A phase II study of modified FOLFOX as first-line chemotherapy for metastatic gastric cancer in elderly patients with associated diseases

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Abstract

Background Elderly patients are generally underrepresented in the study populations of combination chemotherapy trials. This study evaluates the efficacy and safety of a modified FOLFOX regimen in elderly patients with metastatic gastric cancer and presenting associated disease(s).

Methods A total of 43 patients aged ≥ 70 years received oxaliplatin 85 mg/m^2 together with 5-fluorouracil $2,400 \text{ mg/m}^2$ on day 1, followed by a 46-h infusion of 5-fluorouracil $2,400 \text{ mg/m}^2$, every 2 weeks. Assessment of response was performed every four cycles according to RECIST criteria.

Results Median patient age was 74 years (range, 70–83 years). Overall response rate was 34.9 % [95 % confidence interval (CI), 20.6–49.1, with 3 complete responses and 12 partial responses. Grade 3 neutropenia occurred in 4 patients (9.3 %), fatigue in 3 patients (7.0 %), and vomiting in 2 patients (4.6 %). Grade 2 and 3 peripheral neuropathy was observed in 5 patients (11.6 %) and 1 patient (2.3 %), respectively. No treatment-related death was observed. Median progression-free and overall survival were 6.8 and 10.5 months, respectively.

Conclusions This modified FOLFOX regimen is an active and well-tolerated treatment for elderly patients with

metastatic gastric cancer and also represents a good therapeutic option in patients with associated disease(s).

Keywords Elderly · Palliative chemotherapy · Oxaliplatin · Metastatic gastric cancer

Introduction

Despite improvements in the early detection of gastric cancer, this disease remains one of the leading causes of cancer-related death worldwide [1]. A significant proportion of patients have inoperable stages at the time of diagnosis, when systemic chemotherapy is indicated with the aim of palliation. In Western countries, regimens containing 5-fluorouracil (5-FU) and cisplatin remain an accepted standard [2]. The addition of a third drug, basically epirubicin or docetaxel, may be helpful, even if it translates into only a small benefit in terms of overall survival [3, 4]. However, when adding a third drug to a double combination, toxicity may significantly increase, and this aspect should be taken into account when considering triple drug combinations for frail and elderly patients.

The definition of an elderly patient varies according to social and economic situations. However, in most developed and developing countries, 65 or 70 years of age is a commonly used limit because of the decreased role of the subject in the community and society. Although the majority of gastric cancer patients are elderly, patients older than 65–70 years have been often excluded from, or underrepresented in, the study populations of combination chemotherapy trials [5, 6]. Elderly patients may have a functional fall of reserve capacity and may show high incidence of comorbidity. In prospective trials, the

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eligibility criteria are quite stringent, and a low proportion of 70-year-old patients is enrolled. For these reasons, results from the published literature are not fully transferable to the elderly population. Consequently, there is uncertainty about the type and the extent of systemic palliative chemotherapy that should be offered to elderly patients with gastric cancer.

In gastric cancer patients, oxaliplatin has shown a more favorable toxicity profile than cisplatin [4, 7]. Furthermore, a combination chemotherapy of 5-FU with oxaliplatin, mainly FOLFOX regimens, has been investigated in numerous phase II studies, using different doses and schedules [8–12], and has shown considerable antitumor activity. Insofar as toxicity is concerned, significant toxicities, including myelosuppression and peripheral neuropathy, are a major issue for elderly patients. When compared to standard FOLFOX schedules, both weekly and biweekly reduced-dose combinations of oxaliplatin/5-FU without 5-FU bolus showed a more favorable toxicity profile with lower rates of peripheral neuropathy and myelosuppression [9, 10, 12].

During the past decades, various studies [13–17] have assessed the role of combination chemotherapy containing oxaliplatin and 5-FU for elderly patients with advanced gastric cancer. However, in this setting little attention was paid to the presence of comorbidities of elderly patients.

