JBUON 2013; 18(2): 377-384
ISSN: 1107-0625 • www.jbuon.com
E-mail: info@jbuon.com

ORIGINAL ARTICLE

A modified DCF regimen as primary treatment for patients with metastatic gastric cancer

D. Koca[1], E. Dogan[1], H. Yardim[2], O. Duzen[2], S. Karaca[3]

[1]Department of Internal Diseases, Division of Medical Oncology, [2]Department of Internal Diseases, [3]Department of Radiology, Van Yuzuncu Yil University, Regional Training and Research Hospital, Van, Turkey

Summary

Purpose: *To retrospectively assess the efficacy and toxicity of a modified docetaxel, cisplatin, fluorouracil (mDCF) regimen as primary treatment in patients with metastatic gastric cancer (MGC).*

Methods: *mDCF included folinic acid 400 mg/m² (day 1) + 5-fluorouracil (5-FU) 400 mg/m² i.v. bolus (day 1) + 5-FU 2400 mg/m² 46-h infusion (days 1 and 2) + docetaxel 60 mg/m² (day 1) + cisplatin 50 mg/m² (day 1) and was administered once every two weeks in MGC patients.*

Results: *Eighty-nine patients (median age 59 years, range 31-79) were enrolled. The median number of courses was 6 (range 2-12), and the total number was 492. The median follow-up duration was 8.6 months (range 2-14). Three (3.3%) patients showed complete response, 21 (23.6%) partial response, 36 (40.4%) stable disease, and progression was observed in 29 (32.6%) patients. The median progression-free survival (PFS) rate was 7 months (95% CI 5.7-8.2), and the median overall survival (OS) rate was 11 months (95% CI 9.7-12.2). The most common toxicity was neutropenia, which was observed in 52 (58.4%) patients.*

Conclusion: *mDCF with reduced drug doses, given every two weeks, is a rather efficient regimen for MGC patients.*

Key words: *cisplatin, docetaxel, fluorouracil, metastatic gastric cancer, modified DCF, primary treatment*

Introduction

Gastric cancer is one of the most common maligant tumors, and ranks only second after lung cancer in terms of mortality [1,2]. Gastric cancer is mostly registered in developing countries. Its incidence changes according to geographic regions, being more common in east Asia, eastern Europe and south America [1]. Lately, while the incidence of distal gastric cancers is decreasing, there has been an increase in esophagogastric junction (EGJ) tumors (distal esophagus or proximal gastric tumor) that carry the same characteristics with gastric cancer [3,4].

Gastric cancer is one of the most lethal malignacies. Patients with this type of carcinoma have a poor prognosis, with frequent metastases and short life expectancy despite early diagnosis [5-8]. Since it usually advances to metastatic stage, therapeutic options are becoming more of an issue. As a result, studies regarding chemotherapy (CT), the most commonly used therapy option in the metastatic stage, have gained much more importance. In these studies, it has been noted that CT, especially in combination with other therapeutic modalities, improves life expectancy, though it does not offer cure in metastatic disease [9-12].

Agents used in the past, which were beneficial in the treatment of MGC, are now being combined with two of the most frequent current treatment options: docetaxel, an agent whose efficacy has recently been proven, and different combination CT regimens. The single most important result of relevant research has been that adding docetaxel to combination CT in which 5-FU and cisplatin are the main components has led to a noteworthy increase in survival. Moreover, another aspect that merits mentioning in these studies

Correspondence to: Dogan Koca, MD. Van Yuzuncu Yil University, Regional Training and Research Hospital, Department of Internal Diseases, Division of Medical Oncology, Suphan Mah, 65001, Van, Turkey. Tel: +90 432 217 76 00, Fax: +90 432 212 19 54, E-mail: dogankoca@hotmail.com
Received: 30/06/2012; Accepted: 04/08/2012

is the experimentation with different drug doses and time intervals of docetaxel-based regimens in order to find a more advantageous regimen in terms of efficacy and toxicity [13–23].

