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ORIGINAL ARTICLE

Adding taxane to platin-5-fluorouracil combination does not improve survival rate in patients ≥ 65 years of age with advanced gastric cancer: A retrospective-multicenter study

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Summary

Purpose: *Advanced gastric cancer (AGC) has a dismal prognosis. Platin-5-fluorouracil (CF) combination chemotherapy is the most widely used protocol and addition of a taxane (TCF) seems to increase survival and toxicity rates. We aimed to evaluate efficacy and toxicity of TCF as compared to CF in patients older than 65 years and compare them with the patients younger than 65 years.*

Methods: *A total of 341 patients with AGC have been treated at six different oncology centers in Turkey between 2010 and 2014 and evaluated retrospectively. The characteristics of the patients whose tumors were histologically confirmed and whose survival data were available were registered and analyzed. The study group consisted of 234 patients younger than 65 years (group 1) and 107 patients older than 65 years (group 2). All of the data obtained from the patients were statistically analyzed.*

Results: *The median age of the patients was 58.2 years and the mean follow-up time 14.4 months. For the entire group, progression-free survival (PFS) and overall survival (OS) were 9 and 13 months, respectively. Using TCF over CF regimen increased the OS by 4.2 months (i.e., group 1 and 2 together). For group 2, patients with liver metastases and without surgery of the primary tumor were treated with significantly more TCF as compared to CF, respectively. Although TCF yielded significantly higher PFS and OS in group 1 (p=0.0001 and p=0.017), there was no significant difference in group 2 as compared to CF. Also, grade 3-4 toxicity was statistically defined as one of the possible reasons of worsened OS in patients older than 65 years and receiving TCF.*

Conclusions: *The addition of taxanes to CF backbone leads to a significant increase in both PFS and OS in patients younger than 65 years of age but the triplet regimen with taxanes does not provide superior survival in patients older than 65 years of age.*

Key words: *advanced gastric cancer, elderly, prognosis, survival, taxane*

Introduction

GC is the fifth most frequently diagnosed cancer and the third leading cause of cancer related deaths in the world [1,2]. GC is more commonly seen in older age groups and it has significant geographical, ethnic, and socioeconomic differences in its distribution [3,4]. In the US, the Surveillance,

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Epidemiology, and End Results cancer registry reported that 65.6% of the GC cases are diagnosed above the age of 65 [5-7].

Systemic chemotherapy is the main treatment modality for AGC patients but there is no consensus regarding the best initial chemotherapy regimen [8-11]. Although, there is no standard chemotherapy regimen, CF-based regimens are widely used. The addition of a third drug (taxane) to CF may significantly improve the survival parameters and response rate but may also increase hematological and non-hematological toxicity [12,13]. To the best of our knowledge, there is no reliable predictive marker to detect which patients should be treated with triplet regimens. Therefore, candidate patients for triplet regimens, such as TCF, should be decided based on the type of the tumor and the patients' characteristics

In oncology practice, patients should be evaluated individually and patient age is an important parameter to decide the chemotherapy regimens. Older patients may have comorbid diseases and may exhibit poor performance status. In these patients, choosing between CF and TCF when both regimens will not be curative is quite challenging [14]. In this study, we aimed to evaluate the efficacy and toxicity of TCF over CF in patients 65 years or older and compare them with patients younger than 65 years.

Methods

This study included 341 AGC patients who were treated at six different oncology centers in Turkey between 2010 and 2014. The cases were identified according to the International Statistical Classification of Diseases (ICD) codes. Patients whose tumors were histologically confirmed, whose survival data were available and patients treated with at least 4 cycles of cytotoxic chemotherapy were included. The patient characteristics with respect to age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG), comorbid diseases, anemia, histopathological type, localization, metastasis, surgical intervention, chemotherapy regimen administered and toxicity grade (as defined by the National Cancer Institute common toxicity criteria) were recorded for data analyses.

All of the cases were retrospectively evaluated and divided into two groups based on the age at the time of treatment: group 1 consisted of 234 patients younger than 65 years and group 2 was composed of 107 patients aged 65 years or older.