Considering that the aim of treatment in metastatic gastric cancer is palliation, great importance should be given to the tolerability of treatment, and this issue is of particular interest especially if we consider elderly patients. The aim of this study was to examine the efficacy and toxicity of a modified FOLFOX regimen as first-line chemotherapy for elderly patients (aged 70 years or more) with metastatic gastric cancer and suffering from associated disease(s).

Methods

Eligibility

Elderly patients (aged ≥ 70 years) with histologically confirmed, relapsed, or metastatic adenocarcinoma of the stomach, or of the gastroesophageal junction, were eligible if they met the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status 0–2; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST); adequate liver [serum bilirubin $\leq 2.0 \times$ upper normal limit (UNL); serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ UNL, or $< 5 \times$ UNL for patients with liver metastases; serum alkaline phosphatase $\leq 5.0 \times$ UNL], renal (serum creatinine ≤ 1.5 mg/dl or calculated creatinine

clearance by Cockcroft–Gault equation > 40 ml/min), and bone marrow [absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$] functions; estimated life expectancy ≥ 3 months. Patients were excluded if they had only sites of disease previously treated with radiotherapy or had had prior chemotherapy for metastatic disease, except adjuvant chemotherapy completed at least 12 months before enrollment, previous treatment with oxaliplatin, brain metastases, significant gastrointestinal bleeding, peripheral neuropathy $\geq$ grade 2, serious uncontrolled concomitant disease, other primary malignancy (except squamous or basal cell skin cancer or cervical carcinoma in situ) within the last 5 years, or were unable to comply with the requirements of the protocol. In addition to the activities of daily living (ADL) and instrumental activities of daily living (IADL) scales [18], the comprehensive geriatric assessment (CGA) was used at study entry to identify and exclude frail elderly patients [19]. The protocol was approved by a local institutional review board, and written informed consent was obtained from all participants.

Study design and dose modifications

Oxaliplatin 85 mg/m^2 and S-leucovorin 200 mg/m^2 were given as a 2-h intravenous infusion followed by 5-FU $2,400 \text{ mg/m}^2$ as a 46-h continuous infusion. The use of central venous catheters and disposable pumps allowed chemotherapy administration on an outpatient basis. The cycles were repeated every 2 weeks and treatment was continued until disease progression, unacceptable toxicity, patient refusal, or the decision of the patient's physician to terminate treatment. The administration of glutathione was allowed for prevention of oxaliplatin-induced neuropathy. Antiemetic prophylaxis was given according to local protocols. According to treatment policy at each participating institution, the use of growth factors for white cells [granulocyte colony-stimulating factor (G-CSF)] and erythropoietin was allowed in the case of acute toxicity.

Dose modifications were performed on the basis of toxicity. Chemotherapy was delayed for up to 14 days when neutrophil count was $< 1,500/\text{mm}^3$ and/or platelet count was $< 100,000/\text{mm}^3$. In the case of toxicity of grade 2 or greater, except in the case of alopecia, chemotherapy was delayed 1 week, and then restarted after full recovery. Reduction of 20 % in the dosage of all drugs was applied for grade 3 nonhematological toxicity, for grade 4 hematological toxicity, for febrile neutropenia, or for recurrent grade 3 thrombocytopenia and/or neutropenia in the previous cycle. For grade 3 or 4 gastrointestinal toxicities or grade 3 hand–foot syndrome, 5-FU was reduced by 20 %. For grade 2 cardiotoxicity, 5-FU treatment was discontinued. Patients with unsolved toxicity of grade 2 or greater after two consecutive treatment delays, or experiencing

grade 4 nonhematological toxicity, except alopecia, went off the study.

In cases of sensorial neuropathy accompanied by pain lasting longer than 7 days, oxaliplatin was reduced by 20 %. If peripheral neuropathy persisted between the two following cycles, the oxaliplatin dose in the next cycle had to be reduced by 50 %. Treatment withdrawal was planned in cases of grade 3 neuropathy.