In reviewing the literature, we found plenty of studies [13-23] related to drug doses and time intervals involving other regimens that have been applied to MGC. In all CT regimens, especially epirubicin, cisplatin, fluorouracil (ECF) and docetaxel, cisplatin, 5-FU (DCF) authors have used different drug doses and time intervals, mainly once every 1, 2, or 3 weeks. The issues of which drug dose is best and at which intervals courses should be repeated are still a matter of debate.

The aim of the present study was to evaluate the efficacy and toxicity of a mDCF regimen administered to MGC patients.

Methods

Patients

mDCF was administered as primary treatment for all MGC patients that were referred to the Division of Medical Oncology in 2011. All of the patients enrolled had TNM stage IV disease [24].

Inclusion criteria

The patient performance status was evaluated according to the Karnofsky Performance Status (KPS) scale and only KPS ≥ 80 patients were included in the study. Patients included had to be between 18 and 80 years and to have normal renal function with normal BUN and serum creatinine <1.1 mg/dl as well as normal cardiac function. Patients included in the study had also to have liver function tests normal or up to 2.5 times the upper limit of normal.

Response evaluation

Pre-treatment and response to treatment evaluations were done via thoracic and upper and lower abdominal computerized tomography (CT). Abdominal ultrasonography (US), upper and lower abdominal magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT were used in special cases.

Response was evaluated every 3 months or every 6 cycles of CT, according to the tumor response assessment criteria of the World Health Organization [25]. Complete tumor disappearance was considered as complete response (CR), regression of the target lesion ≥ 50% was considered as partial response (PR), regression of the target lesion < 50% or progression of the target lesion < 25% was considered as stable disease (SD), and progression > 25% of the target lesion or appearance of new lesion(s) was considered as progressive disease (PD). CR plus PR were characterized as objective response rate (ORR).

After the 3-month period or 6 cycles of CT, a ≥ 50% reduction of serum carcinoembryonic antigen (CEA) level was considered as tumor marker response.

Treatment

mDCF consisted of administration of folinic acid 400 mg/m^2 (day 1) + 5-FU 400 mg/m^2 i.v. bolus (day 1) + 5-FU 2400 mg/m^2 46-h infusion (days 1 and 2) + docetaxel 60 mg/m^2 i.v. bolus (day 1) +cisplatin 50 mg/m^2 (day 1) administered once every 2 weeks. Cisplatin was given in 250 ml normal saline over one hour. After treatment 2000 ml normal saline were given for diuresis along with antiemetic support. Twenty-four hours after finishing CT, all patients were administered prophylatic granulocyte colony-stimulating factor (G-CSF) for 5 days. When grade 3 toxicity was detected, drug doses were reduced by 25% and with grade 4 toxicity drug doses were reduced by 25% and treatment was postponed for a week.

Toxicity evaluation

Evaluation of toxicity was done according to the National Cancer Institute (NCI)-Common Toxicity Criteria, Version 2.0 [26].

Statistics

The time period from the beginning of the first CT cycle to the development of PD was considered as PFS. The time from the diagnosis to death was considered as OS.

Statistical data analysis was performed using the Statistical Package for Social Sciences (SPSS), version 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Kaplan-Meier method was used for analyzing PFS and OS, and survival curves were compared using the log-rank test. Chi-square test was used to compare independent group ratios. P values of < 0.05 were accepted as statistically significant.

Results

Patient characteristics

Eighty-nine MGC patients were enrolled in the study, and their median age was 59 years (range 31–79). Patient and disease characteristics are summarized in Table 1.

