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A Comparative Analysis of The Efficacy And Safety of Cisplatin and Oxaliplatin-Based Chemotherapy Regimens İn Elderly Patients With Metastatic Gastric Cancer

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ABSTRACT

Gastric cancer is a common type of cancer. While surgical treatment is considered the standard approach in early stages, there is currently no standard chemotherapy regimen for advanced and metastatic stages. The incidence of gastric cancer increases with age, making treatment more challenging. The choice of chemotherapy becomes more important in the elderly due to comorbidities, drug interactions and drug side effects. In our study, we investigated the efficacy and side effects of treatments applied to elderly patients.

For our study, patients with recurrent or metastatic gastric cancer who were treated and followed up at Van Yuzuncu Yil University Medical Faculty Hospital between January 2008 and January 2024 were evaluated. Medical records were collected including patient demographics, treatment regimens and responses, grade 3-4 toxicities, date of progression, last follow-up and death. Performance score was assessed according to the Eastern Cooperative Oncology Group (ECOG) criteria.

The mean age of the patients was 73 years. The most common site of tumour occurrence was the gastric cardia. There were more male patients and the treatment responses were similar. However, there were notable differences in the incidence and severity of side effects. The survival data were comparable.

Oxaliplatin and cisplatin-based chemotherapies have comparable effects in advanced gastric cancer in the elderly. However, the incidence of adverse effects differs, and cisplatin should be avoided in patients with nephrotoxicity. The number of patients is insufficient to draw definitive conclusions and further studies are needed.

Keywords: metastatic gastric cancer, elderly patients, cisplatin, oxaliplatin, side effect

Introduction

Gastric cancer is the fifth most diagnosed malignancy in the world with more than one million new cases annually and the third most common cause of cancer-related deaths with more than 760,000 deaths (1). Curative surgical resection is the primary treatment for patients with early stage gastric cancer, but recurrence develops in approximately 40-80% of patients after surgery, depending on the stage (2, 3). In a meta-analysis of three studies comparing chemotherapy with best supportive care, a significant benefit was seen in favor of chemotherapy compared to supportive care alone in overall survival (OS), translating into an improvement in median survival from 4.3 months to 11 months (4). There is no globally accepted standard chemotherapy regimen for the first-line treatment of metastatic gastric cancer and practice is variable. In a study conducted in the Netherlands, a total of 45 distinct first-line systemic treatment regimens were administered. The most frequently administered regimen was that comprising capecitabine and oxaliplatin (21%) (5). The European Society for Medical Oncology (ESMO) guideline recommends platinum-based dual therapy as a chemotherapy regimen (6). Randomised controlled trials have demonstrated that cisplatin and oxaliplatin are equally efficacious. In older patients (>65 years), oxaliplatin has a superior safety profile and may be associated with better survival. (7)

As the world's population ages, the incidence of gastric cancer is increasing and the management of gastric cancer in the elderly is becoming more

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challenging. Older patients generally have more comorbidity, shorter overall survival (OS), less frequent surgery and a higher risk of complications (8). Current guidelines for the management of gastric cancer are based on evidence from clinical trials in younger patients, with no majority of geriatric patients, but older cancer patients have a worse overall survival (OS) compared to younger patients (9). The choice of chemotherapy regimen for elderly patients, chemotherapy efficacy and avoiding overtreatment or undertreatment should be carefully considered. There is conflicting information in the literature regarding the efficacy and safety of oxaliplatin-based and cisplatin-based chemotherapy regimens in elderly patients with metastatic gastric cancer, and they have not been adequately compared. We compared the objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and adverse events in patients aged 70 years and older treated with oxaliplatin-based or cisplatin-based chemotherapy regimens in the first-line treatment of metastatic gastric cancer.

Material and Methods

For our study, patients with recurrent or metastatic gastric cancer who were treated and followed up at Van Yuzuncu Yil University Medical Faculty Hospital between January 2008 and January 2024 were evaluated. The following criteria were used to determine eligibility for inclusion in the study: The inclusion criteria were as follows:

Age over 70 years, cytological or histological proven recurrent or metastatic gastric cancer, HER-2 negative, no previous treatment for recurrent metastatic disease, receiving one of the regimens containing cisplatin or oxaliplatin as a chemotherapy regimen and having received at least two cycles of chemotherapy.

Exclusion criteria:

1- Younger than 70 years.

2- Without pathological or cytological diagnosis.

3- HER-2 positive

4- Metastatic disease

5- Patients who received any previous treatment for recurrent disease

6- Patients who received treatment other than chemotherapy (such as targeted therapies, immunotherapies)

7- Patients who did not use regimens that include cisplatin or oxaliplatin.

