Cancer Chemother Pharmacol (2005) 56: 563–568
DOI 10.1007/s00280-005-1024-1

ORIGINAL ARTICLE

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Gemcitabine (GEM) plus oxaliplatin, folinic acid, and 5-fluorouracil (FOLFOX-4) in patients with advanced gastric cancer

Received: 4 October 2004 / Accepted: 7 January 2005 / Published online: 23 July 2005

Abstract Background and aims: oxaliplatin in combination with folinic acid (FA) and infusional 5-fluorouracil (5-FU) has shown significant anti-tumor activity in gastric cancer patients (FOLFOX). Previous studies have shown that gemcitabine (GEM), a new fluorinated anti-metabolite, enhances the individual anti-tumor activity of either 5-FU or oxaliplatin. We have therefore designed a multi-center phase II trial in order to test a novel GEM + FOLFOX-4 regimen in patients with metastatic gastric cancer. Methods: we enrolled 36 patients, 28 males and 8 females, with an average age of 64.4 years (range 37–78), who received bi-weekly treatment with GEM (1,000 mg/m^2 on day 1), levo-FA (100 mg/m^2 on days 1 and 2), a 5-FU (400 mg/m^2) bolus injection followed by 22-h continuous infusion (800 mg/m^2) on days 1 and 2, and oxaliplatin 85 mg/m^2 in a 4–6 h intravenous (i.v.) infusion before the second FUFA administration on day 2. Results: the most frequent side effect was grade 1–2 hematological toxicity and late sensorial neurotoxicity. Two patients developed hypersensitivity to oxaliplatin while another developed an aseptic eosinophilic pneumonitis. Two patients refused to continue the treatment after two cycles of chemotherapy and were lost at the follow-up. Among the remaining 34 patients four achieved a complete response, 15 a partial response, 12 had a stable disease and three progressed. Conclusions: these results may grant the rationale to evaluate this multi-drug combination in randomized phase III trials in advanced gastric cancer.

Keywords Gastric cancer · Gemcitabine · Oxaliplatin · 5-Fluorouracil · Folinic acid

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Introduction

Gastric carcinoma is one of the most common malignancies and even though its incidence is progressively decreasing worldwide, it still remains one of the principal causes of death due to cancer [1]. The prognosis for these patients is in fact very poor and the majority finally succumbs to disease progression and complications within 1 year [2]. Curative, radical surgery is possible only in the early stages and is associated with an 80% rate of loco-regional relapse and metastases; in addition, more than 50% of these patients are currently diagnosed with stage III–IV disease [3] with a poor performance status which prevents any kind of surgery or treatment. For almost 50 years the fluoropyrimidine, 5-fluorouracil (5-FU) has been the most used drug for the treatment of advanced gastric cancer; it was able to induce only few objective responses and showed a minimal effect in prolonging the life of these patients [4, 5]. The anti-tumor activity and effectiveness of 5-FU has subsequently been improved by combining it with bio-modulators such as folinic acid (FA) or with other cytotoxic drugs such as cisplatin (CDDP), etoposide, anthracyclines, mitomycin-C or methotrexate, which had shown a minimal anti-tumor activity when used in mono-chemotherapy [6–9],

and more recently, when used as pro-drug, in different oral formulations (capecitabine or UFT).

Among all the possible combinations, the two regimens designated as ECF (epirubicin, cisplatin, and infusional 5-FU) and FP (cisplatin and 5-FU) are nowadays accepted as the standard palliative treatments for advanced gastric cancer [10, 11]. Several studies have reported on the latter combination's contrasting results in term of response rate (20–70%) with a median survival of 6–8 months. Both treatment schedules are associated with significant mucosal toxicity, leucopenia, and anemia and can be utilized only on patients with a good performance status [12, 13]. More recently, new drugs such as taxanes (paxlitaxel and docetaxel), type 1 topoisomerase inhibitors (CPT-11), are being tested for the treatment of gastric cancer alone or in combination with 5-FU or cisplatin [14–17]; preliminary results of some of these studies have reported encouraging results especially for the two multi-drug regimens designated as DCF (docetaxel, cisplatin, and 5-FU) and IF (CPT-11 and 5FU) [14–17] which surely deserve to be better investigated in phase III trials than the standard treatment platinum and 5-FU ± anthracyclines. Among the newest drugs, a significant anti-tumor activity with a very low level of toxicity in the first/second line treatment for advanced gastric cancer has been more recently shown for the novel diaminocyclohexane (DACH) carrier ligand-based/platinum compound, oxaliplatin, alone or in combination with 5-FU and FA (FUFA) [17–19]. In conclusion, multiple studies investigating different chemotherapeutic agents and regimens, have demonstrated that chemotherapy is definitely superior to the best supportive care in patients with advanced gastric carcinoma even though its impact on patient clinical outcome and survival is minimal and definitely needs to be improved. We believe that in addition to the continuous discovery of new and more active drugs, the design of more active multi-drug regimens designed on the results of pharmacological and translational studies could certainly improve the clinical response rate and survival in these patients. In this context, based on the preclinical results of previous studies demonstrating that the difluorinated analogue of deoxy-cytidine difluoro-2′,2′-deoxycytidine also designated as gemcitabine (GEM), synergistically interacts with 5-FU [20–24] as well as with oxaliplatin in terms of anti-tumor activity in vitro [25], we investigated in patients with advanced gastric carcinoma the anti-tumor activity and toxicity of a novel triplet multi-drug regimen combining GEM with oxaliplatin, and FUFA administered following the schedule proposed by de Gramon [26] and designated as FOLFOX-4.