Response and toxicity assessment

In addition to a full medical history and physical examination, baseline assessments included complete blood counts, chemistries, urinalysis, and electrocardiography before starting, ECOG performance status, computed tomography (CT) of the abdomen and pelvis, and chest X-ray or CT scan. ADL and IADL scales and the CGA were calculated before enrollment in the study. Other investigations, for example, bone scan or bone X-ray, or a magnetic resonance imaging (MRI) scan of some sites of disease, were performed, if clinically indicated, to document metastatic disease. The baseline assessment of disease was carried out within 4 weeks before the start of the treatment. Full medical history and physical examination including ECOG performance status and blood chemistries were assessed before each treatment cycle. Responses were classified according to RECIST criteria for every four cycles of modified FOLFOX. Responses were confirmed by subsequent CT scans every 4–6 weeks after the initial response documentation. All eligible patients were included in the response and survival analysis on an ‘intent-to-treat’ basis.

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0.

Statistical analysis

This was a multicenter phase II study. The primary endpoint was the cumulative objective response rate of the planned modified FOLFOX. Secondary endpoints were toxicity, progression-free survival (PFS), and overall survival (OS). The optimal two-stage phase II design was adopted for this phase II trial. The treatment program was designed to reject an overall response rate for the modified FOLFOX regimen of less than 20 % (p_0) and to provide a statistical power of 80 % in assessing the activity of the regimen (in terms of response rate) as 40 % (p_1). Early discontinuation of the study was provided for in the case of fewer than three responses in the first 13 assessable patients treated with modified FOLFOX (α and β error probabilities, 0.05 and 0.02, respectively). Otherwise, more than 12 responses from among a total of 43 patients are required to consider this regimen as acceptable for elderly patients

with metastatic gastric cancer. PFS was measured from the onset of chemotherapy to the date of progression (per investigator assessment), or death from any cause. OS was calculated from the onset of chemotherapy until death or until the censoring date for follow-up (31 December 2010). Patient survival was examined using the Kaplan–Meier product limit method.

Results

Forty-three patients were enrolled from two institutions (Pesaro and Fermo). The characteristics of the patients are summarized in Table 1. Median patient age was 74 years

Table 1 Patient characteristics

Characteristics	<i>n</i>	%
Number of patients	43	
Sex, male/female	27/16	62.8/37.2
Age, years median (range)	74 (70–83)	
Performance status		
0	19	44.2
1	20	46.5
2	4	9.3
Lauren classification		
Intestinal type	23	53.5
Diffuse type	16	37.2
Mixed	4	9.3
Primary tumour		
Oesophagogastric junction	9	20.9
Stomach	32	74.4
Anastomosis	2	4.7
Prior therapy		
Surgery	26	60.5
Adjuvant chemotherapy	6	14.0
Number of organs involved		
1	10	23.3
2	20	46.5
3–5	13	30.2
Metastatic sites		
Lymph nodes	17	39.5
Liver	13	30.2
Peritoneum	18	41.9
Bone	1	2.3
Lung	6	13.9
Other	10	23.2
Royal Marsden Hospital Prognostic Index		
Good	11	25.6
Moderate	30	69.8
Poor	2	4.6

Table 2 Pretreatment classification of comorbidity

Associated disease	<i>n</i>	%
Hypertension	30	69.8
Cardiac disease ^a	14	32.6
Respiratory disease ^b	5	11.6
Diabetes mellitus	9	20.9
Liver disease ^c	2	4.6
Neurological disease ^d	5	11.6
Renal disease ^e	5	11.6
Others ^f	5	11.6
Number of associated disease(s)		
1	19	44.2
2	15	34.9
3	9	20.9

^a Arrhythmia, valvular heart disease, coronary heart disease, myocardial infarct

^b Emphysema, asthma, chronic obstructive pulmonary disease

^c Liver cirrhosis, chronic hepatitis C

^d Cerebral infarct disease

^e Chronic renal insufficiency, kidney polycystosis

^f Rheumatoid arthritis, hypothyroidism, obesity, ulcerative colitis

(range, 70–83 years). Twenty-seven patients (62.8 %) were men, and 39 patients (90.9 %) had an ECOG performance status of 0–1. Metastases were primarily in the peritoneum (41.9 %), lymph nodes (39.5 %), and liver (30.2 %). At least two organs were involved in nearly 75 % of patients. All except 2 patients had a good to moderate Royal Marsden Hospital (RMH) Prognostic Index [20]. All patients had comorbidities with a median number of associated diseases of 2 (range, 1–3) (Table 2). Hypertension and cardiac disease were the most frequent associated diseases.