Medical records were collected including patient demographics, treatment regimens and responses, grade 3-4 toxicities, date of progression, date of last follow-up and date of death. Performance score was assessed according to the Eastern Cooperative Oncology Group (ECOG) criteria. The progression-free survival (PFS) was calculated as the time from the first-line treatment to the date of progression or death. OS was calculated as the time from the date of recurrence or the date of diagnosis if de novo metastatic to death or last follow-up.

Patients were divided into two groups as cisplatin containing chemotherapy regimens and oxaliplatin containing chemotherapy regimens. For radiological evaluations, contrast-enhanced thorax and abdomen CT or PET CT was performed every 8 weeks in the absence of clinical progression. Treatment response was assessed according to RECIST 1.1. Toxicity was evaluated on day 1 of each cycle. Toxicity was graded according to NCI CTC version 3.0. Only grade 3-4 toxicities were recorded. The study was conducted in full compliance with the principles of the Declaration of Helsinki.

The Ethics Committee: Van Yuzuncu Yil University non-interventional ethics committee date and number (Ethics Committee Decision and Date: 2024/03-16/ 08.03.2024) were obtained.

Results

A total of 200 patients, 150 cisplatin-based and 50 oxaliplatin-based, were included in our study. The mean age of the patients was 73 years, 27.5% were female, 51.5% had ECOG PS1 and the most common tumour localisation was in the cardia region, occurring in 38.5% of cases. There was no statistically significant difference between the two groups except for the frequency of hypertension. The response rate was 31.3% for cisplatin-based regimens and 26% for oxaliplatin-based regimens. Other clinicopathological and tumour characteristics are summarised in table-1.

Neuropathy and allergic reactions were statistically significantly higher in the oxaliplatin arm while nephrotoxicity and nausea and vomiting were statistically significantly higher in the ciplatin arm. Other side effects and incidence rates are summarised in table-2.

Among the cisplatin regimens, the most frequently utilized was DCF, accounting for 28% of cases. In patients receiving oxaliplatin, the most commonly employed regimen was FOLFOX, representing

Table 1: Demographic and Clinicopathologic Characteristics

Age, years		73 (70-85)	
Female sex		55 (27.5%)	
ECOG-PS:0		37 (18.5%)	
ECOG-PS:1		103 (51.5%)	
ECOG-PS:2		60 (30%)	
Diabetes mellitus		18 (9%)	
Hypertension		53 (26.5%)	
Curative intent surgery		28 (14%)	
Palliative surgery		20 (10%)	
Tumor localization	Cardia	77 (38.5%)	
	Corpus	43 (21.5%)	
	Antrum	58 (29%)	
	Diffuse	19 (9.5%)	
Metastasis sites	Liver	61 (30.5%)	
	Periton	71 (35.5%)	
	Lung	40 (20%)	
	Bone	18 (9%)	
	Brain	2 (1%)	
	Other	38 (19%)	
	Cisplatin-based regimen n=150	Oxaliplatin based regimens n=50	p-value
Female sex	38 (25.3%)	17 (34%)	0.273
ECOG-PS	1 (0-2)	1 (0-2)	0.901
DM	16 (10.7%)	2 (4%)	0.252
HT	33 (22%)	20 (40%)	0.016
CEA	7 (1-1397)	18 (1-9050)	0.446
CA19-9	31 (1-23203)	27 (1-2600)	0.333
Albumin	3.4 (2-4.4)	3.2 (2.3-4.7)	0.245
Lactate dehydrogenase	202 (11-849)	255 (137-1282)	0.096
Hemoglobin	11.1 (5.5-16)	11.1 (7.3-14.2)	0.806
CR	6 (4%)	0	p=0.109
PR	41 (27.3%)	13 (26%)	
Stable disease	20 (13.3%)	13 (26%)	
Progressive disease	83 (55.4%)	24 (48%)	

8.5% of instances. The remaining regimens and their respective rates are presented in Table 3.

The mean survival of all patients was 9.9 months (Figure 1). The mean survival between both groups was 9.9 months (p=0.906) (Figure 2). The mean PFS was 6.04 (4.8-7.2) months in the cisplatin group and 6.8 (4.7-8.9) months in the oxaliplatin group, which was not statistically significant (p=0.566) (Figure 3).

Discussion

In our study, we found no significant difference between cisplatin-based chemotherapy regimens and oxaliplatin-based chemotherapy regimens in terms of ORR, PFS and OS. In terms of side effects, nephrotoxicity and nausea and vomiting were more common with cisplatin-based regimens while allergic reactions and neuropathy were more common with oxaliplatin-based regimens.

