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Efficacy and Safety of the Irinotecan, Capecitabine, and Oxaliplatin (IOX) Regimen in Metastatic Gastric Cancer: A Single Arm Phase II Trial

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Abstract

Background: Gastric cancer is one of the most common malignancies worldwide with a high case mortality rate. In metastatic gastric cancer, a proper combination of chemotherapy could increase the survival rate. The goal of this study is to evaluate the efficacy and safety of the combination regimen of irinotecan, oxaliplatin, and Xeloda in metastatic gastric cancer.

Methods: A total of 45 patients with metastatic gastric cancer and good performance status according to the Eastern Cooperative Oncology Group (score: 0-1) received the irinotecan, oxaliplatin, and Xeloda chemotherapy regimen. Demographic data, responses to treatment, and adverse effects were gathered for all cases. Overall survival and progression-free survival rates for patients were calculated using the Kaplan-Meier estimate.

Results: Patients' mean age was 58.3 ± 11.3 years (range: 24-81). There were 73.4% male patients and 26.6% female patients. Anorexia and weight loss were the most common symptoms. Overall response rate was 50%. The majority of toxicities were anemia, nausea and vomiting (grades 1 and 2), diarrhea (grades 1 and 2), neutropenia, alopecia, and hand and foot syndrome. The one-year progression-free survival rate was 31.5 ± 7.5%, whereas the two-year progression-free survival rate was zero. The one-year overall survival rate was 34.91 ± 8.5%. Patients had a two-year overall survival rate of 7.7 ± 6.6%. Diffuse type cancer was linked to an inferior outcome.

Conclusion: Regardless of our limited number of patients, this combination could be a suitable regimen for metastatic gastric cancer in terms of low toxicity, acceptable response rate, and survival results.

Keywords: Stomach neoplasms, Antineoplastic combined chemotherapy protocols, Neoplasm metastasis, Survival analysis

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Introduction

Gastric cancer is one of the most common cancers in the world.[1] The worldwide incidence of gastric cancer has declined in recent few decades.[2] However, the absolute number of new cases per year is increasing, mainly due to aging of the population.[3] There is also marked geographic variation, with the highest rates in East Asia, South America and Eastern Europe, and the lowest rates in the United States and Western Europe.[4] The disease is also one of the most common cancers in our region. Epidemiologic studies in Iran have revealed an age standardized rate (ASR) of 26.1 per 100,000 persons per year for men and 11.1 for women.[5] Despite advances in diagnosis of gastric cancer, approximately two-thirds of gastric cancer patients have inoperable locally advanced or metastatic disease at the time of diagnosis or develop a recurrence after surgery, which is incurable. These patients have a prognosis of a few months with best supportive care (BSC).[6] Former reviews have shown that chemotherapy is of substantial survival benefit compared to BSC. Additionally, evidences are available that favor combination chemotherapeutic regimens rather than single agent therapy with a hazard ratio (HR) of 0.37 for treatment versus BSC and 0.82 for combination therapy.[7] There is no standard first-line chemotherapeutic regimen for metastatic gastric cancer. However, the combination of fluoropyrimidine and cisplatin is the backbone of treatment, with or without other chemotherapeutic agents such as epirubicin or docetaxel.[8,9] The existing 5-fluorouracil-based (5-FU-based) regimens need central venous access catheters and infusion devices, whereas substitution of Xeloda for 5-FU could lead to increased convenience. On the other hand, cisplatin-containing regimens are difficult to administer in this chiefly debilitated population and have the potential for severe toxicity. A recent phase III study that has compared a docetaxel/cisplatin/5-FU (DCF) regimen with CF showed that DCF significantly improved survival compared to CF alone. However, the modest benefits in that trial were gained at the cost of increased toxicity.[10] Therefore, these benefits should be weighed against treatment-related toxicities.[11] Studies reported response rates (RR) of approximately 40% for combination therapies with the epirubicin/cisplatin/5-FU (ECF) or DCF regimens.[12] Recently, Xeloda and oxaliplatin have replaced 5-FU and cisplatin with equivalent efficacy and significantly less toxicity.[13] The activity of irinotecan, as well as clinical outcomes have been certainly improved by combination of