All of the patients had received chemotherapy as first-line. Also these two groups were divided into 2 subgroups based on the chemotherapy regimens received (CF vs TCF, described below). Subgroups were formed as follows: Group 1a patients <65 years received CF (n=160); Group 1b patients <65 years received TCF (n=74); Group 2a patients ≥ 65 years received CF (n=71); Group 2b patients ≥65 years received TCF (n=36).

The following chemotherapy regimens were assessed in this study:

TCF: Docetaxel (D) 75 mg/m^2 (day 1), Cisplatin (C) 75 mg/m^2 (day 1), and 5-Fluorouracil (5-FU) 750 mg/m^2 5-day continuous infusion (CI) repeated every 3 weeks.

CF: Cisplatin (C) 75 mg/m^2 (day 1), 5-FU 750 mg/m^2 5-day CI repeated every 3 weeks or Cape-C: Capecitabin (Cape) 850-1000 mg/m^2 days 1-14, orally, and Cisplatin (C) 75 mg/m^2 day 1 repeated every three weeks.

In all of the regimens, for patients with impaired renal function, dose-adjusted carboplatin (n=20) had substituted cisplatin based on the attending physician's decision. PFS and OS of the groups were calculated according to patients' data. PFS was calculated from the time of diagnosis until the date of progression, relapse, or death from any cause, or the date the patient was last known to be in remission. OS was calculated from the time of diagnosis until the date of death or the date the patient was last known to be alive.

This study was approved by the institutional review board of the Bakirkoy Dr. Sadi Konuk Education and Research Hospital, and complied with Helsinki Declaration and its later amendments. Every patient (or parent/guardian) had given written informed consent.

Statistics

All analyses were performed with the SPSS 17.0 software. Categorical and continuous variables were summarized using descriptive statistics (e.g., median, range, frequency, and percentage) and compared with Chi-square and Mann-Whitney-U tests, respectively. Cancer specific survival rates were estimated by the Kaplan-Meier method and log-rank test was used for univariate statistical comparisons. Cox regression (proportional hazard) was used in multivariate analysis and variables with $p<0.15$ in univariate analysis were included into multivariate analysis. Adjusted hazard ratio (HR) and 95% confidence intervals (95% CIs) were used for estimation of survival analysis. A p value <0.05 was considered statistically significant.

Results

Patients

Of the 341 patients, 243 (71.3%) patients were male. Median age was 58.2 years (range 30-81). The number of patients in the group 1 (younger than 65 years) and 2 (equal to 65 years or older) were 234 (68.6%) and 107 (31.4%), respectively. In this 4-year retrospective study, the mean follow-up time was 14.4 months (range 1-48) and 248 (72.7%) patients died during the follow-up period. Of the 341 patients, 259 (75.9%) had histologically adenocarcinoma, while 82 (24.1%) had signet ring cell histology. The most common metastatic site was the liver with 187 (54.8%) patients. The rate of grade 3-4 toxicities was 32.8% (101 patients) in the whole group. Patient and tumor characteristics are detailed in Table 1.

According to gender, BMI, ECOG performance score, histology, tumor localization, metastatic sites, and number of patients with surgical excision of the primary tumor, comorbidity, anemia, and chemotherapy toxicity we noticed that there was no statistical difference between group 1a (<65 years treated with CF) and 1b (<65 years treated with TCF) and between group 2a (≥65 years treated with CF) and 2b (≥65 years treated with TCF) (p≥0.05 for all). Comorbidites and toxicity were recorded from hospital data according to the patient's complaints and whether they needed medical treatment.

After a mean follow-up time of 14.4 months (range 1-48), median PFS and OS were 9 (95% CI, 8.0-10.0) and 13 (95% CI, 10.9-15.1) months in the whole group, respectively. In addition, TCF yielded significantly higher survival rate compared to CF with regard to PFS and OS with p value of 0.0001 and 0.003 in the whole group.

For group 1, median PFS and OS were 9 (95% CI, 4.0-10.0) and 14 (95% CI, 9.0-14.5) months, respectively. For group 2, median PFS and OS were 8 (95% CI, 6.1-9.9) and 11.6 (95% CI, 7.3-15.9) months, respectively. In group 1, addition of taxanes to CF produced significant increase in PFS and OS with p value of 0.0001 and 0.017, respectively (Figures 1 and 2). On the contrary, addition of taxanes to CF in group 2 did not increase PFS and OS (p= 0.186 and 0.238) (Figures 3 and 4).