Response and survival

ORR was 67.4 %. Three patients (3.3%) achieved CR, 21 (23.6%) PR, and 36 (40.4%) SD. PD was seen in 29 patients (32.6 %) (Table 2). The median PFS was 7 months (95% CI 5.7-8.2; Figure 1), and the median OS was 11 months (95% CI 9.7-12.2; Figure 2). An interesting observation was that patients with a history of

Table 1. Patient and disease characteristics

Characteristics	*N (%)*
Gender	
Male	67 (75.2)
Female	22 (24.8)
Age (years)	
≥65	20 (22.5)
<65	69 (77.5)
Gastric cancer history in first-degree relatives	11 (12.4)
Comorbid diseases	13 (14.6)
Diabetes mellitus	11 (12.4)
Coronary artery disease	4 (4.5)
Hypertension	4 (4.5)
COPD	3 (3.4)
Habits	
Smoking	25 (28.1)
Alcohol	3 (3.4)
Symptoms consistent with the tumor	62 (69.6)
KPS	
≥80, <90	54 (60.7)
≥90, =100	35 (39.3)
Previous treatments	
Total gastrectomy	23 (25.8)
Subtotal gastrectomy	7 (7.9)
Palliative gastrectomy	9 (10.1)
Chemotherapy	20 (22.5)
Chemoradiotherapy	18 (20.2)
Tumor localization	
Cardia	44 (49.4)
Corpus	15 (16.9)
Antrum	23 (25.8)
Unspecified	7 (7.9)
Histology	
Adenocarcinoma	71 (79.8)
Intestinal	34 (38.3)
Diffuse	4 (4.5)
Unspecified	33 (37.0)
Signet ring cell carcinoma	13 (14.6)
Mucinous adenocarcinoma	5 (5.6)
Grade	
1	11 (12.4)
2	12 (13.5)
3	25 (28.1)
Unspecified	41 (46.1)
CEA (before treatment) ≤5ng/ml	8 (8.9)
CEA (before treatment) 5-50ng/ml	14 (15.7)
CEA (before treatment) >50ng/ml	67 (75.2)
Number of metastatic organs	
1	48 (53.9)
2	29 (32.6)
3	12 (13.5)
Metastatic organs	
Liver	41 (46.0)
Lymph nodes	37 (41.6)
Peritoneum	22 (24.8)
Lung	20 (22.5)
Ascites	18 (20.2)
Bone	11 (12.4)
Brain	2 (2.2)

COPD: chronic obstructive pulmonary disease, KPS: Karnofsky performance status

gastric cancer in first-degree relatives had a higher mortality rate (p=0.007). However, in terms of OS , patients under 65 years of age or above, female or male gender, low or high grade, and tumor localization showed no statistically significant differences (p=0.789, p=0.465, p=0.130, p=0.871, respectively). However, patients with more than one metastatic organ had significantly shorter survival compared to those with one metastatic organ (p=0.001).

Toxicity

Grade 1/2 neutropenia was seen in 32 (35.9%) patients and grade 3/4 in 20 (22.5%). Neutropenia of all grades was seen in 52 patients (58.4%) and was the most common kind of toxicity; only 2 (2.2%) patients developed neutropenic fever. The toxicity data are displayed in Table 3.

Discussion

Gastric cancer is a common, highly metastatic, lethal disease with a survival of mere months when metastatic. Because of this, chemotherapy given to such patients should be most efficient and less toxic.

It is well known that combination regimens are more effective in the treatment of MGC [9-12]. Current combination regimens applied to MGC and their response rates are shown in Table 4.

ECF, a 3-agent combination has shown considerable efficacy with acceptable toxicity when given once every 3 weeks. This regimen produced 71% ORR and a median OS of 9.4 months [27–29]. In the randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL–2) trial in which ECF, epirubicin, cisplatin, and capecitabine (ECX), epirubicin, oxaliplatin, and 5-FU (EOF) and epirubicin, oxaliplatin, and capecitabine (EOX) regimens, also given once every 3 weeks, were compared, the activity of oxaliplatin and capecitabine was evaluated. ORR was 40–50%, while the median OS rate was between 9.3 and 11.2 months. Toxicity was well tolerated [30]. In other studies in which oxaliplatin was used (FOLFOX, EOX, EOF, XELOX), the ORR were 40–70%, and the median OS ranged between 8 and 15 months [30–37].

