

## RESEARCH ARTICLE

# Oxaliplatin, 5-Fluorouracil and Leucovorin (FOLFOX-4) as First Line Chemotherapy in Elderly Patients with Advanced Gastric Cancer

Shirin Haghghi<sup>1</sup>, Hadi Kasbkar<sup>2</sup>, Keihan Esmaeilpour<sup>2</sup>, Mehrdad Yasaei<sup>2\*</sup>

## Abstract

**Background:** Gastric cancer is considered the fourth most common cancer and second most common cause of cancer-related mortalities worldwide. Gastric cancer develops more frequently among elderly. The oxaliplatin/5FU/leucovorin (FOLFOX) regimen has shown a notable activity against gastric cancer. **Aim:** To evaluate the responses and complications of FOLFOX-4 regimen as first line chemotherapy in elderly patients with advanced gastric cancer. **Materials and Methods:** From October 2014 to November 2015, a total of 21 patients with metastatic or local AGC (advanced gastric cancer) were analyzed. All patients were administered a FOLFOX-4 regimen consisting of a 2h infusion of oxaliplatin 85 mg/m<sup>2</sup> (day 1), continuous infusion of 1000mg/m<sup>2</sup> 5-Fu in 24h., and leucovorin 200 mg/m<sup>2</sup> in 2h infusion as a first-line chemotherapy. **Results:** A total of 18 patients were assessable for efficacy and toxicity. One of 18 patients achieved a complete response, and 12 had partial responses, giving an overall response rate of 72.6%. Three (16%) patients demonstrated stable disease and 2 (12%) progression. The median progression free survival was 7.3 months, and the median overall survival was 11.9 months. One patient had grade 3 neuropathy. No other grade 3 or 4 NCI-CTC were seen. **Conclusions:** The FOLFOX-4 regimen used in our study was both active and acceptable for AGC in elderly patients as neoadjuvant and main therapy.

**Keywords:** Stomach neoplasms - folfox protocol - antineoplastic combined chemotherapy protocols/therapeutic use

*Asian Pac J Cancer Prev*, 17 (7), 3277-3280

## Introduction

Gastric cancer is considered the fourth most common cancer and second most common cause of cancer-related mortalities worldwide (Crew and Neugut, 2006; Brenner, Rothenbacher, and Arndt, 2009). Approximately two thirds of these cases occur in developing countries in Eastern Europe, South America and Asia (Chen et al., 2014). In Iran, gastric malignancies are the most common fatal cancers and their incidence rates are above the world's average (Zamani et al., 2013). Although its incidence in individuals below 50s has been increased, gastric cancer develops more frequently among patients in their 70s and 80s (Kim et al., 2012). Despite the development of early gastric cancer detection programs, only about 30% of patients are subject to be operated on presentation, and the incidence of relapse is high (Oh et al., 2007).

Various chemotherapy regimens have been developed for advanced gastric cancer patients based on understanding that chemotherapy can increase the length and quality of life (Lee et al., 2010). A systematic review and meta-analysis by the Cochrane collaboration suggests that combinational chemotherapy seems to offer an improved survival benefit albeit at the expense of increased toxicity

(Li et al., 2012). The older-generation 5-fluorouracil (FU) and cisplatin-based combination regimens have proven unsatisfactory, with a response rate of only 11% to 20%, and a median survival time ranging between 6 to 8 months (Lee et al., 2010). Oxaliplatin has shown a notable activity against colorectal cancer in combination with 5FU and leucovorin which led to several phase II trials in gastric cancers. The oxaliplatin/5FU/leucovorin (FOLFOX) regimen in different schedules yielded RRs in the range of 38-52% with median survival time from 8 to 11 months with tolerable toxicity (Mohammad et al., 2011). Data shows clinical trials involving only elderly cancer patients are rare not because of lack of efficacy but because of lack of evidence and resources (Cho et al., 2012).

We conducted this prospective study to evaluate the efficacy of modified FOLFOX-4 (mFOLFOX-4) regimen as a first line chemotherapy regimen in elderly patients with advanced gastric cancer in terms of response rate and toxicity.

## Materials and Methods

**Treatment:** Between October 2014 and November 2015, a total of 24 patients with metastatic or locally AGC

<sup>1</sup>Department of Oncology, Gastroenterology and Liver Disease Research Center, <sup>2</sup>School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran \*For correspondence: mehrdad.yasaei@gmail.com

were analyzed in this study. All patients administered a FOLFOX-4 regimen consisting of a 2h infusion of oxaliplatin 85 mg/m<sup>2</sup> (day 1), 5-FU continuous infusion of 1000mg/m<sup>2</sup>, 5-fu in 24h., and leucovorin 200 mg/m<sup>2</sup> 2h infusion as a first-line chemotherapy.

