Title
Weekly oxaliplatin, 5-fluorouracil and folinic acid as first-line chemotherapy for elderly patients with advanced gastric cancer: results of a phase II trial

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Running title: OXALF regimen is effective in elderly advanced gastric cancer patients

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Summary

Introduction. The primary end point of this study was to determine the response rate and the toxicity of the weekly OXALF regimen in elderly patients with advanced gastric cancer. The secondary objective was to measure the time to disease progression and the survival time. Material and Methods. Chemotherapy-naive patients with advanced gastric cancer aged 70 or older were considered eligible for study entry. Patients received weekly oxaliplatin 40 mg/m2, fluorouracil 500 mg/m2 and folinic acid 250 mg/m2 (OXALF). All drugs were given intavenously on a day-1 schedule.

Results. A total of 42 elderly patients (≥ 70 years old) were enrolled. Median age was 73 years and all patients had metastatic disease. The response rate was 45.2% (95% CIs: 30–56%) with two complete responses, 17 partial responses, 13 stable diseases and 10 progressions, for an overall tumor rate control of 76.2% (32 patients). Toxicity was generally mild and only three patients discontinued treatment because of treatment related adverse events. The most common treatment-related grade 3/4 adverse events were fatigue (7.1%), diarrhoea (4.8%), mucositis (2.4%), neurotoxicity (2.4%) and neutropenia (4.8%). The median response duration was 5.3 months (95% CIs: 2.13 – 7.34), the median time to disease progression was 5.0 months (95% CIs: 3.75 – 6.25) and the median survival time was 9.0 months (95% CIs: 6.18 – 11.82). Conclusions. OXALF represents an active and well-tolerated treatment modality for elderly patients with locally advanced and metastatic gastric cancer.
Introduction

Current epidemiological data show that gastric cancer rarely occurs before the age of 40 years, its incidence increases thereafter and peaks in the seventh decade. Patients older than 65 years have been often excluded from or underrepresented in the study populations of combination chemotherapy trials. Excluding all trials of hormonal therapy for breast cancer, the overall enrollment of patients aged ≥65, ≥70, and ≥75 years decreased to 25%, 12%, and 4%, as compared with 60%, 46%, and 31%, respectively, for the corresponding age group in the US cancer population (1). This demographic selection occurred in the populations of gastric cancer patients treated with intensive combination chemotherapy regimens like the ECF or the weekly PELF. Demographic analysis of phase II and III studies in literature show that only a minority of patients treated with the weekly PELF regimen were older than 65 years (2,3). In 2003, Graziano et al. (4) demonstrated that weekly PLF (cisplatin/leucovorin/fluorouracil) chemotherapy may represent for elderly patients with advanced gastric cancer a valid and safety alternative to more expensive combinations including CPT-11 or docetaxel and to more toxic combinations including cisplatin. Oxaliplatin is an alkylating agent inhibiting DNA replication by forming adducts between two adjacent guanines or guanine and adenine molecules. The adducts of oxaliplatin appear to be more effective than cisplatin adducts with regard to the inhibition of DNA synthesis (5). Many studies are ongoing to test the combination in non colorectal gastrointestinal tumors and other malignancies. Few studies have been published in literature suggesting a role for oxaliplatin-based combinations in advanced gastric cancer (6,7,8). Moreover, oxaliplatin has a more favorable toxicity profile compared to cisplatin. The dose-limiting toxicity is a cumulative sensory peripheral neuropathy. To minimize toxicity, we chose, in the present phase II study, a weekly protocol with oxaliplatin substituting cisplatin of the PLF regimen.
Material and Methods