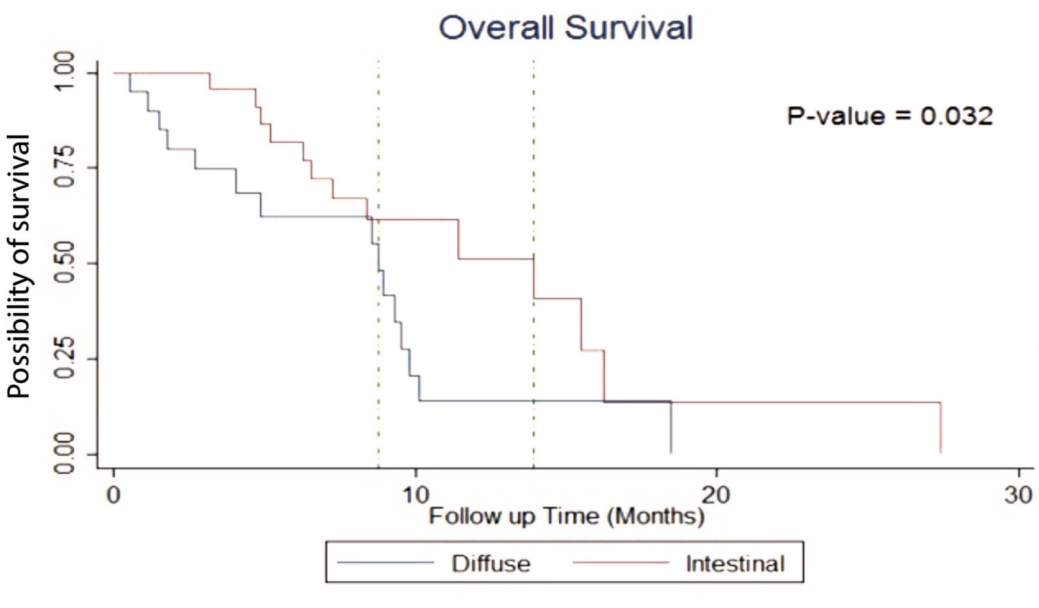

Figure 1. Overall survival (OS) curves based on pathology

Table 1. Patients' characteristics at baseline (n = 45).

Characteristics	Category	No. of patients (%)
Age	Years	Mean: 58.3 ± 11.3
Gender	Male	33 (73.4)
	Female	12 (26.6)
ECOG performance status	0	23 (51.1)
	1	22 (48.9)
Pathology	Intestinal	25 (55.6)
	Diffuse	20 (44.4)
Number of metastases	Single	16 (35.5)
	Multiple	29 (64.5)
Organs involved	Liver	10 (22.2)
	Ascites and LAP	6 (13.3)
	Peritoneum	5 (11.1)
	Lung	4 (8.9)
	Liver and lungs	4 (8.9)
	Liver and LAP	4 (8.9)
	LAP	3 (6.7)
	Ascites	2 (4.4)
	Brain	1 (2.2)
	Rectus abdominis muscle	1 (2.2)
	Pancreas	1 (2.2)
	Appendix	1 (2.2)
	Diaphragm	1 (2.2)
	Adrenal glands	1 (2.2)
	Peritoneum and LAP	1 (2.2)

LAP: Lymphadenopathy; ECOG: Eastern Cooperative Oncology Group

these most active drugs.[14] Therefore, there is a great interest in new efficacious treatment regimens with acceptable toxicity profiles as well as increasing attention towards patient convenience and quality of life.[15-17] The combination of a 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX) regimen has been used in some studies.[18] The aim of this study was to investigate