Response evaluation

Among the 43 patients who received chemotherapy, the tumor response was evaluable according to the RECIST criteria in 41 patients. Two patients died after the second cycle of chemotherapy: 1 patient of myocardial infarction, and the other of cerebrovascular disease, occurring 10 and 12 days, respectively, from the date of the second cycle, without showing signs of toxicity or early progression. After the modified FOLFOX regimen, 3 patients achieved complete response, 12 patients showed partial response, 15 patients had stable disease, and 11 patients progressed, with an overall response rate of 34.9 % (95 % CI, 20.6–49.1) (Table 3). The 3 patients reporting a complete response were free from progression at 20, 23+, and 55+ months, respectively, and alive as of 31 December 2010.

Table 3 Objective tumor response rates in advanced untreated elderly gastric cancer patients (*n* = 43), according to RECIST

Response	Number (%)
Complete response	3 (7.0)
Partial response	12 (27.9)
ORR (95 % CI)	34.9 (20.6–49.1)
Stable disease	15 (34.9)
Progressive disease	11 (25.6)
Not assessable	2 (4.6)

CI confidence interval, ORR overall response rate, RECIST Response Evaluation Criteria in Solid Tumors

Fig. 1 Kaplan–Meier curve of progression-free survival (*n* = 43)

Survival analysis

Forty-three patients were included in the survival analysis on an intention-to-treat basis. After a median follow-up of 38 months, PFS was 6.8 (range, 1–55+) months (Fig. 1) and OS was 10.5 (range, 1–55+) months (Fig. 2), with 46.1 % of patients alive at 1 year. Second-line chemotherapy was administered to 14 patients (32.6 %): 10 patients received FOLFIRI; and 1 patient received irinotecan plus capecitabine, paclitaxel, docetaxel, or irinotecan alone.

Treatment administration

A total of 324 cycles were administered, with a median of 8 cycles (range, 1–15 cycles) for patients. Of 43 patients, 29 (67.4 %) received at least 6 cycles, 25 patients (58.1 %) received at least 8 cycles, and 13 patients (30.2 %) received at least 10 cycles. The relative dose intensities of oxaliplatin and 5-FU were 90.8 % and 91.3 %, respectively. The median cumulative dose of oxaliplatin was

Fig. 2 Kaplan–Meier curve of overall survival ($n = 43$)

612 mg/m² (range, 85–1,262) and that of 5-FU was 17,280 mg/m² (2,400–35,640).

Twenty-two of the 324 (6.8 %) cycle intervals were delayed in 14 patients (32.6 %). Most cycle delays were caused by neutropenia and thrombocytopenia. Twenty-five patients (58.1 %) had at least one dose reduction in a total of 119 cycles (36.7 %). The main reason for discontinuing study treatment was disease progression. Other reasons included death (4 patients) and refusal (1 patient). Only 1 patient was taken off the study treatment because of grade 3 neurotoxicity after receiving 15 cycles of chemotherapy.

Toxicity

The toxicity profile of the modified FOLFOX regimen was acceptable (Table 4). The incidence of severe adverse events was very low and no grade 4 toxicity was observed. The most common toxicities were hematological. NCI-CTCAE grade 3 neutropenia and anemia were recorded in 9.3 % and 2.3 % of cases, respectively. Grade 1–2 anemia, thrombocytopenia, and neutropenia occurred in 51.2 %, 23.2 %, and 23.2 % of patients, respectively. No patient experienced febrile neutropenia. Among nonhematological toxicities, fatigue was frequently reported (39.5 %), but it was of grade 3 only in 2 (7.0 %) patients. Other toxicities were generally mild (Table 4). As expected, peripheral neuropathy was observed in 41.9 % of the population and was graded as severe (grade 3) in 1 (2.3 %) patient, who received a cumulative dose of oxaliplatin of 1,020 mg/m². The incidence of the peripheral neuropathy correlated with the cumulative dose of oxaliplatin, with 12 of 18 (66.6 %) patients reporting grade 1–3 toxicity and receiving a cumulative oxaliplatin dose >600 mg/m². There was no treatment-related mortality.