Patients characteristics
Chemotherapy-naive pts with advanced gastric cancer (at least one measurable lesion) aged 70 or older were considered eligible for study entry. Inclusion criteria consisted of: ECOG performance status 0 or I, normal renal, liver, bone marrow functions and measurable disease. The Katz and Lawton scales were used to assess activities of daily living (9); the Katz activities of daily living (ADL) measures the ability to perform routine activities as bathing, dressing, feeding oneself or getting into or out of bed, chairs and vehicles. The Lawton instrumental activities of daily living (IADL) measures more particular functions as the ability to use the telephone, to shop, to handle money, to prepare food or to perform other household tasks. As an adjunct to general and cancer-specific diagnostic procedures, the comprehensive geriatric assessment (CGA) was used at the study entry to identify and exclude frail elderly patients. Frail elderly pts were excluded after baseline geriatric assessment according to the following criteria: age > 85 years, dependence in one or more activities of daily living, presence of three or more comorbidity conditions and presence of one or more geriatric syndromes. Classic geriatric syndromes which had to be excluded before study inclusion were: dementia, delirium, severe depression, frequent falls, neglect and/ or abuse, and spontaneous fractures (10). Life expectancy ≥3 months, no concurrent uncontrolled medical illness, no other malignancies. Patients were excluded from the study if they had peripheral neuropathy of National Cancer Institute common toxicity criteria grade ≥2. The protocol was approved by each local institutional review board and written informed consent was obtained from all participants.

Study design and doses modifications
Patients received weekly oxaliplatin 40 mg/m2, fluorouracil 500 mg/m2 and folinic acid 250 mg/m2 (OXALF). All drugs were given intravenously on a day-1 schedule. Chemotherapy was given in an outpatient setting. Antiemetic prophylaxis was given according to local protocols. The use of hemopoietic growth-factors for white and red lines was always allowed in case of acute toxicity and this was always decided by the
experimenter in order to safeguard the patient’s life. However, priority was always given to the patient’s needs.

Full doses of the anticancer drug were given if granulocyte count was $\geq 1500$ microL and platelet count was $\geq 100000$ microL. In the case of any grade 2 or more toxicity except alopecia, chemotherapy was delayed a week and then restarted after full recovery. Reduction of 25% in all drugs dosing was applied for G3 non-hematological toxicity or for G4 hematologic toxicity in the previous cycle. Patients with unsolved grade 2 or more toxicity after two consecutive treatment delays, or experiencing grade 4 non-hematological toxicity except alopecia went off study.

If peripheral neuropathy persisted between two following cycles, the next cycle had to provide a reduction of 50% in oxaliplatin dosing. If pain was associated to the peripheral neuropathy reduction of 25% in oxaliplatin dosing was applied. If pain persisted between two following cycles, the next one had to provide a reduction of 40% in oxaliplatin dosing. In case of persistent neuropathy with pain (G3) also after the dose reduction, treatment interruption was provided.

Statistical plan

The primary end point of this study was to determine the response rate and the toxicity of the weekly OXALF regimen in elderly patients with advanced gastric cancer. The secondary objective was to measure the time to disease progression and the survival time. The expected number of patients for this study was calculated according to a Simon optimal two-stage design. An interim analysis was carried out when the first 18 assessable patients had been recruited. If more than six responses (33.3%) were observed, 24 additional patients were to be recruited; otherwise, the study was to be terminated. The regimen was considered sufficiently active to be submitted for further evaluation if the response rate exceeded 30%. The time to disease progression (TTP) was measured from the date of registration to the date of documented disease progression or death. The survival time was measured from the time of registration to the date of death resulting from any cause.
Response and toxicity assessment

Responses were classified according to RECIST criteria (11). Computed tomography (CT) scans of measurable lesions were carried out within 4 weeks before the start of the treatment and at every disease restaging. Responses were to be confirmed by subsequent CT scans 4 to 6 weeks after the initial response documentation. Patients were considered assessable for response if they had early disease progression or had received at least 8 cycles of treatment with at least one tumor assessment.

Patients with responsive or stable disease received six additional weekly cycles and they underwent a second measurement at the end of the treatment program. Follow-up controls were performed every 2 months thereafter. All patients had physical examination and blood chemistries before each weekly administration of chemotherapy and toxicity was graded according to National Cancer Institute common toxicity criteria.

