JBUON 2019; 24(2): 650-655
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Addition of taxanes to combination chemotherapy in distal intestinal gastric cancer is more beneficial than proximal ones: A multicenter retrospective study of Turkish Oncology Group

Ali Murat Sedef[1], Fatih Kose[1], Ahmet Taner Sumbul[1], Ali Ayberk Besen[2], Bekir Hacioglu[3], Meral Gunaldi[4], Erdinc Nayir[5], Ozgur Tanriverdi[6], Erkan Arpaci[7], Huseyin Abali[8], Ozgur Ozyilkan[1]

[1]Department of Medical Oncology, Medical Faculty, Baskent University, Adana, Turkey; [2]Adana Numune Research and Training Center, Medical Oncology Clinic, Adana, Turkey; [3]Department of Medical Oncology, Medical Faculty, Trakya University, Edirne, Turkey; [4]Department of Medical Oncology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey; [5]Department of Medical Oncology, Necip Fazil Hospital, Kahramanmaras, Turkey; [6]Department of Medical Oncology, Mugla Sitki Kocman University, Mugla, Turkey; [7]Department of Medical Oncology, Medical Faculty, Bulent Ecevit University, Zonguldak, Turkey; [8]Department of Medical Oncology, Medical Faculty, Acibadem University, Adana, Turkey

Summary

Purpose: *Advanced gastric cancer has a dismal prognosis. Platin/5-fluorouracil (PF) combination chemotherapy is the main treatment modality for metastatic gastric cancer patients. Third drug addition to PF is a controversial issue. The aim of this study was to evaluate the predictive role of tumor localization and histopathology on choosing three- or two-drug combination regimens.*

Methods: *This study was designed as a hospital-based retrospective observational case-series study. A total of 516 patients with advanced gastric cancer has been treated at eight different oncology centers in Turkey between 2006 and 2016. Laboratory results and demographic data were collected and analyzed.*

Results: *The median patient age was 59 years (range 25-85). Proximal intestinal and distal intestinal cancers were found in 357 (69.2 %) and 159 (30.8 %) patients, respectively. 5-fluorouracil (5FU) and cisplatin (PF) and cisplatin+5FU+docetaxel (PFtax, also known as DCF) were administered to 240 (46.5%) and 276 (53.5%) patients, respectively. Median progression free survival (PFS) was 5.0 (95% CI 4.21-5.29) and 8 months (95% CI 7.22-8.77) for PF and PFtax groups, respectively (p<0.01). When tumor localization was used as stratum in PFS survival, PFtax produced significantly higher PFS rates only in distal intestinal type gastric cancer compared to PF (p<0.01). Median overall survival (OS) was 12 (95% CI 9.8-14.2) and 16 months (95% CI 13.6-18.4) for the PF and PFtax groups, respectively (p=0.01). When tumor localization was used as stratum in OS, PFtax showed significantly higher OS rates only in the distal intestinal type gastric cancer compared to PF (p=0.01).*

Conclusion: *Pathology and tumor location in gastric cancer may affect the outcome. Addition of taxanes as a third drug may significantly increase PFS and OS rates only in distal intestinal type gastric cancer but not in patients with proximal type gastric cancer.*

Key words: *gastric cancer, tumor location, pathology, outcome*

Introduction

Gastric cancer is one of the most common malignancies worldwide and most patients with gastric cancer have advanced incurable disease at the time of presentation [1-3]. Histopathologi-

Correspondence to: Ahmet Taner Sumbul, MD. Department of Medical Oncology, Medical Faculty, Baskent University, Kisla Saglik Yerleskesi, 0113, Yuregir, Adana, Turkey.
Tel: +90 5056166338, E-mail: drtanersu@yahoo.com

cally, gastric cancers are classified as intestinal or diffuse (undifferentiated) adenocarcinoma [4,5]. Intestinal type adenocarcinomas are further classified as proximal and distal with the Lauren classification. The proximal tumors share demographic and pathological features with Barrett's associated esophageal adenocarcinoma and are more likely to occur in men. The proximal tumors also differ from distal tumors in that they are not associated with a severe form of gastritis characterized by atrophy and/or intestinal metaplasia. The difference in tumor localization may lead to the identification of two different diseases with different patterns of behavior.