**Eligibility:** Patients were considered eligible for the study if they met all of the following criteria: 1) Age >60 years, 2) Pathologically confirmed unresectable locally advanced or metastatic gastric cancer, 3) At least one measurable lesion, 4) ECOG performance status < 2, 5) Normal hepatic, renal and bone marrow function, 6) No active infection, 7) No history of previous malignancy and chemotherapy. Based on the mentioned criteria a number of 21 patients were entered in the study but 2 were excluded due to lack of paraclinical evidence such as abdomen/pelvis CT scan.

**Response and toxicity evaluation:** At baseline physical examination was performed and patients underwent paraclinical tests including CT scans of chest, abdomen and pelvis, CBC with Differential, serum level of creatinine, bilirubin, AST, ALT, LDH, alkaline phosphatase. Physical examination, CBC and hepatorenal function tests were repeated each cycle. Tumor assessment was carried out every 4 cycles according to RECIST criteria.

Complete Response (CR) is defined as disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm. Partial Response (PR) is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD) is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. the appearance of one or more new lesions is also considered progression. If tumor response does not meet the CR or PR criteria and it is not a PD it is defined as Stable Disease (SD) (Eisenhauer et al., 2009).

Toxicity was assessed before starting and each 2-week cycle using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 4.03, except neurotoxicity. Peripheral neuropathy was graded according to the following oxaliplatin-specific scale: grade 1, paresthesia or dysesthesias of short duration, but resolving prior to the next cycle; grade 2, paresthesia persisting between two cycles without functional impairment; grade 3, persistent paresthesia interfering with function.

## Results

### *Patient characteristics and clinical outcomes*

21 patients were included in this trial and 3 patients were lost to follow up. A total of 18 patients were enrolled in the study From July 2013 to August 2014. The patients' characteristics are shown in Table-1.

The patients comprised of 15 male and 3 female with median age of 73.6 (range 62 to 84). 5 patients have ECOG 2.4 patients had metastasis at the beginning of the treatment and 14 had locally advanced tumors. The predominant site of metastases was in the liver. Of the 18

patients, 12 patients (66%) had adenocarcinoma and the other 6 had signet ring carcinoma. A total of 107 cycles of modified FOLFOX-6 were delivered with a median number of 5.9 cycles per patient (range, 4 to 13).

### *Tumor response and survival*

All the 18 patients were assessable for the response evaluation and received more than 3 cycles.

1 patient achieved complete response and 12 had partial response which results in an overall response rate of 72%. 3 (16%) patients were stable disease and 2 (12%) had progressive disease.

During a median follow-up of 11.2 months, 9 death events and 14 progression events occurred. The median PFS was 7.3 months (range 4-24). The median OS was 11.9 months (range 4-24); with a 1-year survival rate of 61% from the start of chemotherapy.

### *Toxicities*

The incidence of the main toxicities is summarized in Table 2. 1 patient (5%) underwent dose reduction due to grade 3-4 toxicities. The most common hematological toxicity was grade 1-2 anemia, which was observed in 8 patients (44.4%). Neutropenia occurred in 6 patients (33.3%) as grade 1 or 2. Grade 1 and 2 thrombocytopenia occurred in 3 of patients (16.7%). No grade 4 hematological toxicities were observed. Non-hematological toxicities were almost mild. Grade 1-2 nausea was seen in 7 patients (38.9%), grade 1-2 vomiting occurred in 4 cases (23.3%) and grade 1 diarrhea were observed in 5 (27.8%). Grade

**Table 1. Patient's Characteristics**

	No. of patients (%)
Age (years)	
Median	73.6
Range	(62-84)
Gender	
Male	15 (83.3%)
Female	3 (16.7%)
Histology	
Intestinal type	12 (66.6%)
Diffused type	6 (33.3%)
Disease Status	
Locally advanced	14 (77.7%)
Metastatic	4 (22.3%)
Lymph nodes involvement	
Perigastric	3 (16.6%)
Peripancreatic	1 (5.5%)
Para aortic	2 (11.1%)