Taxanes are important agents that have been shown to be beneficial in the treatment of MGC. In a 3- drug combination study using paclitaxel along with etoposide and cisplatin, the median OS was 12 months but with considerable toxicity [38,39]. Docetaxel, another taxane, is an agent commonly used in MGC. Studies

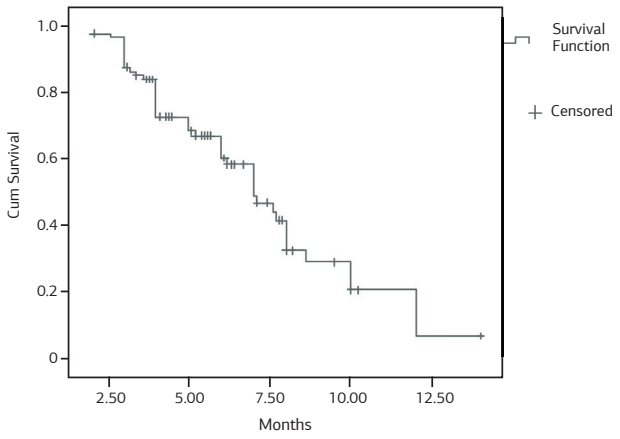

Figure 1. Progression-free survival (median 7.0 months) of patients treated with mDCF (N=89).

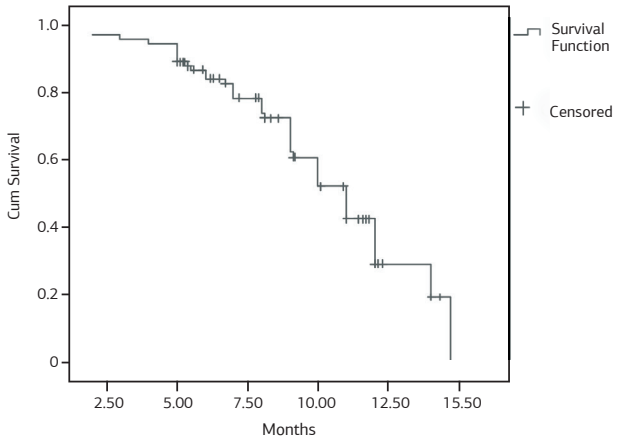

Figure 2. Overall survival (median 11.0 months) of patients treated with the mDCF (N=89).

conducted with docetaxel showed considerable survival advantage, especially when used as part of a combination therapy [13–23]. In the influential TAX-325 two-arm trial, a combination of 5-FU and cisplatin (CF) was given every 28 days in one arm, and a combination of 5-FU (750 mg /m^2, days 1-5), cisplatin (75 mg/m^2, day 1), and docetaxel (75 mg/m^2, day 1) (DCF) was given in 21-day cycles in the second arm [13]. In the DCF arm, the ORR was 37 %, the PFS 5.6 months, and the OS 9.2 months. Grade 3/4 toxicity was 82% in the DCF arm and 57% in the CF arm. However, DCF has been reported to be well tolerated [13,21,22].

In one of the studies in which DCF was given once every 3 weeks (docetaxel initially 85 mg/m^2 on day 1 and later reduced to 75 mg/m^2 as a result of toxicity, cisplatin 75 mg/m^2 on day 1, and 5-FU 300 mg/m^2, days 1-14) the ORR was 36.6%, the median OS 10.4 months, and toxicity 57% [14]. Ajani et al. using the same regimen and intervals (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, both on

Table 2. Factors related with treatment efficacy and survival

Factors	*N (%)*
Total number of treatment cycles	492
Median	6
Range	2-12
Patients receiving 6 cycles	72 (80.8)
Patients with dose reduction	32 (35.9)
Patients with treatment postponements	22 (24.8)
Patients with CEA values < 5 ng mL^{-1} after treatment	7 (7.9)
Patients with CEA values decreased > 50 % after treatment	32 (35.9)
Follow up (months)	
Median	8.6
Range	2-14
PFS (months)	
Median	7.0
95% CI	5.7-8.2
OS (months)	
Median	11.0
95% CI	9.7-12.2
One-year OS	50 (42.4)
Patients deceased	47 (52.8)

