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ORIGINAL ARTICLE

A multi-institutional evaluation of carboplatin plus docetaxel combination in elderly patients with advanced gastric cancer

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Summary

Purpose: Albeit the majority of gastric cancers occur at advanced age, little is known regarding the optimal systemic treatment of elderly patients with advanced gastric cancer (AGC).

Methods: Patients with AGC who were ≥ 65 years old and were treated with carboplatin (area under the curve/AUC 5, on day 1, every 3 weeks) plus docetaxel (75 mg/m^2, on day 1, every 3 weeks) at 3 institutions were included in this retrospective analysis. The efficacy and the safety data of the regimen were analyzed.

Results: A total of 30 patients were enrolled. They received 128 cycles of chemotherapy, with a median of 4 cycles (range 2-8). Complete response (CR) and partial response (PR) were observed in 2 (6.7%) and 10 patients (33.3%), respectively, amounting to an overall objective response rate (ORR) of 40%. Seven patients (23.3%) had disease stabilization (SD), and 11 (36.7%) showed disease progression (PD). The most common grade 3-4 toxicity was neutropenia occurring in 19 patients (63.3%). The mean progression-free survival (PFS) was 6.0 ± 0.5 months (95% CI: 5.0-7.4), and the mean overall survival (OS) 12.0 ± 1.0 months (95% CI: 9.2-12.1).

Conclusion: Carboplatin plus docetaxel seems to be an active and well-tolerated regimen, representing a valuable alternative to cisplatin- and/or fluoropyrimidine-containing regimens for the treatment of elderly patients with AGC.

Key words: carboplatin, docetaxel, elderly, gastric cancer

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Introduction

Despite the decreasing incidence of gastric cancer in western countries, the disease ranks third and the fifth leading cause of cancer-related deaths worldwide among men and women, respectively [1].

A recent meta-analysis demonstrated superiority of chemotherapy over best supportive care alone, and survival advantage of combination chemotherapy compared to single agents in the treatment of AGC [2]. Albeit a typical chemotherapy regimen consists of a platinum compound (mostly cisplatin) plus a fluoropyrimidine, the addition of docetaxel or an anthracycline as a third agent improves survival rates in AGC [2,3]. In randomized studies, the triple drug regimens epirubicin+cisplatin+5-fluorouracil (5-FU) (ECF) and docetaxel+cisplatin+5-FU (DCF) have been demonstrated to exhibit significant survival advantage than the older combination 5-FU+adriamycin+methotrexate and the platinum-based doublet cisplatin+5-FU, respectively [4,5]. Currently, ECF or ECF-like regimens including oxaliplatin and/or capecitabine, DCF and trastuzumab plus cisplatin-based chemotherapy for human epidermal growth factor receptor 2 (HER2) overexpressing tumors have been widely accepted as the standards of care for the treatment of AGC in western countries [2,6-8]. Though these triple drug regimens improve outcome, most of these combinations are associated with considerable toxicities.

Elderly patients are especially susceptible to the side effects of chemotherapy. These patients usually suffer from comorbid conditions as well as age-related functional problems, and show deterioration in functional or emotional measurements after chemotherapy, which preclude establishing an effective therapy [9-11]. For these reasons, elderly cancer patients are underrepresented in most clinical trials and may receive suboptimal therapy due to physicians' concerns regarding treatment-related toxicities.

To constitute an effective and more tolerable chemotherapy regimen for the treatment of elderly AGC patients, S-1 alone or S-1 plus cisplatin, irinotecan or oxaliplatin plus 5-FU plus folinic acid regimens have been tested in a few trials. These trials have shown that the efficacy and the safety of the employed regimens were broadly similar to the younger patients [11-13]. Given the limited data regarding the treatment of elderly patients with AGC, it appears that newer combinations should be tested in this condition. Interestingly, the association of the less emetogenic and nephrotoxic platinum analog carboplatin and an active agent docetaxel has not been studied in this particular subgroup of patients, despite the fact that carboplatin and taxanes have been known to act synergistically, and are increasingly being used in many solid tumors including gastric cancer [14-17].

In the present study, we aimed to investigate the efficacy and tolerability of carboplatin plus docetaxel regimen in elderly patients with AGC.

Methods

Patients

Elderly patients with Ristologically diagnosed AGC, who had been treated with carboplatin plus docetaxel regimen at the Medical Oncology Departments of the Uludag University, Ege University, and Karadeniz University from May 2007 to October 2011, were enrolled into this retrospective analysis.