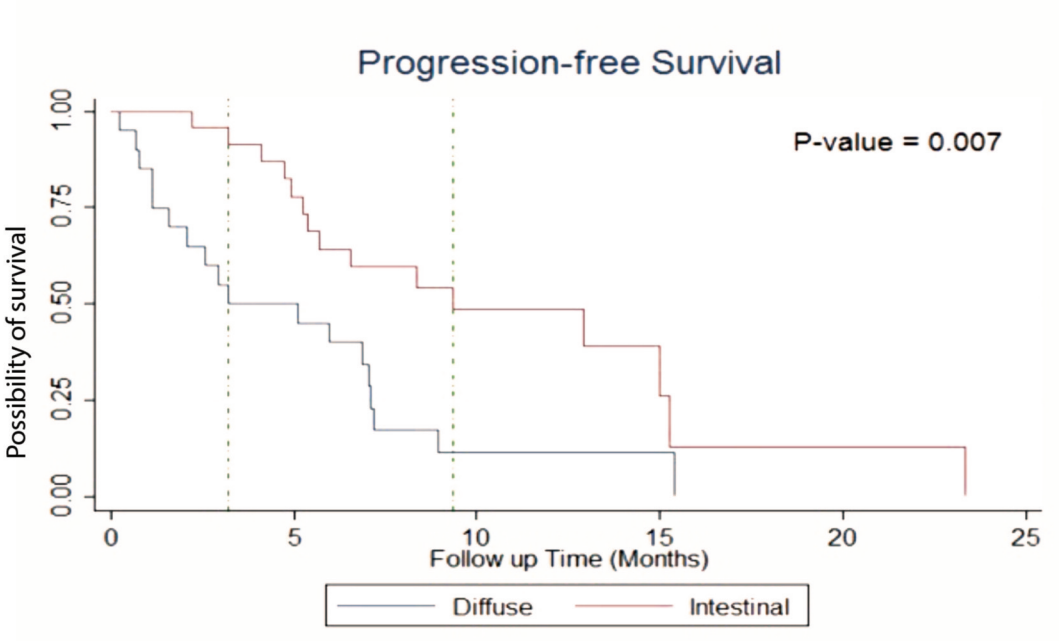

Figure 2. Progression-free survival (PFS) curves based on pathology

Table 2. Worst grade of toxicity per patient (n = 12) according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Event	No. of patients	Grades 1 and 2 n (%)	Grades 3 and 4 n (%)
Neutropenia	11	7 (15.5)	4 (8.9)
Anemia	31	31 (68.8)	-
Diarrhea	10	10 (22.2)	-
Nausea and vomiting	30	30 (66.6)	-
Neuropathy	6	6 (13.3)	-
Oral ulcers	3	3 (6.6)	-
Thrombocytopenia	6	6 (13.3)	-

the efficacy and safety of the triplet regimen of irinotecan, oxaliplatin, and capecitabine (Xeloda®) (IOX) in patients with metastatic gastric cancer. This regimen has been experienced in some preliminary studies like the study by Bajetta et al. and under investigation in randomized clinical trials.[19]

