predictor of survival and chemotherapy response, and is related to various factors including patients' nutritional status, comorbidities and age (Wilson et al., 2005). Previous studies indicate that an ECOG status of 2 has a significant negative effect on survival (Lee et al., 2007). In our study patients with an ECOG status of 2 were found to have poorer outcomes in terms of both OS and PFS compared with patients who scored 0-1. For that reason, it may be more suitable to choose less intense therapies for patients with ECOG status greater than 1. Studies demonstrated that patients younger than 50 with gastric cancer often have different clinical features (Qiu et al., 2011; Schildberg et al., 2012). Patients over 50 were found to have poorer outcomes, especially in terms of overall survival, compared to patients younger than 50 years old (Pisanu et al., 2014). In our study patients younger than 60 had poorer PFS and OS rates in multivariate analysis. This may be related to more aggressive behaviour of gastric cancers in younger patients.

Her-2 overexpression is a poor prognostic factor in advanced stage gastric cancer (Arteaga et al., 2003). Phase 3 TOGA (trastuzumab for gastric cancer) studies have demonstrated that adding trastuzumab to cisplatin and fluorouracil regimen improved PFS and OS rates in Her-2-positive metastatic gastric and gastroeosophageal cancer patients (Bang et al., 2010). One of the limitations of our study was that it was retrospective, which meant that we had no information on Her-2 status.

Due to retrospective nature of study design, current study had several limitations. Side effects of EOX regimen were retropectively obtained from patient files. Some of recorded patients, were living urban areas which were far away from our hospital. We think that they might have possibility to admit other hospitals for their chemotherapy related side effects. Therefore, especially non-haematological side effects might be underestimated. In contrast to this, we included to patient population who had received at least two cycles of EOX regimen with regular follow up. In this context, early relapses following one cycle of EOX therapy and patient who lost follow up might be get rid of from results of study. This situation might cause the overestimated response rate of EOX. By choosing patients who had received at least two cycle of therapy some toxic deaths related to EOX chemotherapy might eliminated.

In conclusion, a modified EOX chemotherapy regimen may be a well-tolerated and effective triple combination in patients with progressive metastatic gastric cancer after docetaxel combination treatment, especially for patients with ECOG scores of 0-1. In order to verify results the effectivity and safety profile of EOX regimen as second line therapy, future randomized trials should be performed

Conflicts of interest

There are no conflicts of interest.

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