Inclusion/ exclusion criteria

Major inclusion criteria were as follows: age ≥ 65 years, histologically proven gastric adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, measurable or assessable metastatic disease, and adequate baseline hematological (absolute neutrophil count ≥ 2000/mm^3, leukocyte count ≥ 3500/mm^3, hemoglobin ≥ 10 g/dL, platelet ≥ 100000/mm^3), renal (serum creatinine <1.5 mg/dL), and liver functions (serum bilirubin ≤1.5 mg/dL, serum aspartate aminotransferase and alanine aminotransferase ≤2 x the upper limit of normal/ULN and serum alkaline phosphatase ≤5 x ULN).

Patients were excluded if they had previous chemotherapy for metastatic disease, concurrent or prior malignancy except for curatively treated cervical carcinoma *in situ* or non-melanoma skin cancer, history of brain or leptomeningeal metastases, and uncontrolled comorbid conditions.

Treatment

The treatment consisted of docetaxel 75 mg/m^2 followed by carboplatin AUC 5 both as 1-h i.v. infusions on day 1, repeated every 3 weeks for up to 8 cycles. Standard premedication with corticosteroids and antiemetics were given before chemotherapy. Secondary prophylaxis with granulocyte-colony stimulating factor (G-CSF) was used in case of grade 4 neutropenia or febrile neutropenia. Toxicities were assessed with the use of the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2.0). Roughly, a dose reduction of 20% both in docetaxel and carboplatin was applied to grade ≥ 3 non-hematologic toxicities except alopecia and nausea-vomiting, grade 3 tRombocytopenia with bleeding or grade 4 trombocytopenia, grade ≥ 3 neutropenia lasting more than 7 days or febrile neutropenia despite prophylactic G-CSF use after the first occurrence. A subsequent cycle was applied provided that the absolute neutrophil count was ≥ 2000/mm^3, and platelet count was ≥ 100000/mm^3.

Response evaluations were performed every 2 months by appropriate imaging. The response was recorded according to the Response Evaluation Criteria for Solid Tumors (RECIST) [18].

Statistics

Data regarding patient and disease characteristics and chemotherapy-related toxicity were expressed as absolute numbers and percents.

PFS was defined as the time from the start of chemotherapy to progression or death from any cause. OS was defined as the time from the start of chemotherapy to death from any cause. Data of patients who were alive or free of disease progression were censored at the date of the last follow-up for OS and PFS, respectively. Survival estimates were made using the Kaplan-Meier method. Statistical computations were carried out using SPSS, version 17.0.

Results

A total of 30 elderly patients with AGC were included in the study. There were 23 males and 7 females, with a median age of 70 years (range 65-79). The demographic and baseline disease characteristics of the patients are summarized in Table 1.

Table 1. Patient and disease characteristics

Characteristics	*N (%)*
Total number of patients	30 (100)
Gender	
Female	7 (23.3)
Male	23 (76.7)
Age	
Median	70
Range	65-79
Histologic grade	
Well-moderately well differentiated	16 (53.3)
Poorly differentiated	14 (46.7)
Site of primary disease	
Proximal	10 (33.3)
Corpus	12 (40)
Distal	8 (26.7)
ECOG PS	
0-1	27 (90)
2	3 (10)
Metastatic sites	
Single	11 (36.7)
Multiple	19 (63.3)

ECOG PS: Eastern Cooperative Oncology Group Performance Status

Response and toxicity

All patients were evaluable for response and toxicity. In total, the patients received 128 cycles of chemotherapy, with a median of 4 cycles (range 2-8). CR and PR were achieved in 2 (6.7%) and 10 patients (33.3%), respectively, amounting to an overall ORR of 40%. The median response duration was 6.0 months (range 3-11). Seven patients (23.3%) had SD and 11 patients (36.7%) PD.

Although the most common grade 3-4 toxicity of chemotherapy was neutropenia occurring in 19 patients (63.3%), the incidence of febrile neutropenia was relatively low, and was detected in only 2 patients (6.7%). Other common grade 3-4 toxicities were as follows: anemia 4 (13.3%) patients, thrombocytopenia 4 (13.3), mucositis/stomatitis 5 (16.6%), and anorexia 3 (10%) patients (Table 2). Dose reduction was needed in 13 patients (43.3%). There were no treatment-related deaths.