Multivariate analysis

Only the variables which showed effect on PFS and OS with p<0.15 in univariate analysis were included into the multivariate Cox regression analysis. In the whole group, multivariate analyses of these variables revealed that addition of taxanes to CF significantly increase PFS and OS (HR=2.298, 95% CI, 1.700-3.105, p=0.0001; HR=1.693, 95% CI, 1.190-2.408, p=0.003, respectively). Multivariate analyses of these variables in group 1 showed that addition of taxanes to CF yielded significant improvement in OS but not in PFS (HR=1.742, 95% CI, 1.114-2.722, p=0.015; HR=4.558, 95% CI, 0.883-23.517, p=0.070, respectively). However, multivariate Cox regression analyses failed to show any significant effect with the addition of taxanes to CF in group 2 with regard to PFS and OS (Tables 2 and 3).

Adverse events

Statistical analysis did not show any significant difference with respect to the rate of grade 3-4 adverse events neither between group 1a and 1b nor between group 2a and 2b (p=0.438 and p=0.430).

Table 1. Patient demographics and clinical characteristics

Characteristics	*No. of patients*	*%*
	341	100
Age, years		
≥65	107	31.4
<65	234	68.6
Sex		
Female	98	28.7
Male	243	71.3
BMI		
≥25	127	37.1
<25	214	62.9
ECOG PS		
0	75	21.9
1	203	59.5
2	63	18.6
Comorbidity		
Yes	94	27.6
No	247	72.4
Anemia		
Yes	214	62.8
No	127	37.2
Histology		
Adeno	259	75.9
Signet ring cell and others	82	24.1
Localization		
Cardia	59	17.4
Non-cardia	282	82.6
Liver metastasis		
Yes	187	54.8
No	154	45.2
Bone metastasis		
Yes	31	9.1
No	310	90.9
Surgery		
Yes	113	33.1
No	228	66.9
Chemotherapy		
CF	266	78
TCF	75	22
Toxicity		
Grade 3-4	101	32.8
Grade 1-2	240	67.2
Final status		
Died	248	72.7
Alive	93	27.3

BMI: body mass index, ECOG PS: Eastern Cooperative Oncology Group performance status, CF: cisplatin + fluorouracil, TCF: taxane + cisplatin + fluorouracil

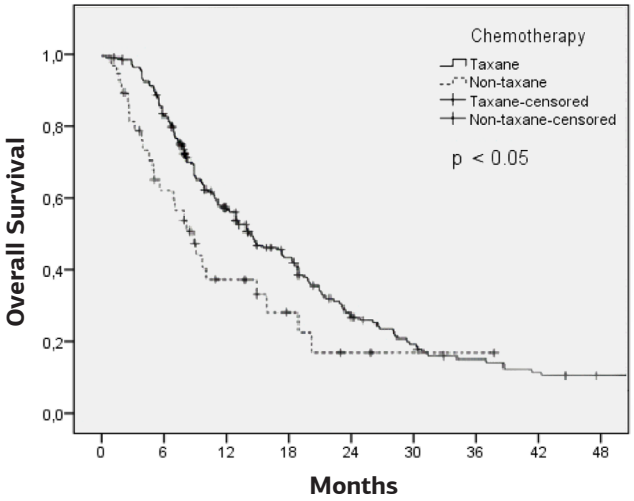

Figure 1. Kaplan-Meier curves for overall survival of patients <65 years of age treated with taxane and non-taxane regimens.

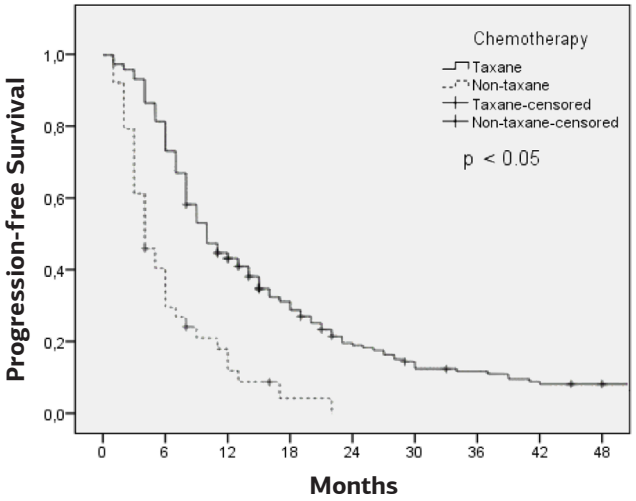

Figure 2. Kaplan-Meier curves for progression-free survival of patients <65 years of age treated with taxane and non-taxane regimens.