In a retrospective study of 242 elderly patients in Japan, survival did not differ significantly between

Table 2: Grade 3-4 Adverse Reactions

	Cisplatin-based regimen	Oxaliplatin based regimens	
Neutropenia	39 (26%)	17 (34%)	0.262
Anemia	29 (19.3%)	9 (18%)	0.835
Thrombpcytopenia	10 (6.6%)	3 (6%)	0.584
Febrile neutorpenia	16 (10.7%)	3 (6%)	0.414
Mucositis	13 (8.7%)	1 (2%)	0.196
Diarrhea	9 (6%)	1 (2%)	0.449
Paresthesia	2 (1.3%)	5 (10%)	0.011
Nausea-vomiting	28 (18.7%)	2 (4%)	0.011
Allergic reaction	0	3 (6%)	0.015
Thrombotic event	10 (6.6%)	4 (8%)	0.755
Nephrotoxicity	10 (6.6%)	0	0.07
Hepatotoxiciy	0	1 (2%)	0.250
Cardiotoxicity	2 (1.3%)	1 (2%)	0.745
Dose reduction	54 (36%)	17 (34%)	0.734
Treatment delay	43 (28.7%)	21 (42%)	0.117

Table 3: Chemotherapy Regimens

Chemotherapy regimen	n	%
FOLFOX	17	8.5
Cape-Ox	14	7.0
Cisplatin-Capecitabine	26	13.0
Cisplatin+5FU	16	8.0
mDCF	18	9.0
DCF	56	28.0
ECF	24	12.0
DOF	16	8.0
Cisplatin+ Docetaxel	6	3.0
ECX	4	2.0
EOX	3	1.5
Total	200	100.0

FOLFOX: Fluorouracil, Leucoverin and Oxaliplatin
Cape-ox: Capecitabin and Oxaliplatin
5-FU: 5- Fluorouracil
DCF: Docetaxel, Cisplatin and 5FU
mDCF: Modified Docetaxel, Cisplatin and 5FU
ECF: Epirubicin, cisplatin and 5-FU
DOF: Docetaxel, Oxaliplatin and 5-FU
ECX: Epirubicin, cisplatin and Capecitabin
EOX: Epirubicin, Oxaliplatin and Capecitabin

elderly patients with advanced gastric cancer treated with oxaliplatin-based and cisplatin-based regimens; however, the oxaliplatin-based regimen was associated with less granulocyte colony-stimulating factor use(10). In a meta-analysis of three randomised trials comparing cisplatin and oxaliplatin, 1294 patients were analysed and oxaliplatin improved progression-free survival and overall survival to statistical significance (11).

Another meta-analysis of five phase II or III randomised controlled trials including 2046 patients showed that there was no significant difference between oxaliplatin-based treatment and cisplatin-based treatment in terms of ORR, PFS and OS (12).

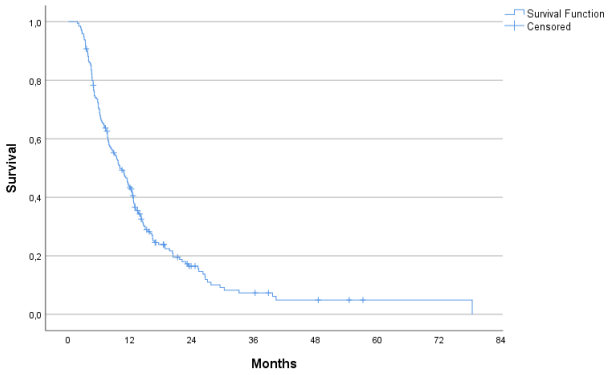

Fig.1. 9.9 (8.1-12.8) months Overall survival of all the patients

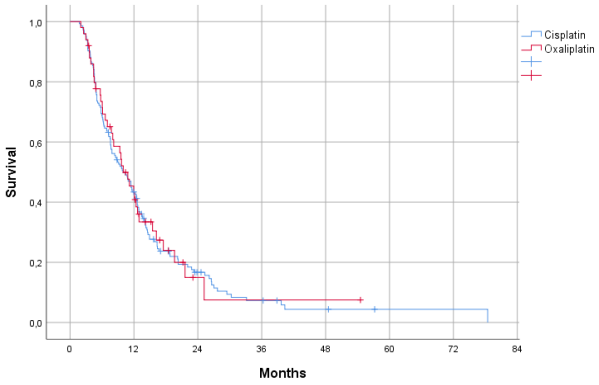

Fig.2. 9.9 (7.6-12.3) months vs 9.9 (7.1-12.8) p=0.906

In our study, we did not found significant difference in both PFS and OS between patients who receiving oxaliplatin-based chemotherapy regimens and patients who receiving cisplatin-based chemotherapy regimens.