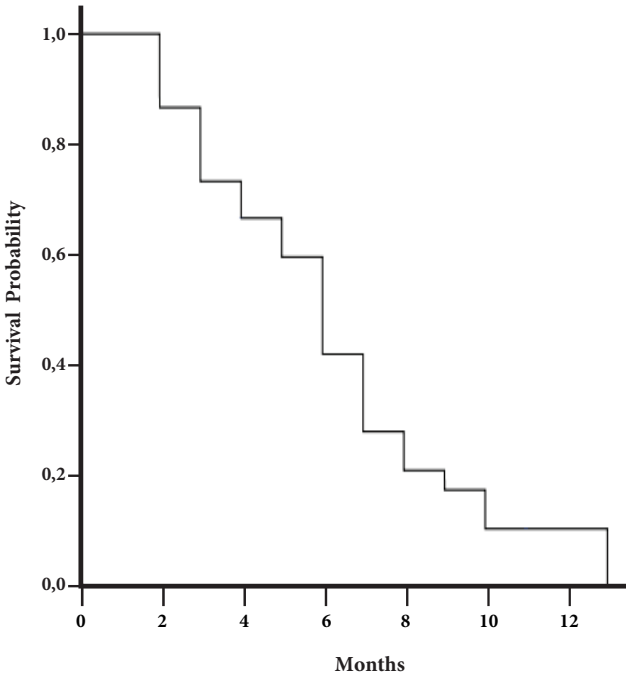

Figure 1. Kaplan-Meier plot for progression-free survival.

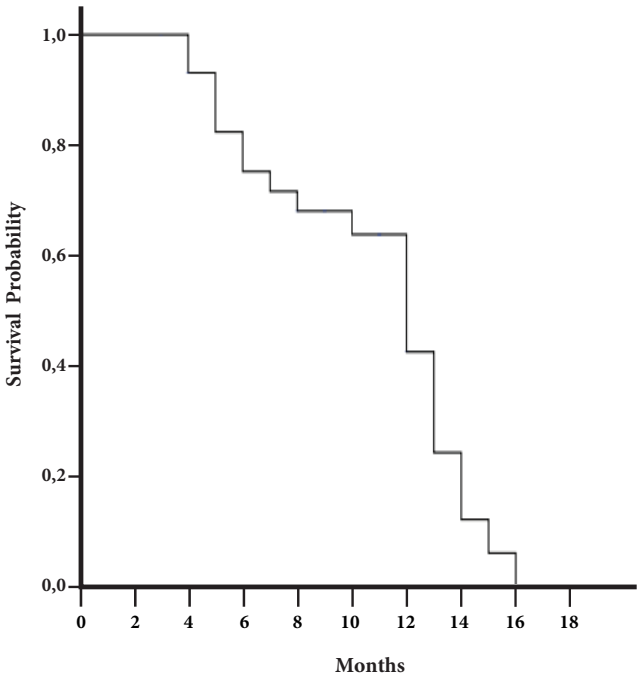

Figure 2. Kaplan-Meier plot for overall survival.

Table 2. Grade 3-4 toxicities

Toxicities	*Grade 3* *N (%)*	*Grade 4* *N (%)*	*Overall* *N (%)*
Neutropenia	9 (30)	10 (33.3)	19 (63.3)
Anemia	4 (13.3)	-	4 (13.3)
Thrombocytopenia	3 (10)	1 (3.3)	4 (13.3)
Mucositis/Stomatitis	4 (13.3)	1 (3.3)	5 (16.6)
Anorexia	3 (10)	-	3 (10)

Table 3. The present trial and selected trials investigating chemotherapy effectiveness for the treatment of elderly patients with advanced gastric cancer

Study [Reference]	*Regimen*	*No. of patients*	*ORR %*	*PFS months*	*OS months*
Tsushima et al. [11]	S-1	37	46.7	5.2	10.9
	S-1 plus C	21	50	5.0	14.4
Fonck et al. [12]	FU+FA+IRI	42	26	7.0	10.0
Choi et al. [13]	Ox+FU+FA	37	41.2	5.7	9.8
Zhao et al. [28]	Ox+FU+FA	46	45.6	6.2	9.8
Liu et al. [29]	Ox+FU+FA	44	52.5	6.5	10.0
Dong et al. [30]	Cap+Ox	44	51.2	5.6	9.8
Al-Batran et al. [31]*	FU+FA+Ox	46	41.3	6.0	13.9
	FU+FA+Cis	48	16.7	3.1	7.2
Cho et al. [32]**	Ox+FU+FA	31	50	5.8	10.3
The present study	D+Cb	30	40	6.0	12.0

ORR: overall objective response rate, PFS: progression-free survival, OS: overall survival, Cis: cisplatin, FU: fluorouracil, FA: folinic acid, IRI: irinotecan, Ox: oxaliplatin, Cap: capecitabine, D: docetaxel, Cb: carboplatin

*Subgroup of patients older than 65 years from a phase 3 trial

**An arm of a retrospective study comparing the effectiveness of chemotherapy between younger and older gastric cancer patients

Survival analysis

The mean PFS was 6.0 ± 0.5 months (95% CI: 5.0-7.4), and the mean OS was 12.0 ± 1.0 months (95% CI: 9.2-12.1). Figure 1 and Figure 2 show the Kaplan-Meier curves for PFS and OS, respectively.

Discussion

The relative paucity of data makes it difficult to perform evidence-based approach for the management of elderly patients with AGC, and this prompted us to investigate the carboplatin plus docetaxel regimen in this situation.