Materials and Methods

From July 2012 to October 2016, 45 patients enrolled in this study. The last follow up was January 11, 2017 and the first death occurred on July 23, 2013. Inclusion criteria consisted of patients who previously did not receive chemotherapy or did not have an adequate response to previous treatments, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1, completed informed consent form, life expectancy of at least 12 weeks, and followed in terms of geographic location. Exclusion criteria consisted of patients with non-metastatic disease, underlying medical condition that prevented chemotherapy, patients who developed treatment-related complications, or had uncontrollable disease complications. Eligible patients had histologically confirmed metastatic adenocarcinoma of the stomach, who were above 18 years of age. This prospective phase 2 clinical trial was conducted as a single center study. The treatment protocol consisted of irinotecan (130 mg/m^2 on day 1), oxaliplatin (85 mg/m^2 on day 1), and Xeloda (625 mg/m^2 BD on days 1 to 14), accompanied by granulocyte colony stimulating factor (G-CSF) support for 5 days after chemotherapy. We reduced the dose of irinotecan from 180 mg/m^2 to 130 mg/m^2 in order to limit the toxicities observed in the first few patients. Treatment continued each 3 weeks up to a total of 6 cycles, in the absence of disease progression or unacceptable toxicities. An expert radiologist evaluated response according to the Response Evaluation Criteria in Solid Tumors (RECIST) after the 3rd and 6th courses of chemotherapy. We used the 3rd course CT for response evaluation in cases who died before the 6th course or the CT was not available before the 3rd course. Baseline evaluations included history and physical examination before each treatment cycle, complete blood count (CBC) on day 1 prior to each treatment cycle and days 7-10, metabolic panel that included creatinine and liver function tests once per cycle on day 1 prior to each treatment cycle, symptom assessment at each visit, neurotoxicity assessment prior to each treatment cycle, and weekly observation for complications and drug toxicity. Adverse events were assessed before each cycle according to the National Cancer Institute Common Toxicity Criteria (version 2.0; NCI-CTC199). Peripheral neuropathy was grouped according to the oxaliplatin-specific scale. All patients received antiemetic prophylaxis. Treatment was discontinued in the presence of grade 2 or higher events, with the exception of alopecia, nausea or vomiting, and anemia, and was not resumed until the adverse event resolved or improved to grade 1 or less. In cases of severe toxicity, continuation of treatment required reduction by 25% for the doses of all cytotoxic agents during subsequent cycles, except for grades 3 or 4 diarrhea in which only irinotecan and Xeloda doses were reduced by 25%. The Xeloda dose was reduced by 25% in

case of grades 3 or 4 stomatitis or hand-foot syndrome. In patients with grades 2 and 3 peripheral neuropathy, we only reduced the dose of oxaliplatin by 25% or 50%, respectively. We did not discontinue oxaliplatin because of peripheral neuropathy that persisted between the treatment courses. The goal of the study was a preliminary assessment of the feasibility and activity of the IOX regimen as a treatment for metastatic gastric cancer. The primary endpoint was the RR. The study protocol and all the procedures performed were approved by the Ethical Committee of hematology, oncology and stem cell transplantation research center and were in accordance with the 1964 Declaration of Helsinki and its later versions. All study participants provided informed consent. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Descriptive statistical methodology was used to analyze the results. All patients who had received at least one cycle of the study treatment were included in analyses of safety and survival on an intent-to-treat basis. Progression-free survival (PFS) was measured from the date of the first cycle to the first observation of progressive disease. Overall survival (OS) was measured from the date of onset of treatment until the time of death from any cause. Time-related efficacy parameters for all patients were updated up to October, 2016. Progression-free survival and OS were estimated using the Kaplan-Meier method. Results were reported with 95% confidence intervals (CI).

Table 3. Response and overall response rates.

Type of response (RECIST criteria)	No. of patients (%)
Complete response	9 (23.7)
Partial response	10 (26.3)
Stable disease	5 (13.2)
Progressive disease	14 (36.8)
Overall response rate	50%

RECIST: Response Evaluation Criteria in Solid Tumors.

Analyses were done in Stata software version 11.2 and R software for Windows version 3.3.2.

Results

A total of 50 patients enrolled in this study. We included 45 patients who were assessed from July 2012 to October 2016. Table 1 summarizes the patients' baseline characteristics.

Patients had a mean age of 58.31 ± 11.34 years (range: 24-81). There were 4 patients (8.9%) that had a positive family history of gastric cancer. Smoking was positive in 10 (22.2%) patients, all males. The liver (22.2%) was the most common site of metastasis followed by ascites and lymphadenopathy (LAP, 13.3%), peritoneum (11.1%), and lungs (8.9%). There were 29 (64.5%) patients who died by the end of the follow up period. All 45 patients were evaluated for toxicity, of which there were 4 toxicity-related deaths in the study cohort. Table 2 summarizes the treatment-related adverse effects.