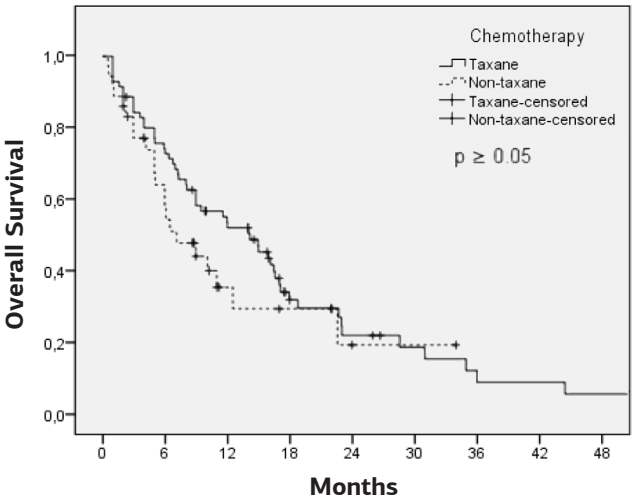

Figure 3. Kaplan-Meier curves for overall survival of patients ≥65 years of age treated with taxane and non-taxane regimens.

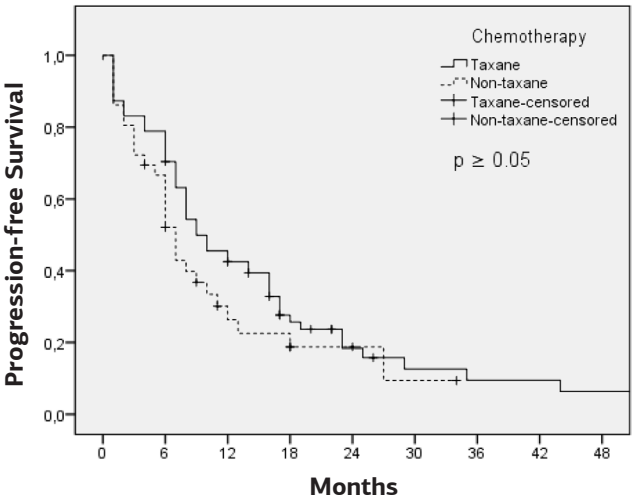

Figure 4. Kaplan-Meier curves for progression-free survival of patients ≥65 years of age treated with taxane and non-taxane regimens.

Table 2. Multivariate analyses of overall survival in patients ≥ 65 years of age

*Variables**	*Multivariate analysis*		
	p	*OR*	*95%CI*
Sex	0.518	0.833	0.478 to 1.451
BMI	0.851	1.048	0.643 to 1.708
Histology	0.247	1.488	0.759 to 2.915
Tumor localization	0.825	1.089	0.512 to 2.315
ECOG PS	0.567	1.124	0.753 to 1.677
Presence of liver metastases	0.178	1.383	0.862 to 2.219
Presence of bone metastases	0.244	1.550	0.742 to 3.238
Resection of primary tumor	0.196	1.405	0.840 to 2.352
TCF vs CF chemotherapy	0.243	1.353	0.814 to 2.251
Gr 3-4 chemotherapy toxicity	0.600	1.152	0.679 to 1.954
Anemia	0.999	1.000	0.602 to 1.662

OR: Odds ratio, BMI: Body mass index, ECOG PS: Eastern Cooperative Oncology Group performance status, Gr: Grade, CF: Platin-flourouracil, TCF: Platin-flourouracil-taxane *Only variables with p<0.15 were included into multivariate analysis

Table 3. Multivariate analyses of progression-free survival in patients ≥ 65 years of age