Results

Response and survival

From October 2002 to April 2005, 42 elderly patients entered on this study (median age, 73 years; range, 70-81). Three patients did not complete eight weekly cycles due to early progression (two patients), refusal after grade III fatigue (one patient). The toxicities reported by these three patients were included in the overall analysis of toxicity and they were considered as progressions in the intention-to-treat analysis of response. The baseline clinico-pathologic characteristics of the 42 patients are reported in Table 1. At the end of the treatment program, the best intention-to-treat overall response rate in the 42 patients was 45.2% (95% CIs: 30–56%) with two complete responses (4.7%), 17 partial responses (40.5%), 13 stable diseases (31.0%) and 10 progressions (23.8%), for an overall tumor rate control (responses plus stabilizations) of 76.2% (32 patients) (Table 2).

The complete responses were obtained in local disease plus lymphnodal metastases and in liver disease. In all, 15 patients had partial response after eight weekly cycles and two other patients with initial stable disease showed partial response after 14 cycles.
In the whole group, the median response duration was 5.3 months (95% CIs: 2.13 - 7.34), the median time to disease progression was 5.0 months (95% CIs: 3.75 - 6.25) and the median survival time was 9.0 months (95% CIs: 6.18 – 11.82) (Table 3). Time To Progression (TTP) and Overall Survival (OS) were assessed by Kaplan-Meier-Analysis shown in Figure 1 and 2.

Safety

42 patients received a total of 540 treatment cycles. The median number of cycles administered was 12 (range, 3 to 24 cycles). The median cumulative doses in each patient were 480 mg/m² (range, 80 to 960 mg/m²) for oxaliplatin, 6,350 mg/m² (range, 1,150 to 12,200 mg/m²) for 5-FU, and 1,500 mg/m² (range 250 to 3,000 mg/m²) for FA. Toxicity was generally mild and every grade of haematologic and nonhaematologic toxicities per patient is reported in Table 4. 42 patients were included in the safety analysis. Toxicity was generally mild and only three patients discontinued treatment because of treatment related adverse events. Two refused for persistent grade 3 fatigue and the third discontinued for persistent grade 3 neurotoxicity. At all, 3 patients (7.1%) experienced grade 3 fatigue, 1 patient (2.4%) showed grade 3 neurotoxicity, 2 patients (4.8%) grade 3 neutropenia and another (2.4%) grade 3 mucositis resolved after 1 week delay. Two patients (4.8%) experienced one episode of grade 3 diarrhea resolved after dose reduction. No other grade 3-4 toxicities including peripheral neuropathy were reported in during the study and no toxic deaths occurred. Grade 2 nausea and fatigue resulted the commonest non-hematologic toxicity (both, 26.2% of patients). Other grade 2 non-hematologic toxicities were: diarrhea (16.6%), mucositis (11.9%), hyperbilirubinemia (7.1%) and neurotoxicity (11.9%). Two patients (4.8%) reported grade 2 thrombocytopenia, no patient reported grade 2 anemia. Overall, adverse events were reversible and manageable with dose reduction, dose delay or treatment interruption and with symptomatic treatment. Twenty four (57.2%) patients received full doses of all the drugs throughout the study. Dose reduction was required for 5-fluorouracil alone in 4 patients (9.5%), for oxaliplatin alone in 3 patients (7.1%), and for both agents in 11 patients (26.2%). The majority of dose reductions were by one level (reduction to 75% of starting dose of fluorouracil and/or of oxaliplatin). Only three patients (7.1%) required a second level dose reduction, to 50% of starting dose of 5-fluorouracil and/or of oxaliplatin. Adverse events most commonly leading to dose
reduction were fatigue and neurotoxicity. The incidence of dose reductions was similar in the subgroups of male and female patients. Only three patients (7.1%) reported a toxicity-related withdrawal with median time to toxicity-related withdrawal of 3.9 months (range: 1.8 – 6 months). The median time to reduction was 2 months (range: 1.0 – 5.3) and the median time to first delay was 1.3 months (range: 0.5 – 3) (Table 5).
Discussion