Actually, the combination of carboplatin plus a taxane doublet has been investigated in only a few trials in AGC. In some of these trials, carboplatin plus paclitaxel has been demonstrated to exhibit an appreciable activity against AGC with response rates of 33% and 22%, and median OS of 7.5 months and 8 months, in the first- and second-line settings, respectively [16,17]. After the incorporation of docetaxel into the management of AGC, various docetaxel plus platinum doublets (cisplatin or oxaliplatin) have been examined in several phase 2 trials, which showed response rates of 24-56%, and median OS of 8.3-11.6 months [19-26]. In our elderly patients, 40% ORR, 6.0 months PFS and 12.0 months median OS could be achieved with the use of carboplatin plus docetaxel. Taken together, the efficacy results of our study are in agreement with these trials using docetaxel and platinum doublets, as well as the efficacy of the more complex regimens such as ECF or DCF, which were associated with response rates of 45% and 37%, time to progression of 7.4 and 5.6 months, and median OS of 8.9 and 9.2 months, respectively, in the treatment of younger patients with AGC [4,5].

Similar to the results of our retrospective study, previous trials concerning the management of elderly AGC patients pointed out that the efficacy of the treatments was similar to those reported in younger AGC patients (Table 3). According to the results of these trials, 26-65.6% of elderly patients with AGC exhibited a response to the chemotherapy regimens applied, with a median survival duration of 9.8-14.4 months [11-13,27-32]. As seen in Table 3, oxaliplatin appears to be the drug most commonly used in the treatment of elderly AGC patients, and the trials using oxaliplatin consistently showed more than 40% response rates, and an approximate PFS of 6 months and OS of 10 months. A recent meta-analysis has supported the effectiveness of oxaliplatin in AGC, in which a significant survival benefit was demonstrated in favor of oxaliplatin compared to cisplatin, with better tolerability that was more prominent in older patients [33]. In addition, a subgroup analysis of a phase 3 trial comparing oxaliplatin- and cisplatin-based regimens in advanced gastro-esophageal cancer showed superiority of oxaliplatin over cisplatin in terms of response rate and survival in patients older than 65 years [31]. Interestingly, our results showed that the efficacy of the regimen was similar to the oxaliplatin-containing arm, and seemed to be better than the cisplatin-containing arm of the previous trial. Our results are also in accordance with other studies using different chemotherapy regimens for the treatment of elderly AGC patients (Table 3). Based on these findings, it is plausible to conclude that oxaliplatin- and carboplatin-based regimens offer considerable treatment benefits with similar efficacy in the management of elderly AGC patients.

With respect to treatment toxicities, neutropenia was the adverse event mostly encountered in gastric cancer patients receiving docetaxel-based chemotherapy. The rate of neutropenia as well as several non-hematologic side effects usually increase with the use of triple drug regimens. In the landmark V325 study, the rates of grade 3-4 neutropenia, stomatitis, diarrhea, and lethargy in the DCF arm were 82, 21, 19, and 19%, respectively [5]. Although some non-hematologic toxicities decrease by using docetaxel-platinum doublets, grade 3-4 neutropenia remains the most significant event ranging from 17.4 to 86% [20,22,24-26]. Being the most common treatment-related adverse event in our study, grade 3-4 neutropenia occurred in 63.3% of patients, the rate of which is comparable to the above-mentioned studies. The percentage of our patients developing neutropenia seems to be higher compared to the previous trials evaluating oxaliplatin- or irinotecan-based chemotherapy for the treatment of elderly AGC patients, in which the reported grade 3-4 neutropenia rates were 6.8-19.5%

[12,13,28-30]. However, it should be stated that the rate of neutropenic complications in our study was low, since only 2 of our patients (6.7%) experienced febrile neutropenia and there were no treatment-related deaths. Also, grade 3-4 non-hematologic toxicities were not frequent and generally manageable. From this viewpoint it appears that elderly patients with AGC reliably benefit from the drug combination we used, without compromising the safety of treatment, paying greater attention on the management of adverse events, proper dose modifications and prophylactic G-CSF administration if needed. In order to achieve further improvement in the rate of severe neutropenia, prophylactic G-CSF use or weekly docetaxel administration may be helpful, as indicated previously [21,23].

In conclusion, given the encouraging efficacy and the acceptable toxicity data of our study, carboplatin plus docetaxel combination seems to be a reasonable approach for the treatment of elderly patients with AGC. Apart from its activity, we claim that carboplatin is a more suitable alternative to cisplatin for the treatment of elderly AGC patients in terms of safety, since this drug is a less emetogenic, nephrotoxic, and neurotoxic platinum compound [34], is easily administered, and does not need excessive hydration, all of which are important advantages in the care of older cancer patients.

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