We observed that 8.9% of patients had hematologic toxicity (grades 3 and 4); however, non-hematologic toxicity (grades 3 and 4) was not

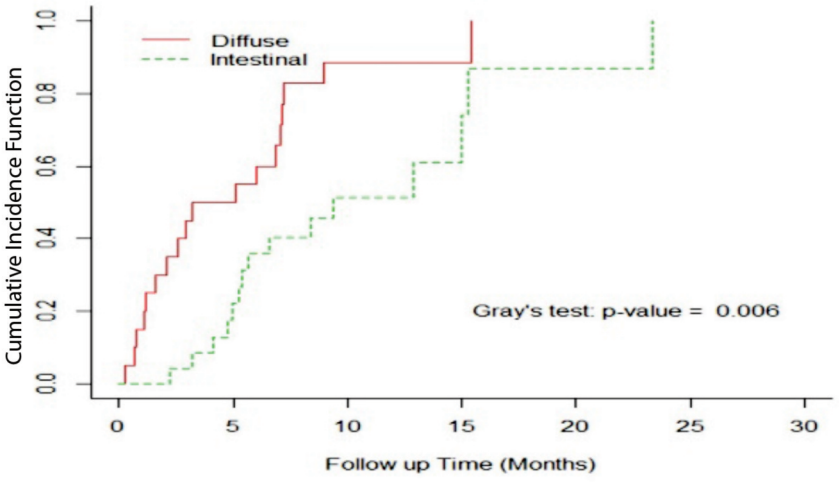

Figure 3. Cumulative incidence of progression based on pathology.

Table 4. Univariate and multivariate Cox regression model for OS and PFS.

Covariate		OS				PFS			
		Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age		0.98 (0.95-1.02)	0.469			0.97 (0.93-1.0)	0.07	0.97 (0.94-1)	0.117
Sex	Female	1.91 (0.78-1.88)	0.15	1.65 (0.68-3.98)	0.265	1.58 (0.7-3.57)	0.262		
	Male	Ref.		Ref.					
Pathology	Intestinal	0.43 (0.2-0.95)	0.037	0.42 (0.19-0.93)	0.033	0.38 (0.19-0.78)	0.009	0.35 (0.17-0.73)	0.005
	Diffuse	Ref.		Ref.		Ref.		Ref.	

CI: Confidence interval; PFS: Progression-free survival; OS: Overall survival; PI: Progression incidence; HR: Hazard ratio

seen. A total of 4 patients died before the 3rd course of chemotherapy and imaging was not available in 3 cases. Table 3 lists the details of treatment efficacy.

The median follow-up time was 11.4 ± 0.8 months, with a one-year PFS of 31.5 ± 7.5%. The two-year PFS was zero. The OS at one year was 34.91 ± 8.5%. Patients had an OS rate at 2 years of 7.7 ± 6.6%. Median PFS was 6.9 months; for OS, it was 9.3 months. Males had a maximum follow up time of 27.4 months and the maximum follow up for female patients was 10.2 months. The log-rank test results showed that the probability of survival significantly differed based on pathologic subtype. One-year OS rate was 13.83% for the diffuse type and 52.83% for the intestinal type (*P*=0.032). Additionally, the one-year PFS rate was 11.56% for the diffuse type and 48.53% for the intestinal type (*P*=0.007) as seen in figures 1 and 2. Differences between male and female groups did not reach the statistical threshold of significance. The 6-month OS for male patients was 72.81% and for female patients, it was 74.56% (*P*=0.14). We noted similar results for PFS when categorized by sex. The 6-month PFS was 55.34% for males and 46.87% for females (*P*=0.26). According to the Cox proportional hazard model, pathology subtypes of the tumor was the only variable found to have a significant effect on outcome (multivariate analysis for OS: *P*=0.033 and PFS: *P*=0.005). Table 4 shows the influence of other variables.

The cumulative incidence of progression at one-year was 68.11%. According to pathology subtypes, patients with the diffuse subtype had significantly higher incidences of progression. Progression incidence at 6 months was 60.00% (34.57-78.21%) for the diffuse type. At 12 months, it was 88.57% (55.55-97.53%) for the diffuse type. Progression incidence at 6 months was 35.81% (16.60-55.57%) and 51.23% (27.64-70.62%) at 12 months for the intestinal type (Gray's test; *P*=0.006; Figure 3).