Metastatic gastric cancer is not curable, and the goals of therapy include palliation of symptoms and prolongation of survival. Systemic chemotherapy is the most effective treatment modality for patients with metastatic disease. The combination of 5FU plus cisplatin (PF) was adopted as a safe and effective standard regimen. Other studies focused on the benefit of adding a third agent to the PF backbone. Taxanes and anthracyclines are the most tried drugs in these studies for addition to PF backbone. Addition of third drug may significantly improve survival parameters but choosing of patients is not clear. There are also increased toxic effects when adding the third drug. Therefore, it is very important to estimate which patients will benefit from the third drug addition.

In our previous study, we showed that PFS and OS are improved of adding taxane to PF for distal type gastric cancer in 110 metastatic gastric cancer patients [6]. With this study, we aimed to evaluate the predictive role of tumor localization and histopathology on choosing three- or two-drug combination regimens with a larger number of patients.

Methods

This study was designed to evaluate the prognostic and predictive role of tumor localization and histopathology as a helping means over which drug combination regimens to choose in metastatic gastric cancer patients. This study was a hospital-based retrospective observational case-series study. 516 patients were included in the study from Medical Oncology Departments of Baskent Univeristy, Adana Numune Research and Training Center, Trakya University, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Necip Fazil Hospital, Mugla Sitki Kocman University, Bulent Ecevit University, and Acibadem Mehmet Ali Aydinlar University between 2006-2016. Patients who were treated with

Table 1. Patient and tumor characteristics

Characteristics	*n (%)*
Median age, years	59 (25-85)
Gender	
Men	356 (69)
Women	160 (31)
ECOG perf.status	
0	80 (15.5)
1	332 (64.3)
2	100 (19.4)
3	3 (0.6)
4	1 (0.2)
Histology	
Adenocarcinoma	418 (81)
Signet ring cell carcinoma	98 (19)
Localization	
Gastroesophageal junction	86 (16.7)
Cardia/fundus	21 (4.1)
Corpus	250 (48.4)
Antrum/pylorus	159 (30.9)
Tumor region	
Proximal	357 (69.2)
Distal	159 (30.8)
Grade	
1	28 (5.4)
2	97 (18.8)
3	185 (35.9)
4	9 (1.7)
Unknown	197 (38.2)

Table 2. Treatment and outcomes

Characteristics	*n (%)*
Gastric surgery	
Yes	194 (37.6)
No	322 (62.4)
Chemotherapy regimen	
PF	240 (46.5)
PF-Tax	276 (53.5)
Regimens and localization	
Proximal tumor	
PF	146 (28.2)
PF-Tax	211 (40.8)
Distal tumor	
PF	94 (18.2)
PF-Tax	65 (12.5)
Survival analysis (months)	
Median PFS	7
Median OS	14
Final status	
Dead	347 (67.2)
Alive	169 (32.8)

trastuzumab were excluded. Demographic and clinicopathological characteristics of patients and tumors were recorded and analyzed. The patients were divided into two groups as proximal and distal type cancer according to their tumor localizations. Patients were administered chemotherapy every 3 weeks as PF or PFtax. PF included i.v. 5-FU 750 mg/m^2, days 1-5 and cisplatin 75 mg/m^2, day 1. Docetaxel 75 mg/m^2 was also given i.v. on day 1.

Statistics

All results were presented as rates for categorical variables or mean and median for continuous variables. Clinical and statistically significant correlation between continuous variables was calculated by Spearman's rank correlation test (Spearman's correlation coefficient). Two-tailed p values were performed. OS was defined as the time period from the first day of chemotherapy the date of death or last seen. Survival curves were constructed according to the Kaplan-Meier method, and log-rank test was used for univariate statistical comparisons. Adjusted hazard ratio (HR) and 95% confidence interval (95% CI) were used for survival estimation. All statistical analyses were performed using the SPSS version 17.0, and a p value <0.05 was considered statistically significant.