Table 4 Toxicity according to treatment (NCI-CTCAE)

Grade	n (%)			
	1	2	3	4
Neutropenia	5 (11.6)	5 (11.6)	4 (9.3)	0
Anemia	18 (41.9)	4 (9.3)	1 (2.3)	0
Thrombocytopenia	6 (13.9)	4 (9.3)	0	0
Nausea	2 (4.6)	5 (11.6)	0	0
Vomiting	1 (2.3)	5 (11.6)	2 (4.6)	0
Diarrhea	5 (11.6)	5 (11.6)	1 (2.3)	0
Stomatitis	0	1 (2.3)	0	0
Fatigue	6 (13.9)	8 (18.6)	3 (7.0)	0
Anorexia	3 (7.0)	3 (7.0)	1 (2.3)	0
Neurological	12 (27.9)	5 (11.6)	1 (2.3)	0
Others	1 (2.3)	7 (16.3)	0	0

NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

Discussion

Although the number of deaths from gastric cancer has declined during the past, a large proportion of elderly patients are primarily affected by the disease. SEER data from the United States showed that 65.5 % of patients with gastric cancers are diagnosed when older than 65 years: the median age at diagnosis of such patients was 71 years, and the median age of gastric cancer-related death was 74 years [6]. Elderly cancer patients often suffer multiple comorbidities, take many medications, and have age-associated physiological problems, such as impaired organ function and functional changes, that make the selection of optimal treatment difficult [21, 22]. This aspect is also hampered by the underrepresentation of older patients in cancer clinical trials. Overall, from 1997 to 2000, only 32 % of participants in phase II and III trials sponsored by the National Cancer Institute were elderly, compared with 61 % of new cancer cases who are elderly [23]. Age is a significant barrier to recruitment. Chronological age alone is not a sufficient reason to withhold palliative treatment from an elderly gastric cancer patient. Elderly patients who fulfill the inclusion criteria of clinical trials could experience the same advantages and toxicities from chemotherapy as younger patients. In contrast to physicians' perceptions, older patients do not recognize their age as an important issue for refusing trials [24]. Furthermore, performance status is not helpful to estimate the general condition of elderly patients, and other factors regarding their functional, social, and mental status should be considered [25].

In a recently published meta-analysis, Wagner et al. [26] concluded that further research on the risks and benefits of palliative chemotherapy in elderly gastric cancer patients is necessary before applying a recommendation for this group

of patients. In fact, they observed that the median age in the participants included in various trials [26] was well below the median age (64–65 years) reported in some trials [4, 7].

There is a lack of prospective studies directly comparing the outcomes and the tolerability of chemotherapy in young and elderly patients, although some data are available in gastric cancer from a retrospective analysis [27]. Trumper et al. [27] evaluated retrospectively 1,080 patients who were enrolled into three randomized controlled trials assessing 5-FU-based combination chemotherapy. They found that elderly patients obtained similar benefits from palliative chemotherapy in terms of symptomatic response, tumor regression, and survival, without increased toxicities.

One may suggest that elderly patients without significant comorbidities should be treated with the same regimens as younger patients with advanced gastric cancer. However, extrapolation of the results from retrospective reviews or meta-analyses to elderly patients should be done with caution. It is strongly suggested that specific clinical trials limited to older patients should be planned to evaluate response, benefit treatment tolerability, and the effect of comorbid conditions, so that clinicians may optimize their treatment of older cancer patients.