**Table 2. Toxicity Profile by Grade**

Toxicity	Grade 1-2 no (%)	Grade 3-4 no (%)
<b>Hematological toxicities</b>		
Neutropenia	6 (33.3%)	0
Anemia	8 (44.4%)	0
Thrombocytopenia	3 (16.6%)	0
<b>Non-hematological toxicities</b>		
Nausea	7 (38.8%)	0
Vomiting	4 (22.2%)	0
Diarrhea	5 (27.8%)	0
Peripheral neuropathy	3 (16.6%)	1 (5.5%)

**Table 3. Comparison with Previously Published Studies**

Study	No. of evaluable patients	%RR (%CR)	Median TTP (Months)	Median OS (Months)
(Louvet et al. 2002)	49	45(4)	6.2	8.6
(Al-Batran et al. 2004)	37	43(2.7)	5.6	9.6
(De Vita et al. 2005)	61	38(7)	7.14	11.2
(Cavanna et al. 2006)	56	42.9(1.8)	6	10
(Nardi et al. 2007)	31	32(13)	6.4	-
(Oh et al. 2007)	42	50(2.4)	7.7	11.2
(Luo et al. 2008)	51	41.2(5.9)	5.4	12.1
(Kim et al. 2012)	23	31.8(0)	3.5	9.2
(Cho et al. 2012)	31	50(-)	5.8	10.3
(Yeh et al. 2012)	73	36(0)	8.1	11.9
(Catalano et al. 2013)	43	34.9(7.3)	6.8	10.5
(Hacibekiroglu et al. 2015)	58	31.8(-)	3.5	9.2
Haghighi et al (2016)	18	72(5.5)	7.3	11.9

3-4 nausea vomiting and diarrhea were not seen in any patient. Grade 1 and 2 neuropathy, paresthesia with decreased deep-tendon reflexes occurred in 3 patients (16.6%). 1 patient had grade 3 neuropathy.

## Discussion

During the past decade, new chemotherapeutic agents, such as docetaxel, paclitaxel, capecitabine, S-1, irinotecan and oxali-platin, have been developed and tested extensively in AGC (Kim et al., 2012). Gastric cancer develops more frequently among elderly patients who have poor PS (Kim et al., 2012; Keam et al., 2008). Because of poor PS these patients cannot tolerate the toxicities of docetaxel or cisplatin, Thus develop-ment of optimal regimens for those patients is crucial.

In this article we administered FOLFOX-4 regimen as neoadjuvant chemotherapy for locally advanced and chemotherapy for metastatic gastric cancer in elderly patients with locally advanced or metastatic gastric cancer. In order to lower the toxicity of 2h bolus infusion of 400mg/m<sup>2</sup> 5-fu and 22h infusion of 600mg/m<sup>2</sup> maintenance dose of 5-fu; The bolus dose has been omitted and continuous infusion of 1000mg/m<sup>2</sup> 5-fu in 24h was replaced.

With the median age of 73.6, the RR was 72% the TTP and OS were 7.3 months and 11.9 month respectively. In comparison to other prospective study of FOLFOX administration as the first line treatment of AGC, our study demonstrates a noticeable activity and tolerability in elderly patients (Al-Batran et al., 2004; Louvet et al., 2002; De Vita et al., 2005; Cavanna et al., 2006; Nardi et al., 2007; Oh et al., 2007; Kim et al., 2012; Cho et al., 2012; Catalano et al., 2013; Hacibekiroglu et al., 2015). Table 3 summarizes the results of our study in comparison with the 12 previously published clinical trials of oxaliplatin, FA and 5-FU as first-line therapy in AGC patients. The RR, TTP and OS were almost higher than other studies. In the studies of Yeh YS et al and lou et al median TTP and median OS for elderly patients was 8.1 and 12.1 respectively which are slightly better than our results (Yeh et al., 2012; Luo et al., 2008). It should be considered that only 4 of these articles have assessed the therapy on elderly separately (Yeh et al., 2012; Nardi et al., 2007; Catalano et al., 2013; Cho et al., 2012). The

overall RR in patients with distal tumors (5 patients) was 100% (1 complete response and 4 partial responses); 13 patients had proximal tumors with overall RR of 61%. 5 patients received FOLFOX as neoadjuvant and after that underwent operation. The median OS of these 5 patients is 16.8 months (range 12-24) and the median PFS was 17 months. Toxicities were acceptable and only 1 patient had grade3 neuropathy. Hematological toxicities were manageable and all of them were grade 1-2. The most common non-hematological toxicities were nausea (38.9%). We should consider that lack of patients is negative point of our study and we recommend studies with more patients to re-evaluate the results.