*Variables**	*Multivariate analysis*		
	p	*OR*	*95%CI*
Sex	0.260	0.306	0.039 to 2.397
BMI	0.379	0.548	0.143 to 2.095
Histology	0.493	0.479	0.058 to 3.932
Tumor localization	0.222	0.428	0.110 to 1.670
ECOG PS	0.271	0.583	0.223 to 1.523
Presence of liver metastases	0.941	1.045	0.329 to 3.313
Presence of bone metastases	0.536	0.044	0.000 to 864.5
Resection of primary tumor	0.250	2.459	0.532 to 11.37
TCF vs CF chemotherapy	0.646	1.372	0.356 to 5.288
Gr 3-4 chemotherapy toxicity	0.216	0.471	0.143 to 1.552
Anemia	0.942	1.052	0.269 to 4.116

For abbreviations see footnote of Table 2. *Only variable with p<0.15 were included into multivariate analysis

Discussion

A considerable number of studies have clearly shown that systemic chemotherapy for patients with AGC statistically increases survival rate. Although no single standard chemotherapy regimen exists, platinum (CF)-based chemotherapy regimens are the most widely used. Addition of taxanes or anthracyclines to CF (triplet regimen) significantly improves survival and response rate beyond CF but also results in significant increase in hematological and non-hematological toxicities. Therefore, patients who would be treated with intensive triplet regimen such as TCF, should be defined according to the tumor and patients characteristics [10,13-16]. The patient age along with their functional capacity, especially in geriatric cancer patient population, should be considered. To the best of our knowledge, there is no strong convincing evidence as to whether AGC patients aged 65 years or older would gain the same benefit from intensive triplet regimens when compared to younger patients or not [17,18]. In this study, we evaluated the effect of addition of taxanes to CF on survival parameters in a geriatric population and compared these results with younger counterparts.

Addition of docetaxel to CF-based regimens produced significantly higher objective response (37 vs 25%, p=0.01) and survival rate (PFS 7.4 vs 4.0 months, OS 17.3 vs 9.0 months) in the pivotal V-325 study [13]. Significant increase in survival and response rate was accompanied with higher incidence of grade 3 or 4 diarrhea (20 vs 8%) and neutropenia (30 vs 14%) [13]. Similar to V-325 study, TCF compared to CF resulted in significantly higher PFS and OS in the whole study population. In our study, however, we found that TCF failed to show significant effect on OS and PFS in patients over 65 years in contrast to patients younger than 65 years old. In other words, benefit of TCF over CF was restricted to patients younger than 65 years [13,19].

Formal definition of the old, senior, or geriatric persons is not universal but age of 65 is generally accepted [17,18,20]. However, chronological age is not the only parameter in the treatment decision in oncology and "older" does not have the same meaning with "elder" or "frail". But, it is clear that there is inverse correlation between chronological age and glomerular filtration rate, bone marrow reserve, and a trend to neurotoxicity [17,20]. Thus, due to the possibility of comorbidities and accompanied toxicity in a geriatric age group, chronological age is used along with other patient characteristics to decide whether aggressive chemotherapy regimens should be chosen or not. There is no standard approach or regimen in geriatric AGC patients and most data in the literature comes from subgroup analyses of phase III studies [17,18,21]. However, increased cardiac risk due to chemotherapeutics, polypharmacy and insufficient social support should be considered in geriatric patients [22]. This study, therefore, indicates that addition of taxanes to CF in patients over 65 years should not be in oncological routine practice. In our study, statistical analysis failed to show significant difference in grade 3-4 toxicity between patients over 65 years treated with CF and TCF.

Our results provide compelling data for not using TCF in older patients but some important limitations are worth noting. Although our report was supported with inclusion of a considerable num-

ber of patients, the study design was retrospective and toxicity data were not detailed in the whole group and specifically in older patients. Technical difficulty to reaching whole data of the individual patients from different oncology centers was the main reason for the incomplete and undetailed toxicity data registration. So only comorbidities and grade 3-4 toxicity data were included into the final analysis. Future work should therefore include detailed toxicity data along with geriatric assessment and a prospective design in geriatric patients could minimize these limitations.

To the best of our knowledge, this is the first study that specifically focused on the benefits of TCF over CF regimen in patients over 65 years or older with AGC. Our results showed that in contrast to patients younger than 65 years old, triplet regimen with taxanes in patients aged 65 years or older did not provide significant benefit in OS and PFS.

Conflict of interests

The authors declare no conflict of interests.

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