For the palliative treatment of metastatic gastric cancer, a doublet containing oxaliplatin and fluoropyrimidines could be considered as an option. Results from a prospective randomized trial showed the non-inferiority of oxaliplatin, as compared to cisplatin, in the treatment of advanced gastric cancer, while decreasing toxicity [4]. Of interest, a subgroup analysis from a phase III randomized trial [7] reported significantly better results for elderly patients treated with oxaliplatin as compared to cisplatin. In this trial, patients with advanced gastric cancer were randomized to receive a 5-FU-based regimen with cisplatin (FLP regimen) or oxaliplatin (FLO regimen). The primary endpoint of the study, PFS, was unmet. However, in the subgroup of patients older than 65 years, the FLO regimen achieved improved efficacy in terms of response rate, PFS, and OS as compared with the FLP regimen [7]. In a subsequent randomized study on elderly gastric cancer patients, the FLO regimen has formed the basis for the addition of a third drug, docetaxel (FLOT regimen) [17]. The FLOT regimen improved efficacy with manageable toxicity compared with the FLO chemotherapy.

This trial aimed to assess a chemotherapy regimen in elderly patients who had associated disease(s). We used a modified FOLFOX regimen with the omission of bolus 5-FU with the aim to improve tolerability of such regimen in the elderly population, while preserving the outcome. This strategy was adopted based on the results of previous [9] and ongoing studies [13–16] of oxaliplatin/5-FU combination regimens. The population consisted of patients

with a median age of 74 years, which is among the highest reported in this setting. The overall response rate was 34.9 %, which compares favorably with other phase II studies of FOLFOX chemotherapy, ranging from 32.2 % to 52.5 % [13–16, 28] (see Table 5). This overall response rate is noteworthy if we consider that all the patients had metastatic or recurrent gastric cancer compared with other studies in which a variable percentage (from 8 % to 35 %) of enrolled patients had locally advanced disease [8, 11, 14, 15, 17, 28]. In our study we omitted the 5-FU bolus injection to reduce myelosuppression. This modified FOLFOX regimen showed a 9.3 % occurrence of grade 3–4 neutropenia, which is lower than the 36–38 % shown with the FOLFOX-4 and FOLFOX-6 regimens [8, 11].

The dose of oxaliplatin was 85 mg/m², every 2 weeks, to avoid an increased incidence of peripheral sensory neuropathy associated with higher doses of oxaliplatin [8], which could be an important issue especially for elderly patients with associated disease (e.g., diabetes). In the present series, no grade 4 peripheral sensory neuropathy occurred, whereas grade 2–3 neurotoxicity was reported in 13.9 % of cases. Only 1 patient experienced grade 3 neuropathy, a proportion similar to that of the original FOLFOX-4 [11] or of other modified FOLFOX regimens used in elderly patients employing an 85 mg/m² dose of oxaliplatin [14–16], but lower than that reported by Louvet et al. [8] with the FOLFOX-6 regimen (grade 3 neurotoxicity in 21 % of cases) (Table 5). However, in our study the median cumulative dose of 612 mg/m² for oxaliplatin is lower than in the original FOLFOX-6, in which a dose of oxaliplatin of 100 mg/m² was used with a median cumulative dose of 901 mg/m² for oxaliplatin.

Together with the omission of bolus 5-FU and the oxaliplatin dose, the use of 5-FU at 2,400 mg/m² continuous infusion in 46 h seems tolerable. We observed no grade 4 toxicities, whereas grade 1–3 gastrointestinal toxicities were reported in a moderate number of patients (Tables 4, 5). Moreover, the dose intensities of oxaliplatin and 5-FU were nearly 90 % of those pre-planned, thus verifying the tolerability of this regimen. These results indicate that a modified FOLFOX regimen of 85 mg/m² oxaliplatin could be considered an option for elderly patients with unresectable or recurrent gastric cancer and with associated comorbidities.

In elderly gastric cancer patients, different trials have assessed palliative chemotherapy regimens, including fluoropyrimidines with oxaliplatin (see Table 5) or irinotecan [29], but large-scale trials are lacking. For this reason, in this subset of patients there is uncertainty about the use of systemic palliative chemotherapy. It is crucial to select palliative treatments that are active, but at the same time these treatments need to be sufficiently tolerable. Hematological toxicity, cardiotoxicity, neurotoxicity, renal