PFS: progression free survival, OS: overall survival, CEA: carcinoembryonic antigen

day 1, and 5-FU 750 mg/m^2/d as continuous infusion on days 1-5), reported an ORR 43% , PFS 5.9 months, and median OS 9.6 months. Neutropenia for this particular study was 86% [15]. In another DCF study given once every 3 weeks, the dose of docetaxel was decreased to 50 mg/m^2 in order to lower the toxicity rates (docetaxel 50 mg/m^2 on day 1, cisplatin 80 mg/m^2 on day 1, and 5-FU 1200 mg/m^2/d on days 1–3). This study resulted in an ORR of 40%, a median PFS of 4.6 months, and a median OS of 9.7 months [16]. Overman et al. tested DCF given once a week so as to lower the side effects (20 mg/m^2 of cisplatin, 350 mg/m^2 of 5-FU, and 20 mg/m^2 of docetaxel administered once a week for 6 consecutive weeks followed by a 2-week break). This kind of administration yielded an ORR of 34%, a median PFS of 4.1 months, a median OS of 8.9 months, and a grade 3/4 neutropenia rate of 4.0% [17].

There are also studies in which docetaxel has been combined with capecitabine and carboplatin instead of cisplatin and 5-FU. The outcomes of these studies revealed an ORR between 40–50%, a median PFS of approximately 5 months, a median OS of between 8 and 12 months, and toxicity rates

Table 3. Toxicities encountered

Toxicities	*N (%)*
Hematologic toxicities	
Neutropenia grade 1/2	32 (35.9)
Neutropenia grade 3/4	20 (22.5)
Anemia grade 1/2	29 (32.6)
Anemia grade 3/4	10 (11.2)
Thrombocytopenia grade 1/2	5 (5.6)
Thrombocytopenia grade 3/4	4 (4.5)
G-CSF prophylaxis	89 (100.0)
Neutropenic fever	2 (2.2)
Erythrocytes' transfusion	
Patients with transfusions	8 (8.9)
Number of transfusions	17 (19.1)
Thrombocytes' transfusion	
Patients with transfusions	2 (2.2)
Number of transfusions	3 (3.4)
Lethargy, fatigue	40 (44.9)
Stomatitis	16 (17.9)
Nausea	12 (13.5)
Diarrhea	9 (10.1)
Vomiting	9 (10.1)
Hand–foot syndrome	5 (5.6)
Renal failure	5 (5.6)
Gastrointestinal bleeding	3 (3.4)
Deep vein thrombosis	2 (2.2)

G-CSF: granulocyte colony-stimulating factor

ranging from 40-50% [18-20,23].

Another potent agent in the treatment of MGC is irinotecan. A combination of docetaxel, irinotecan, and cisplatin (TPC) had an ORR of 54%, a median PFS of 7.1 months, and a median OS of 11.9 months [40]. In an irinotecan plus 5-FU (FOLFIRI) regimen, the ORR was 40%, the median PFS 6.9 months, and the median OS 11.3 months [41]. In a capecitabine plus irinotecan (XELIRI) regimen, the ORR was 43.6%, the median PFS 5.0 months, and the median OS 11.0 months [42]. In addition, a regimen composed of irinotecan, oxaliplatin, and 5-FU (FOLFOXIRI) yielded an ORR of 67%, a median PFS of 9.6 months, and a median OS of 14.8 months [43]. Finally, an ORR of 50%, a median PFS of 6.5 months, and a median OS of 11.5 months were reported with another regimen combining irinotecan, docetaxel, and oxaliplatin [44].