Results

Patients

Patient baseline characteristics are shown in Table 1. The median age of the patients was 59 years (range 25-85) and 356 (69%) patients were male. Of the patients, 104 (20.2%) had ≥ECOG 2 performance status (PS), and 412 (79.8%) had ECOG PS 0 and 1. The most common site of tumor localization was the corpus (n=250, 48.4%). Proximal intestinal and distal intestinal gastric cancers were found in 357 (69.2%) and 159 (30.8%) patients, respectively. Histologically, patients were divided into two groups as adenocarcinoma and signet ring cell carcinoma (n=418;81% and n=98;19%, respectively). The majority of patients (n=185;38.1%) had grade 3 tumor. 194 patients (37.7%) underwent gastric surgery for primary tumor site. PF and PFtax were administered to 240 (46.5%) and 276 (53.5%) patients, respectively (Table 2). PF and PFtax were administered to 146 (28.2%) and 211 (40.8%) patients, respectively, for the proximal intestinal type

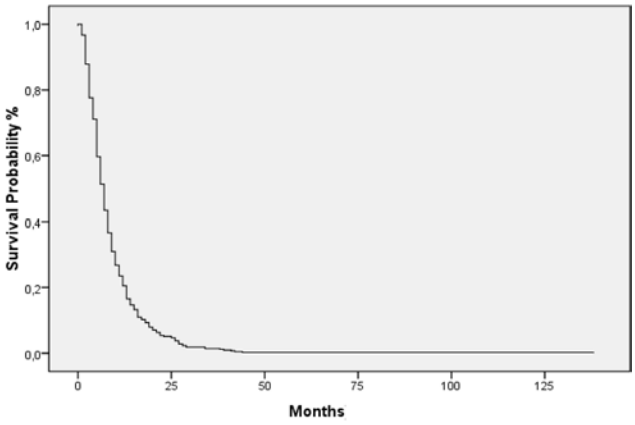

Figure 1. Kaplan-Meier estimates of progression-free survival.

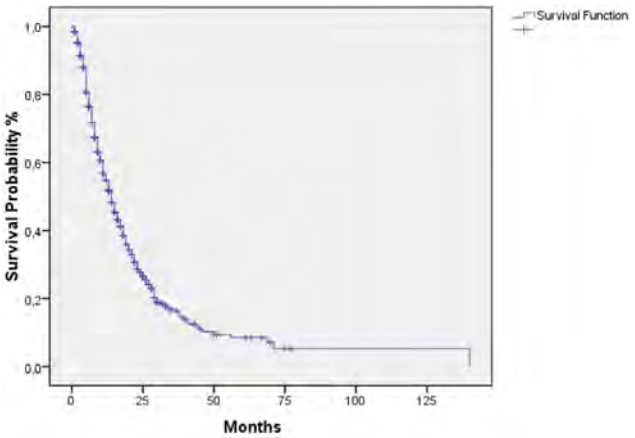

Figure 2. Kaplan-Meier estimates of overall survival.

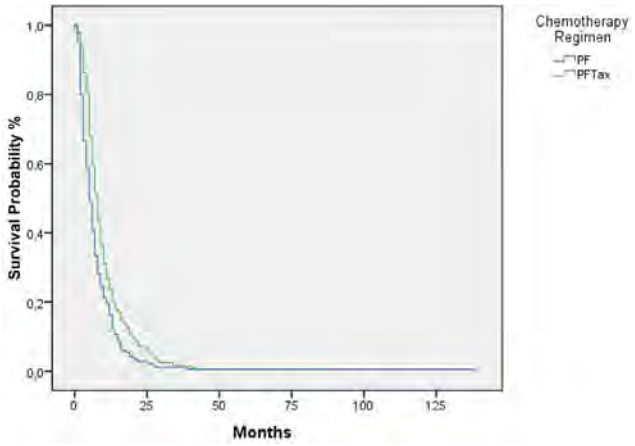

Figure 3. Kaplan-Meier estimates of progression-free survival for whole group (p=0.01).