In conclusion, the FOLFOX-4 regimen used in our study was both active and acceptable for AGC in elderly patients as neoadjuvant and main therapy. Our results suggest that this regimen may be an effective option for those patients.

## References

- Al-Batran SE, Atmaca A, Hegewisch-Becker S, et al (2004). Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. *J Clin Oncol*, **22**, 658-63.
- Brenner H, Rothenbacher D, Arndt V (2009). Epidemiology of stomach cancer. *Methods Mol Biol*, **472**, 467-77.
- Catalano V, Bissoni R, Graziano F, et al (2013). A phase II study of modified FOLFOX as first-line chemotherapy for metastatic gastric cancer in elderly patients with associated diseases. *Gastric Cancer*, **16**, 411-9.
- Cavanna L, Artioli F, Codignola C, et al (2006). Oxaliplatin in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic gastric cancer (MGC). *Am J Clin Oncol*, **29**, 371-5.
- Chen W, Shen J, Pan T, et al (2014). FOLFOX versus EOX as a neoadjuvant chemotherapy regimen for patients with advanced gastric cancer. *Exp Ther Med*, **7**, 461-67.
- Cho YH, Kim SY, Hong Lee M, et al (2012). Comparative analysis of the efficacy and safety of chemotherapy with oxaliplatin plus fluorouracil/leucovorin between elderly patients over 65 years and younger patients with advanced gastric cancer. *Gastric Cancer*, **15**, 389-95.
- Crew KD, Neugut AI (2006). Epidemiology of gastric cancer<sup>1</sup>. *World J Gastroenterol*, **12**, 354-62.
- De Vita F, Orditura M, Matano E, et al (2005). A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and

- folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. *Br J Cancer*, **92**, 1644-9.
- Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.
- Hacibekiroglu I, Kodaz H, Erdogan B, et al (2015). Comparative analysis of the efficacy and safety of oxaliplatin plus 5-fluorouracil/leucovorin (modified FOLFOX6) with advanced gastric cancer patients having a good or poor performance status. *Asian Pac J Cancer Prev*, **16**, 2355-9.
- Keam B, Im SA, Han SW, et al (2008). Modified FOLFOX-6 chemotherapy in advanced gastric cancer: Results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. *BMC Cancer*, **8**, 148.
- Kim HS, Kim JH, Kim HJ, et al (2012). Oxaliplatin, 5-fluorouracil and leucovorin (modified FOLFOX-6) as first-line chemotherapy for advanced gastric cancer patients with poor performance status. *Oncol Lett*, **3**, 425-28.
- Lee HH, Hur H, Kim SH, et al (2010). Outcomes of modified FOLFOX-6 as first line treatment in patients with advanced gastric cancer in a single institution; retrospective analysis. *Cancer Res Treat*, **42**, 18-23.
- Li ZY, Koh CE, Bu ZD, et al (2012). Neoadjuvant chemotherapy with FOLFOX: improved outcomes in Chinese patients with locally advanced gastric cancer. *J Surg Oncol*, **105**, 793-9.
- Louvet C, Andre T, Tigaud JM, et al (2002). Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol*, **20**, 4543-8.
- Luo HY, Xu RH, Zhang L, et al (2008). A pilot study of oxaliplatin, fluorouracil and folinic acid (FOLFOX-6) as first-line chemotherapy in advanced or recurrent gastric cancer. *Chemotherapy*, **54**, 228-35.
- Mohammad HA, Magdy FM, Mahmoud OM (2011). FOLFOX (oxaliplatin and 5 fluorouracil/leucovorin) in patients with untreated metastatic gastric adenocarcinoma Phase II study. *Indian J Cancer*, **48**, 460-5.
- Nardi M, Azzarello D, Maisano R, et al (2007). FOLFOX-4 regimen as first-line chemotherapy in elderly patients with advanced gastric cancer: a safety study. *J Chemother*, **19**, 85-9.
- Oh SY, Kwon HC, Seo BG, et al (2007). A phase II study of oxaliplatin with low dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) as first line therapy for patients with advanced gastric cancer. *Acta Oncol*, **46**, 336-41.
- Yeh YS, Tsai HL, Ma CJ, et al (2012). A retrospective study of the safety and efficacy of a first-line treatment with modified FOLFOX-4 in unresectable advanced or recurrent gastric cancer patients. *Chemotherapy*, **58**, 411-8.
- Zamani N, Hajifaraji M, Fazel-tabar Malekshah A, et al (2013). A case-control study of the relationship between gastric cancer and meat consumption in Iran. *Arch Iran Med*, **16**, 324-9.