Current literature shows that there are some monoclonal antibodies and tyrosine kinase inhibitors that are beneficial in the treatment of MGC. Among these agents, two merit mentioning: trastuzumab and bevacizumab. Trastuzumab, an anti-HER-2 monoclonal antibody, was added to cisplatin and 5-FU in an important study conducted on patients with HER-2 positive MGC [45]. The results of this study showed an ORR of 47 % and a median OS of 13.8 months. Toxicity evaluation showed that the most common toxicity was nausea; all grades of nausea were experienced by 197 (67%) patients and grade 3/4 by 22 (7%). Grade 3/4 neutropenia was experienced by 53% of the patients. The other monoclonal antibody, bevacizumab, was added to DCF, cisplatin plus irinotecan and cisplatin plus capecitabine, and produced an ORR of up to 67%, a PFS of up to 12 months, and a median OS of up to 16.8 months. Several studies showed that grade 3/4 neutropenia was approximately between 30 and 50% [46-48].

When all of the studies are examined, it is observed that there are many CT agents used in the treatment of MGC and that numerous CT regimens exist with various combinations of these agents. Choosing the appropriate CT regimen in patients with a seriously lethal condition like MGC is of utmost importance. Even though new and more efficient agents are constantly being discovered, the questions concerning which agents should be combined, the proper drug dosage to be administered and the interval of cycles' reperition along with efficacy and tolerability are issues that will continue to be discussed in the future.

We observed a satisfactory response rate of 67.4% with the mDCF regimen used in this study. In addition, when the side effects were reviewed, neutropenia was the most common with a rate of 58.4 %, while grade 3/4 neutropenia was registered in 22.5% of the patients. The authors believe that this regimen should be considered safe when these figures are taken into account. Another important point of our study is that 80.8% of the patients received 6 cycles of treatment and we believe that the prophylactic G-CSF administration contributed greatly to this. Along with fewer side effects, we also found a median PFS of approximately 7 months and a median OS of 11 months.

Conclusion

We conclude that the mDCF combination chemotherapy used in our study resulted in a satisfactory response and an advantageous toxicity rate for the treatment of MGC. The authors believe that better results may be obtained in the future if newly discovered agents will be combined with this mDCF regimen or one or two of the individual agents of the regimen, and that the same doses and time intervals should be used.

Table 4. Chemotherapeutic combinations given for gastric cancer

Study	*Regimen*	*ORR (%)*	*Median PFS (months)*	*Median OS (months)*
Murad et al [9]	FAMTX	50.0	8	16.0
Webb et al [28]	FAMTX	21.0	3.4	5.7
Pyrhönen et al [10]	FEMTX	62.0	5.4	12.3
Findlay et al [27]	ECF	71.0	7.0	8.2
Webb et al [28]	ECF	45.0	7.4	8.9
Ross et al [29]	ECF	42.4	7.0	9.4
Cunningham et al [30]	ECF	40.7	6.2	9.9
	ECX	46.4	6.7	9.9
	EOF	42.4	6.5	9.3
	EOX	42.9	7.0	11.2
Our study	mDCF	67.4	8.0	11.2
Van Cutsem et al [13]	DCF	37.0	5.6	9.2
Roth et al [14]	DCF	36.6	4.6	10.4
Ajani et al [15]	DCF	43.0	5.9	9.6
Park et al [16]	DCF	40.0	4.6	9.7
Overman et al [17]	DCF	34.0	4.1	8.9
Shah et al [46]	DCF-Bev	67.0	12	16.8
Evans et al [23]	DCarboX	48.0	-	8.0
Liu et al [36]	FOLFOX4	52.5	6.5	10.0
Bouche et al [41]	FOLFIRI	40.0	6.9	11.3
Oh et al [42]	XELIRI	43.6	5	11.0
Cao et al [43]	FOLFOXIRI	67.0	9.6	14.8
Bang et al [45]	CT-Trastuzumab	47.0	6.7	13.8
Shah et al [47]	IP-Bev	46.0	6.7	12.1
Ohtsu et al [48]	CapeP-Bev	65.0	8.3	12.3