The combination of GEM and 5-FU administered by using different schedules and dosages has already shown a significant anti-tumor activity in patients with different gastroenteric malignancies [21–24, 27–29] including gastric cancer. In addition, based on the same preclinical rationale, we have recently concluded a phase I–II clinical trial testing in patients with advanced colorectal carcinoma the same GEM plus FOLFOX-4 regimen (designated as GOLF), identifying the most effective doses of the four drugs in combination, and reporting a significant anti-tumor activity also in patients who had received one or two previous lines of chemotherapy with very low level of toxicity [30].

Considering the significant anti-tumor activity of different FOLFOX regimens in gastric cancer patients, the bio-modulating activity of GEM on either oxaliplatin and 5-FU and the low level of toxicity of the GEM + FOLFOX-4 (GOLF) schedule, we have decided to investigate in a multi-center Phase II trial the anti-tumor activity of the latter combination in patients with advanced gastric cancer and poor prognosis.

Materials and methods

Eligibility criteria

The inclusion criteria required a histological diagnosis of gastric carcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3, a life expectancy >3 months, normal renal and liver function, a white blood cell count $>2{,}500$ cells/mm^3, hemoglobin >9 g/dl, platelet cell count $>100{,}000$ cells/mm^3, a cardiac ejection fraction $>46\%$, and a normal electrocardiogram. The exclusion criteria included heart, liver or kidney failure, cardiac valvular and wall motion abnormalities, central nervous system involvement, second tumors, active infectious disease, or a history of cardiovascular disease. The study was approved by our local (University) ethics Committee, and respected the guidelines for good clinical practice. All the patients gave their written informed consent. The trial was designed to test the hypothesis that the GEM + FOLFOX 4 combination is tolerated and active in the treatment of gastric cancer. A minimum of 25 patients was required in order to maintain an alpha and beta error of 0.05 and 0.2.

Clinical assessments

A complete history was taken, and a physical examination, complete blood count, and serum chemistry evaluation were performed at the baseline. Complete disease staging by chest X-ray, chest, and abdominal computed tomography, and liver and pelvis ultrasonography was undertaken at the baseline and every 2 months. All the eligible patients were evaluated for survival toxicity, and response. The patients continued the treatment until the onset of unacceptable toxicity or disease progression for a maximum of 12 cycles.

Response criteria

Response and toxicity were assessed according to standard World Health Organization criteria [World Health Organization, 1979].

Results

Clinical trial design, patient characteristics, and treatment schedule

This trial involved patients with advanced gastric cancer and was aimed to test the toxicity and anti-tumor activity of GEM + FOLFOX-4 combination. The trial protocol foresaw early trial discontinuation in the case of unacceptable toxicity or if no clinical response was observed in the first 12 patients. All the patients were administered with GEM plus oxaliplatin, FA, and 5-FU, administered in accord with the previously described GOLF schedule [30]. All the patients received 1000 mg/m^2 of GEM, in a 30-min intravenous (i.v.) infusion on day 1, before any other drug; subsequently, they received levo-FA 100 mg/m^2 in a 30-min i.v. infusion on days 1 and 2; 5-FU 400 mg/m^2 in a 30-min i.v. infusion, followed by a 22-h continuous infusion (800 mg/m^2) on days 1 and 2; and oxaliplatin 85 mg/m^2 in a 2–4 h i.v. infusion before the second FUFA administration on day 2. The treatment was repeated every 15 days. The trial population consisted of 36 patients (28 males and 8 females), with an average age of 64.4 years (range 37–78). They all had a histological diagnosis of gastric carcinoma: 24 had undergone a radical resection of the primary tumor and were in an advanced stage of the disease at the time of the enrolment. Their ECOG performance status ranged from 0 and 3, and their life expectancy was longer than 3 months. Five patients had previously received at least one other previous line of treatment. Other patients' characteristics are shown in Table 1.

Table 1 Patients' characteristics

Characteristics	Number of patients
Patients evaluable for response	36
Patients evaluable for toxicity	36
Age (years)	
Median 64.4 years (range 37–80)	
Sex	
Male	28
Female	8
Performance status (ECOG)	
0	6
1	5
2	14
3	11
Histology	
Tubular adenocarcinoma	13
Poorly differentiated carcinoma	12
Mucinous adenocarcinoma	11
Previous treatment	
None	29
One line of chemotherapy	3
More than one line of chemotherapy	2
Disease extension	
Stage IV	36
Metastatic (A + B)	
(A) Liver	16
(B) No liver (nodes + ovary + lung + pleura + peritoneum)	20