Table 5 Comparison with previous FOLFOX regimens in gastric cancer

Author, year [Ref. number]	<i>n</i>	Regimen (dose oxa/ 5-FU _b /5-FU _{i.c.}) ^a	Median age (range) (years)	ORR (%)	PFS (months)	OS (months)	Toxicity G1–2 (%)	Toxicity G3–4 (%)
All ages								
Louvet, 2002 [8]	54	mFOLFOX (100/400/3000)	61 (31–75)	44.9	6.2	8.6	Anemia (80) Thrombocytopenia (68) Neurotoxicity (66) Neutropenia (30) Nausea (68) Asthenia (55)	Neutropenia (38) Neurotoxicity (21) Anemia (11) Nausea (6)
De Vita, 2005 [11]	61	FOLFOX-4	64 (47–75)	38.0	7.1	11.2	Anemia (37) Thrombocytopenia (32) Neurotoxicity (26) Neutropenia (23) Diarrhea (23) Nausea (21)	Neutropenia (36) Anemia (10) Diarrhea (10) Neurotoxicity (5)
Cavanna, 2006 [28]	56	FOLFOX-4	65 (28–78)	42.9	6.2	8.6	Nausea (69) Vomiting (39) Anorexia (39) Diarrhea (33) Neurotoxicity (34) Neutropenia (25)	Neutropenia (20) Anemia (11) Thrombocytopenia (7) Neurotoxicity (5)
Elderly population								
Choi, 2007 [13]	37	mFOLFOX (100/-/2400)	72 (67–79)	41.2	5.7	9.8	Anemia (54) Nausea (73) Neurotoxicity (35) Neutropenia (24) Vomiting (35) Diarrhea (19)	Neutropenia (8) Anemia (3)
Nardi, 2007 [14]	33	FOLFOX-4	74 (66–79)	32.2	6.4	NR	Nausea (77) Vomiting (61) Diarrhea (51) Neutropenia (48) Neurotoxicity (45) Anemia (35)	Neutropenia (19) Anemia (10) Vomiting (6)
Liu, 2008 [15]	44	mFOLFOX (85/-/2000)	69 (65–83)	52.5	6.5	10.0	Nausea/vomiting (43) Neurotoxicity (41) Diarrhea (32) Stomatitis (27) Neutropenia (16)	Neutropenia (7) Diarrhea (7) Neurotoxicity (2)
Present study	43	mFOLFOX (85/-/2400)	74 (70–83)	34.9	6.8	10.5	Anemia (51) Neurotoxicity (39) Fatigue (32) Neutropenia (23) Thrombocytopenia (23) Diarrhea (23)	Neutropenia (9) Fatigue (7) Vomiting (5) Neurotoxicity (2)

^a FOLFOX-4 refers to the classical schedule; mFOLFOX refers to the modification of FOLFOX regimen (dosage of drugs is provided in brackets)

5-FU_b 5-fluorouracil bolus, 5-FU_{i.c.} 5-fluorouracil continuous infusion, med median, ORR overall response rate, oxa oxaliplatin, OS overall survival, PFS progression-free survival

toxicity, mucositis, and diarrhea should be minimized to preserve a good state of health and quality of life. The presence of comorbidities may preclude the use of drugs such as anthracyclines, cisplatin, docetaxel, or oxaliplatin for elderly gastric cancer patients, and data on these drugs in patients with comorbidities are lacking for reasons of the underrepresentation of such groups in prospective studies. Quality of life is another issue that deserves evaluation, as it could be impaired as the intensity of chemotherapy increases, and until now this has not been studied sufficiently.

Data from this trial are of some value considering that the overall response rate, PFS, and OS are in the range of other trials and that toxicity was restrained.

Standard treatment for metastatic gastric cancer in elderly patients should not be extrapolated from large retrospective subset analyses or from small phase II prospective trials. The results of this study demonstrate that, in advanced gastric cancer, a regimen consisting of a dose of 85 mg/m² oxaliplatin combined with leucovorin plus continuous infusion 5-FU, but omitting the administration of bolus 5-FU, is effective as a first-line treatment and has an acceptable toxicity profile in elderly patients, also presenting with associated disease. Further prospective randomized studies to determine the most effective and tolerable regimen in elderly patients with advanced gastric cancer are warranted.

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