ORR: objective response rate, PFS: progression free survival, OS: overall survival, FAMTX: 5-Fluorouracil (5-FU), doxorubicin, methotrexate, FEMTX: 5-FU, epidoxorubicin, methotrexate, ECF: epirubicin, cisplatin, 5-FU, ECX: epirubicin, cisplatin, capecitabine, EOF: epirubicin, oxaliplatin, 5-FU, EOX: epirubicin, oxaliplatin, capecitabine, mDCF: docetaxel, cisplatin, 5-FU, folinic acid, DCF: docetaxel, cisplatin, 5-FU, DCF-Bev: docetaxel, cisplatin, 5-FU, bevacizumab, DCarboX: docetaxel, carboplatin, capecitabine, FOLFOX: 5-FU, leucovorin, oxaliplatin, FOLFIRI: 5-FU, leucovorin, irinotecan, XELIRI: capecitabine, irinotecan, FOLFOXIRI: 5-FU, leucovorin, oxaliplatin, irinotecan, CT-Trastuzumab: cisplatin, 5-FU or capecitabine plus trastuzumab, IP-Bev: irinotecan, cisplatin, bevacizumab, CapeP-Bev: capecitabine, cisplatin, bevacizumab

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61:69-90.
2. Stewart BW, Kleihues P (Eds). World Cancer Report. IARC Press, Lyon 2003. http://www.scribd.com/doc/2350813/World-Cancer-Report-2003-Stuart-e-Kleihues-WHO-e-IARC.
3. Salvon-Harman JC, Cady B, Nikulasson S, Khettry U, Stone MD, Lavin P. Shifting proportions of gastric adenocarcinomas. Arch Surg 1994; 129:381-389.
4. Wijnhoven BP, Siersema PD, Hop WC, van Dekken H, Tilanus HW. Adenocarcinomas of the distal oesophagus and gastric cardia are one clinical entity. Rotterdam Oesophageal Tumour Study Group. Br J Surg 1999; 86:529-535.
5. SEER Cancer Statistics http://www.seer.cancer.gov/statistics/ (Accessed on March 31, 2011).
6. Nigro JJ, Hagen JA, DeMeester TR et al. Occult esophageal adenocarcinoma: extent of disease and implications for effective therapy. Ann Surg 1999; 230:433-440.
7. Rice TW, Zuccaro G Jr, Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. Ann Thorac Surg 1998; 65:787-792.

8. Folli S, Morgagni P, Roviello F et al. Risk factors for lymph node metastases and their prognostic significance in early gastric cancer (EGC). The Italian Research Group for Gastric Cancer (IRGGC). Jpn J Clin Oncol 2001; 31:495-499.
9. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 1993; 72:37-41.
10. Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 1995; 71:587-591.
11. Glimelius B, Ekström K, Hoffman K et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997; 8:163-168.
12. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006; 24:2903-2909.
13. Van Cutsem E, Moiseyenko VM, Tjulandin S et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24:4991-4997.
14. Roth AD, Fazio N, Stupp R et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007; 25:3217-3223.
15. Ajani JA, Fodor MB, Tjulandin SA et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005; 23:5660-5667.
16. Park SR, Chun JH, Kim YW et al. Phase II study of low-dose docetaxel/fluorouracil/cisplatin in metastatic gastric carcinoma. Am J Clin Oncol 2005; 28:433-438.
17. Overman MJ, Kazmi SM, Jhamb J et al. Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. Cancer 2010; 116:1446-1453.
18. Giordano KF, Jatoi A, Stella PJ et al. Docetaxel and capecitabine in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: a phase II study from the North Central Cancer Treatment Group. Ann Oncol 2006; 17:652-656.
19. Kim JG, Sohn SK, Kim DH et al. Phase II study of docetaxel and capecitabine in patients with metastatic or recurrent gastric cancer. Oncology 2005; 68:190-195.
20. Chun JH, Kim HK, Lee JS et al. Weekly docetaxel in combination with capecitabine in patients with metastatic gastric cancer. Am J Clin Oncol 2005; 28:188-194.
21. Ajani JA, Moiseyenko VM, Tjulandin S et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007; 25:3205-3209.
22. Ajani JA, Moiseyenko VM, Tjulandin S et al. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007; 25:3210-3216.
23. Evans D, Miner T, Iannitti D et al. Docetaxel, capecitabine and carboplatin in metastatic esophagogastric cancer: a phase II study. Cancer Invest 2007; 25:445-448.
24. American Joint Committee on Cancer. Colon and Rectum. Philadelphia: Lippincott-Raven Publishers, 2002.
25. World Health Organization. WHO handbook for reporting results of cancer treatment. http://whqlibdoc.who.int/publications/9241700483.pdf.
26. National Cancer Institute-Common Toxicity Criteria, Version 2.0, 1999. http://www.firm-act.org/documents/appendix4.pdf.
27. Findlay M, Cunningham D, Norman A et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994; 5:609-616.
28. Webb A, Cunningham D, Scarffe JH et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997; 15:261-267.
29. Ross P, Nicolson M, Cunningham D et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002; 20:1996-2004.
30. Cunningham D, Starling N, Rao S et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36-46.
31. Al-Batran SE, Hartmann JT, Probst S et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008; 26:1435-1442.
32. Louvet C, André T, Tigaud JM et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 2002; 20:4543-4548.
33. Al-Batran SE, Atmaca A, Hegewisch-Becker S et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. J Clin Oncol 2004;22:658-663.
34. Jatoi A, Murphy BR, Foster NR et al. Oxaliplatin and capecitabine in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia: a phase II study from the North Central Cancer Treatment Group. Ann Oncol 2006;17:29-34.
35. Neri B, Pantaleo P, Giommoni E et al. Oxaliplatin, 5-fluorouracil/leucovorin and epirubicin as first-line