Gastric carcinoma often occurs in the 60th and 70th decades. The elderly population is expanding and, from the early 1990s, one-quarter of newly diagnosed gastric cancer patients are over 80 years of age (12), but large trials of palliative chemotherapy in elderly patients are almost lacking. To the best of our knowledge, six phase II studies have been published in international journals (13-18). In five of these trials, chemotherapy consisted of leucovorin-modulated 5-fluorouracil in combination with cisplatin, epi-doxorubicin, etoposide or mitomycin-C. A phase II study investigated the toxicity profile and the activity of single-agent doxifluridine (18). In general, the tumour control rate reported was promising and no toxic death was observed across all studies. Unfortunately, these trials often enrolled patients with concomitant illnesses, poor performance status and short life expectancy and consequently, the results in term of survival and safety were heterogeneous and, often, deluding. More recently, Graziano F et (4) have reported the results of a large phase II trial investigating the weekly combination of cisplatin, 5-fluorouracil and folinic acid (PLF) in a population older than 65 year. The regimen showed promising tumour control rate and it was delivered to non frail elderly patients on outpatient basis. The non-haematological toxicity profile was moderate, but the reported haematological toxicity was that usually observed with cisplatin-based regimens. According to the treatment protocol, the 30 patients who experienced grade II/III neutropenia started filgrastim which was maintained until the end of the treatment program. Anaemia was recorded in 31 patients whose haemoglobin concentrations declined to a level of 10–12 g/dl in 26 patients and to 8–9.9 g/dl in 15 patients. Weekly and biweekly FU/FA/oxaliplatin regimens have been mainly explored so far in colorectal cancer with an encouraging efficacy profile. Biweekly combination has also been evaluated in a number of phase II studies in the first- (6,7, 19) and second- (20) line treatment setting of advanced gastric cancer with interesting efficacy and safety profiles. Based on these results, we conducted, for the first time in literature, a phase II study to explore the safety and efficacy of a weekly FU/FA/oxaliplatin in elderly (≥ 70 years old) advanced gastric cancer patients. Compared to PLF regimen, this new study included only ≥ 70 years old patients and produced significantly reduced haematological toxicity with a significant reduction of haematopoietic growth factors’ use. Moreover, in contrast to our results, significantly
higher rates of neutropenia and leucopenia were reported during other cisplatin and oxaliplatin-based protocols in advanced gastric cancer patients (38% and 29%; WHO grade 3/4 neutropenia and 19% and 10% WHO grade 3/4 leucopenia, in ECF and FOLFOX 6 regimens, respectively) (21,19). The absence of any grade 4 toxicity reported in the present study is very important for this setting of elderly population. The overall response rate analysed in 42 assessable patients treated with OXALF was 45.2%, including two CRs (4.7%) and 17 PRs (40.5%), and is comparable to the results reported from studies using FAMTX, ECF, ELF, and FOLFOX6 (22,23,19) and with the results from the study by Graziano F. in the elderly population (4). The median TTP of 42 patients included in this study was 5.0 months, and the median OS was 9.0 months. These results are comparable to those reported from standard combination regimens such as ECF, ELF, CF, and FAMTX (22, 23), but also with those reported from oxaliplatin-based regimens (6). Moreover, our results are comparable with those obtained by Graziano F. et al. (4) with the PLF regimen. As a result of the low toxicity profile and the good activity OXALF represents an active and well-tolerated treatment modality for elderly patients with locally advanced and metastatic gastric cancer and let us to consider further evaluation of the phase II data in randomized multicenter and multimodality trials.
References


patients with advanced gastric cancer: the Japan Clinical Oncology Group study (JCOG 9410). *Jpn J Clin Oncol* **32:** 90–94


Figure 1

Median OS (95% C.I.): 9,00 (6,18 - 11,82)
Median TTP (95% C.I.): 5.00 (3.75 - 6.25)
Additional files provided with this submission:

Additional file 1: table OXALF.doc : 46Kb
http://www.biomedcentral.com/imedia/604550759009496/sup1.DOC