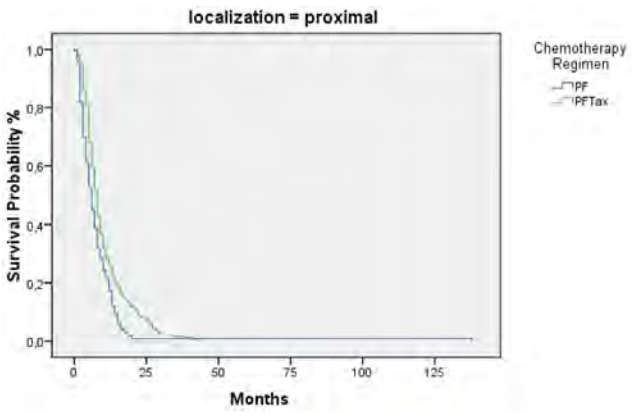

Figure 4. Kaplan-Meier estimates of progression-free survival for proximal gastric cancer (p=0.01).

cancer, and to 94 (18.2%) and 65 (12.5%) patients, respectively, for the distal intestinal type.

Treatment and outcomes

The median follow-up time was 10 months (range 0-140) and 286 (65.1%) patients died. Median PFS and OS were 7 (95% CI, 6.4-7.6) and 14 months (95% CI, 12.3-15.7), respectively (Figures 1 and 2). The median PFS was 5 (95% CI 4.2-5.8) and 8 months (95% CI 7.2-8.8) for the PF and PFtax groups, respectively (p=0.01) (Figure 3). When tumor localization was used as stratum in the PFS survival curve, PFtax produced significantly higher PFS rates only in the distal intestinal type gastric cancer compared to PF (p=0.01) (Figures 4 and 5). Median OS was 12 (95% CI 9.8-14.2) and 16 months (95% CI 13.6-18.4) for the PF and PFtax groups, respectively (p=0.01) (Figure 6). When tu-

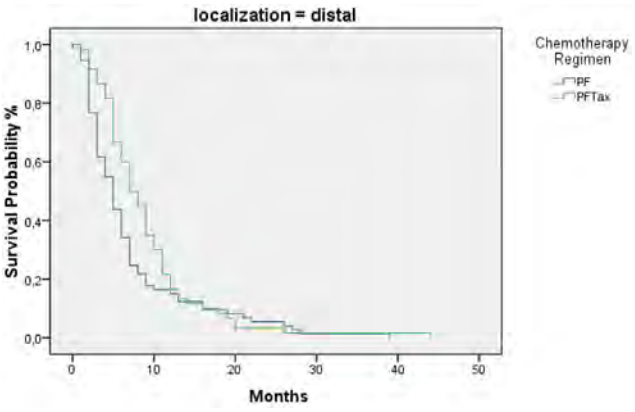

Figure 5. Kaplan-Meier estimates of progression-free survival for distal gastric cancer (p=0.01).

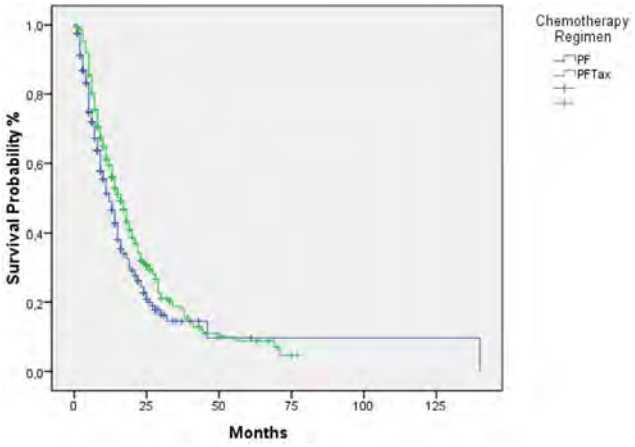

Figure 6. Kaplan-Meier estimates of overall survival for the whole group (p=0.01).