Discussion

This study aimed to explore the efficacy and safety of the IOX regimen in patients with metastatic gastric cancer. Current preliminary results have suggested that the triple regimen administered on an outpatient basis is feasible and well-tolerated. In the 1990s, many trials demonstrated that 5-FU-based regimens provided superior survival in patients with advanced gastric cancer compared with BSC.[20-22] The median survival of BSC (4.3 months) was at least doubled by chemotherapy, which resulted in an HR of 0.37 (95% CI: 0.24-0.55) and a response of 33%-50%. Best supportive care is no longer considered to be an appropriate control arm.[7] A meta-analysis has demonstrated that combination chemotherapy had a statistically significant survival advantage compared with single-agent 5-FU chemotherapy (HR: 0.80; 95% CI: 0.72-0.89). Median PFS was 5.6 versus 3.6 months, median OS time was 8.3 versus 6.7 months, and the pooled objective (RR) was 35% versus 18% in the combination and single agent arms, respectively.[7] Toxicity was higher with combination chemotherapy but the difference was not statistically significant. Death due to toxicity was 1.9% for combination and

0.9% for single-agent 5-FU (OR: 1.69; 95% CI: 0.58-4.94).

The DCF regimen is one of the most successful combinations used for advanced gastric cancer. This regimen has produced acceptable overall response rates of 44.4% in an analysis by Chen et al. on 1089 patients from 12 randomized clinical trials.[23] Roth et al. reported a response rate of 54% among 61 patients treated with the DCF regimen.[24] The IOX regimen, in study by Bajetta et al., induced an overall response rate of 58% among 12 patients.[19] Administration of the IOX regimen in the current study led to an overall response rate of 50% and complete response rate of 23.7%, which seemed to be a satisfactory result compared to other combinations and preliminary results of the IOX regimen. Although similar response rates were observed with the DCF regimen, the IOX regimen in the current study had a considerably lower toxicity profile. We observed grades 3 and 4 hematologic toxicities in 8.9% of patients and there were no grade 3 and 4 non-hematologic toxicities. Bajetta et al. reported grades 3 and 4 hematologic toxicities of anemia in one patient and neutropenia in 2 patients.[19] The analysis by Chen et al. showed that 81.7% of patients who received the DCF regimen reported higher toxicities, particularly for grades 3 and 4 leucopenia (54.1%), grades 3 and 4 neutropenia (61.3%), and grades 3 and 4 febrile neutropenia (23.3%).[23]

Previous reports used the IOX triple regimen in patients with metastatic gastric and colorectal cancers.[19,25,26] When compared to other combinations, in particular the taxane-based protocols, the toxicity profile of the IOX regimen as reported in the current study or according to Bajetta et al. was acceptable for such an effective regimen.

The ACCORD 11 trial showed that first-line FOLFIRINOX regimen significantly improved RR, PFS, and OS compared to gemcitabine monotherapy among 342 patients with metastatic pancreatic adenocarcinoma, although they observed hematologic and non-hematologic treatment-related toxicities. The most common grades 3 and 4 toxicity was neutropenia which occurred in 45.7% of patients treated with FILFIRINOX.[18] The FOLFOXIRI or FOLFIRINOX regimens (both regimens are combinations of folinic acid, irinotecan, fluorouracil and oxaliplatin) were developed in metastatic colorectal cancer to optimize RR and secondary resection of metastases.[27] The most common hematologic toxicity was grade 1 anemia. A total of 4 patients experienced febrile neutropenia (8.9%). The most common non-hematologic toxicities were nausea, vomiting, and diarrhea. The IOX regimen showed promising results in terms of disease control, activity, response rate, OS, and PFS.

Another advantage of the IOX regimen could be the feasibility and latitude in an outpatient setting.

In conclusion it seems that the IOX regimen compared to previous proposed triple regimens such as irinotecan, fluorouracil, and folinic acid (FOLFIRI) and the DCF regimen has relatively less toxicity, equal efficacy, and acceptable survival results. Therefore, it can potentially be an appropriate and safe treatment protocol for treatment of patients with metastatic gastric cancer. Larger multicenter randomized clinical trials are needed to reach a better judgment.

Conflict of Interest

None declared.

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