treatment in advanced gastric carcinoma: a phase II study. Br J Cancer 2007; 96:1043-1046.

36. Liu ZF, Guo QS, Zhang XQ et al. Biweekly oxaliplatin in combination with continuous infusional 5-fluorouracil and leucovorin (modified FOLFOX-4 regimen) as first-line chemotherapy for elderly patients with advanced gastric cancer. Am J Clin Oncol 2008; 31:259-263.
37. Montagnani F, Turrisi G, Marinozzi C, Aliberti C, Fiorentini G. Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer 2011; 14:50-55.
38. Lokich JJ, Sonneborn H, Anderson NR et al. Combined paclitaxel, cisplatin, and etoposide for patients with previously untreated esophageal and gastroesophageal carcinomas. Cancer 1999; 85:2347-2351.
39. Sharma A, Raina V, Lokeshwar N, Deo SV, Shukla NK, Mohanti BK. Phase II study of cisplatin, etoposide and paclitaxel in locally advanced or metastatic adenocarcinoma of gastric/gastroesophageal junction. Indian J Cancer 2006; 43:16-19.
40. Enzinger PC, Ryan DP, Clark JW et al. Weekly docetaxel, cisplatin, and irinotecan (TPC): results of a multicenter phase II trial in patients with metastatic esophagogastric cancer. Ann Oncol 2009; 20:475-480.
41. Bouché O, Raoul JL, Bonnetain F et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803. J Clin Oncol 2004; 22:4319-4328.
42. Oh SC, Sur HY, Sung HJ et al. A phase II study of biweekly dose-intensified oral capecitabine plus irinotecan (bXELIRI) for patients with advanced or metastatic gastric cancer. Br J Cancer 2007; 96:1514-1519.
43. Cao W, Yang W, Lou G et al. Phase II trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) as first-line treatment for advanced gastric cancer. Anticancer Drugs 2009; 20:287-293.
44. Di Lauro L, Nunziata C, Arena MG, Foggi P, Sperduti I, Lopez M. Irinotecan, docetaxel and oxaliplatin combination in metastatic gastric or gastroesophageal junction adenocarcinoma. Br J Cancer 2007; 97:593-597.
45. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376:687-697.
46. Shah MA, Jhawer M, Ilson DH et al. Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. J Clin Oncol 2011; 29:868-874.
47. Shah MA, Ramanathan RK, Ilson DH et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 2006; 24:5201-5206.
48. Ohtsu A, Shah MA, Van Cutsem E et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011; 29:3968-3976.