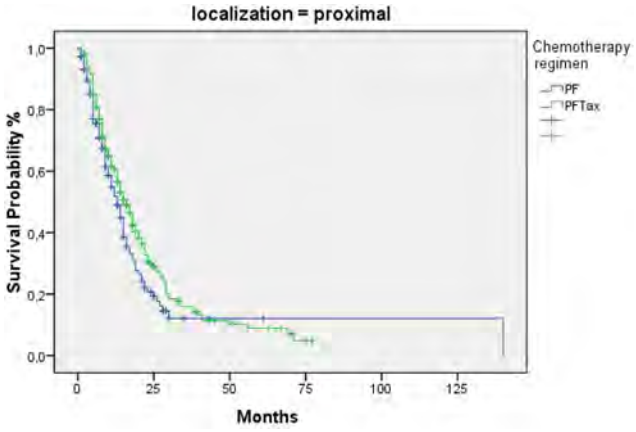

Figure 7. Kaplan-Meier estimates of overall survival for proximal gastric cancer (p<0.01).

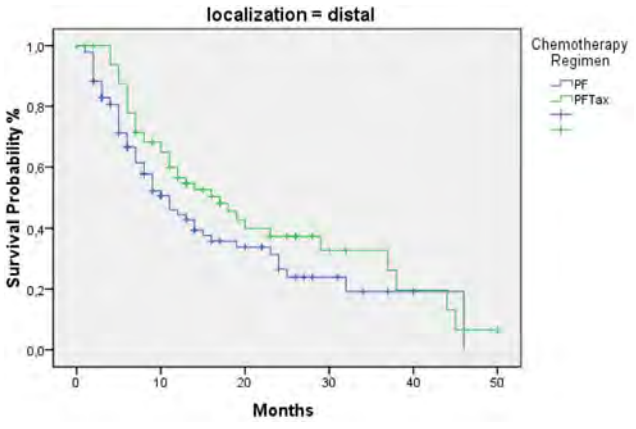

Figure 8. Kaplan-Meier estimates of overall survival for distal gastric cancer (p=0.01).

Table 3. Relationship between tumor localizations and treatment regimens for survival analysis

Variables	*Median OS*		*Median PFS*	
	Months	*p*	*Months*	*p*
Proximal tumors		0.07		0.09
PF	13		6	
PF-Tax	16		8	
Distal tumors		0.0000		0.0000
PF	11		5	
PF-Tax	17		7	

OS: overall survival, PFS: progression-free survival

mor localization was used as stratum in the OS survival curve, PFtax produced significantly higher OS rates only in the distal intestinal type gastric cancer compared to PF (p=0.01) (Figures 7 and 8).

Discussion

In this study, adding taxanes to therapy improved significantly OS and PFS. Median PFS was 3 months longer (8 and 5 months), while the median OS was 4 months longer (16 and 12 months) for PFtax groups. When we used tumor localization as stratum in the PFS survival curve PFtax produced significantly higher PFS only in the distal intestinal type gastric cancer compared to PF (p=0.01) and in the OS survival curve PFtax produced significantly higher OS rates only in the distal intestinal type gastric cancer compared to PF (p=0.01).

In our previous trial in 2014 [6], we aimed to evaluate the predictive role of tumor localization and histopathology on choosing three- or two-drug combination regimens. Median PFS was 4.0 (95% CI 2.5-5.6) and 7.4 months (95% CI 6.0-8.7) for PF and PFtax groups (p=0.03). PFtax produced significantly higher PFS rates only in distal intestinal type gastric cancer, compared with PF (p=0.03). Median OS was 9.0 (95% CI 5.2-12.3) and 17.3 months (95% CI 7.8-27) for PF and PFtax groups (p=0.01). PFtax produced significantly higher OS rates only in distal intestinal type gastric cancer compared with PF (p=0.01). Eventually, we showed the benefit of PFS and OS of the taxane addition as a third drug in distal intestinal type gastric cancer.