In a meta-analysis of 2140 patients from six phase II or III randomised controlled trials, partial remission rates, objective response rates and disease control rates were higher, while complete remission rates were lower in patients receiving oxaliplatin-based therapy compared with cisplatin-based therapy (13). In our study, 4% of patients in the cisplatin arm had a complete response, while no patients in the oxaliplatin arm had a complete response. The objective response rate was 31.4% in the cisplatin arm and 26% in the oxaliplatin arm, which was not statistically significant.

In a phase 3 trial involving 1002 patients, patients were randomly assigned to receive triplet therapy with epirubicin and cisplatin plus fluorouracil (ECF) or capecitabine (ECX) or triplet therapy with epirubicin and oxaliplatin plus fluorouracil (EOF) or capecitabine (EOX). Compared with cisplatin, oxaliplatin was associated with a lower incidence of grade 3 or 4 neutropenia, alopecia, renal toxicity and thromboembolism, but a slightly higher incidence of grade 3 or 4 diarrhoea and neuropathy (14). In our study, neurotoxicity and allergic reactions were higher in oxaliplatin-based regimens while nephropathy and nausea and vomiting were higher in patients receiving cisplatin-based chemotherapy regimens.

In a study evaluating S1+cisplatin and S1 alone, grade 3-4 neutropenia developed in 20% of patients receiving S1+cisplatin (15). In our study, it was 26% in cisplatin-based regimens and 34% in oxaliplatin-based regimens, with no statistically significant difference between them. In a study evaluating the efficacy of capecitabine and capecitabine + oxaliplatin in elderly patients, grade 3-4 neuropathy was observed in 4.2% of patients receiving the CAPE-OX regimen, whereas grade 3-4 neuropathy was not observed in patients receiving capecitabine alone (16). In our study, the incidence of grade 3-4 neuropathy was 10% in oxaliplatin-based regimens and 1.4% in cisplatin-based regimens, with a statistically significant difference between the two groups. In a study comparing cisplatin and oxaliplatin in perioperative treatment of gastric cancer, nephropathy was observed in 2% of patients receiving a cisplatin-based triplet regimen, but not in those receiving oxaliplatin-based treatment (17). In our study, grade 3-4 nephropathy was absent in oxaliplatin-based regimens, while it was observed in 6.6% of patients receiving cisplatin-based regimens, which was statistically significant.

In our study, 38% of patients who received oxaliplatin utilized a triplet regimen, while 68% of patients who received cisplatin employed a triplet regimen. However, no statistically significant difference was observed in the response rate, PFS and OS between the two groups. In order to ensure the homogenise of the patient group, patients with HER-2 positivity and those receiving treatments other than conventional chemotherapies (immunotherapies, targeted therapies) were excluded.

Despite the limitations of our study, including its single-center and retrospective design, the long-term follow-up of patients and the inclusion of a geriatric patient cohort contribute to the value of our findings.

In conclusion, the results of this study indicate that oxaliplatin-based regimens are as effective as cisplatin-based regimens among elderly patients with advanced gastric cancer in a real-life setting in our country, which is a bridge between Asia and Europe. Our findings indicate that oxaliplatin-based regimens are as efficacious as cisplatin-

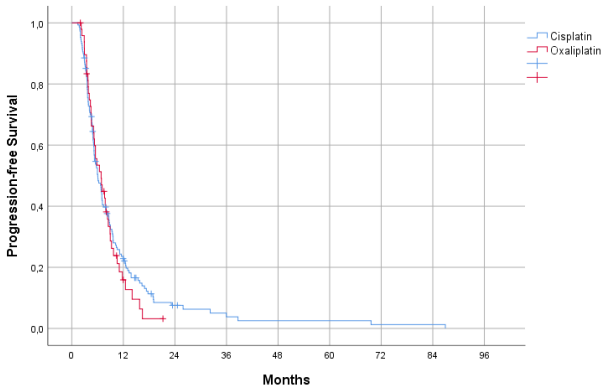

Fig.3. 6.04 (4.8-7.2) months vs 6.8 (4.7-8.9) months p=0.566

based regimens in elderly patients with advanced gastric cancer in a real-world setting in our country, which serves as a bridge between Asia and Europe. Cisplatin should be avoided, particularly in patients at high risk of nephrotoxicity. Large-scale multicentre prospective studies with a larger number of patients are needed to evaluate the efficacy and tolerability of cisplatin and oxaliplatin in elderly patients with metastatic gastric cancer.

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