Of gastric cancers, 15-20% overexpress type II epidermal growth factor receptor (EGFR) (HER2). HER2 can be used as a predictive marker for anti-HER-2 treatment [7-12]. PF+trastuzumab is the standard first-line regimen in advanced gastric cancer. Unfortunately, there is no standard reference regimen or predictive marker for HER-2 negative tumors. PF+epirubicin and PF+taxane are accepted as standard regimens for suitable patients. In the pivotal TAX-325 study, addition of docetaxel to the PF was associated with better objective response (37 versus 25%) and survival rates (two-year survival rate, 18 versus 9%) [13], but grade 3 or 4 toxicities were significantly higher in the docetaxel arm [14]. There were no identified specific subgroups that may derive more benefit from the addition of taxanes in the TAX-325 study.

In our study, we hypothesized that tumor localization may play a role to the choice of the right patient for highly toxic regimens, such as DCF. Similarly to our previous study, we found that tumor localization had a predictive role for the addition of taxanes to PF in advanced gastric cancer patients. There are trials that addressed the predictive role of tumor localization in the literature. In particular, differences in the clinical characteristics and chromosomal and molecular characteristics are known between the right and left side of the colon [15]. In patients with metastatic colon cancer, tumor localization plays a predictive role in the choice of biological treatment (anti-VEGF or anti-EGFR).

In conclusion, we showed that addition of taxanes as a third drug significantly increases PFS and OS only in distal intestinal type gastric cancer but not in proximal type gastric cancer. We believe that our results may assist in the decision-making in advanced gastric cancer for more precise decision about which patients may be treated with the highly toxic regimen DCF.

Conflict of interests

The authors declare no conflict of interests.

References

1. Gotoda T. Endoscopic resection of early gastric cancer: the Japanese perspective. Curr Opin Gastroenterol 2006;22:561-9.
2. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol 2005; 23:4490-8.
3. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma (3rd Engl Edn). Gastric Cancer 2011;14:101-12.
4. Mayanagi S, Takeuchi H, Kamiya S et al. Suitability of sentinel node mapping as an index of metastasis in early gastric cancer following endoscopic resection. Ann Surg Oncol 2014;21:2987-93.
5. Oda I, Suzuki H, Nonaka S, Yoshinaga S. Complications of gastric endoscopic submucosal dissection. Dig Endosc 2013;25 (Suppl 1):71-8.
6. Sedef AM, Köse F, Sümbül AT et al. Patients with distal intestinal gastric cancer have superior outcome with addition of taxanes to combination chemotherapy, while proximal intestinal and diffuse gastric cancers do not: does biology and location predict chemotherapy benefit? Med Oncol 2015;32:476-8.

7. Park YS, Hwang HS, Park HJ et al. Comprehensive analysis of HER2 expression and gene amplification in gastric cancers using immunohistochemistry and in situ hybridization: which scoring system should we use? Hum Pathol 2012;43:413-22.
8. Barros-Silva JD, Leitão D, Afonso L et al. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. Br J Cancer 2009;100:487-93.
9. Takehana T, Kunitomo K, Kono K et al. Status of c-erbB-2 in gastric adenocarcinoma: a comparative study of immunohistochemistry, fluorescence in situ hybridization and enzyme-linked immuno-sorbent assay. Int J Cancer 2002;98:833-7.
10. Liang Z, Zeng X, Gao J et al. Analysis of EGFR, HER2, and TOP2A gene status and chromosomal polysomy in gastric adenocarcinoma from Chinese patients. BMC Cancer 2008;8:363-74.
11. 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;376:687-97.
12. Kim KC, Koh YW, Chang HM et al. Evaluation of HER2 protein expression in gastric carcinomas: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. Ann Surg Oncol 2011; 18:2833-40.
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;24:4991-7.
14. 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;25:3210-6.
15. Yang SY, Cho MS, Kim NK. Difference between right-sided and left-sided colorectal cancers: from embryology to molecular subtype. Expert Rev Anticancer Ther 2018;18:351-8.