Toxicity profile

A total of 220 chemotherapy cycles were administered (a median range of six cycles per patient: range 2–12 cycles). No treatment delay due to neutropenia or thrombocytopenia was required. Moderate and severe asthenia was reported during the second week of treatment. Grade 1–2 hematological toxicity with moderate anemia, neutropenia, and thrombocytopenia was the most common adverse event. No persistent thrombocytopenia was observed after multiple cycles of chemotherapy. None of these patients experienced increased creatinine or blood urea nitrogen, or hypotension. Sixteen patients manifested gastroenteric toxicity with reversible mucositis, nausea/vomiting and diarrhea, and two reversible grade 1–2 peripheral neurotoxicity. Four patients developed hypersensitivity to oxaliplatin, and two of them, starting with the ninth and tenth cycle, had to complete the treatment without the oxaliplatin administration. Another patient during the treatment developed an aseptic eosinophilic pneumonitis completely resolved after appropriate treatment with desametazone. There were no toxicity-related dose reductions or toxic deaths (Table 2).

Response and survival

This study was designed with *intent to treat*, thus all 36 patients were considered for response rate and time to progression. Two of them refused to continue the therapy after two treatment cycles and were lost at the follow-up before any restaging; among the remaining 34 patients, 4 achieved a complete response, 15 a partial response, and 11 a stable disease with clinical benefit improvement. Only three out of 36 suffered an early disease progression just after four cycles of chemotherapy. The clinical response rate (CR + PR) and the disease control rate were, respectively, (CR + PR + SD) 52.8 and 86.1%, while the time to progression and the overall survival were, respectively, 5 and 11 months (Table 3).

Discussion

In this study we report the results of a multi-center Phase II study testing a novel triplet combination of GEM + FOLFOX-4 in patients with very advanced gastric cancer and a very poor prognosis, showing a low level of toxicity and a high rate of responses and disease stabilizations with an effective improvement in clinical benefit. We also report an average time to progression of 5 months (eight in the responsive patients) with 40% of patients alive 1 year after the beginning of treatment. In our study, there was no age limitation and also were included patients with poor performance status (ECOG 2–3) some of whom, despite the very poor prognosis,

Table 2 World Health Organization (WHO) toxicities (number of patients = 36)

	Number of events (%)	Grade 1 *N* (%)	Grade 2 *N* (%)	Grade 3 *N* (%)	Grade 4 *N* (%)
Hematological	15				
Anemia	4	2	2		
Neutropenia	6	1	2	3	
Thrombocytopenia	5	3	2		1
Gastroenteric toxicity	16				
Nausea/vomiting	4	1	3		
Diarrhea	6	2	3	1	
Mucositis	5	2		4	
Transaminase elevation	None				
Fever	12	3	6	3	
Asthenia	5			5	
Anorexia	None				
Neurological toxicity	2		2		
Arrhythmia	2		2		
Hypersensitivity	4	1	1	2	

A total of 220 chemotherapy cycles were administered (a median range of six cycles per patient: range 2–12 cycles).

Table 3 Clinical response of advanced gastric cancer patients to gemcitabine, oxaliplatin, and infusional levo-folinic acid and 5-fluorouracil (GOLF) multi-drug chemotherapy

Patients enrolled in the study	36 (100%)
(A) Complete responses	4 (11.1%)
(B) Partial responses	15 (41.7%)
Objective response rate (A + B)	19 (52.8%)
(C) Disease stabilizations	12 (33.3%)
Disease control rate (A + B + C)	31 (86.1%)
(D) Progressive diseases	3 (8.3%)
Lost at the follow-up	2 (5.6%)
Time to progression	5 months (95% IC, 2.63–6.9 months)
Time to progression in the responsive patients	8 months
Overall survival	11 months (95% IC, 7–13 months)

Two patients were non-evaluated as they refused to continue the treatment and were lost at the follow-up.

showed a clinical improvement and in some cases an objective response.

In the last 10 years several poly-chemotherapy treatments have been shown to have activity against gastric cancer; among them, those based on the use of 5-FU and cisplatin (ECF, PELF, and FP) have shown the best range of response and survival and are currently considered as the standard treatments for these patients [9–14]. Newest drugs such as campothecins, oxaliplatin, and taxanes, combined in different schedules of treatments with 5-FU [±FA], have shown promising results in terms of anti-tumor activity and toxicity profile but so far have not been compared in phase III trials and therefore have not yet shown superiority to the standard treatments [14–18]. These treatment regimens determine high rate of objective responses and are considered effective in prolonging the survival from 3–5 (with best supportive care) up to 9–10 months even though they are complicated by significant side effects (mucosal and hematological toxicity) and very rarely determine a significant improvement in the quality of life of these patients. The majority of these studies have not been conducted in high risk patients with poor performance status and/or older than 70 years. We believe this is an important tool as it should be considered that gastric cancer is not as much chemo-refractory as other gastroenteric malignancies, but very often a large percentage of these patients come to the physician with a very poor performance status due to significant dysfunctions of the digestive tract, often in advanced state of cachexia and other deep metabolic, electrolytic and hematological imbalances. These patients are very often excluded by any systemic chemotherapy and clinical trials testing newer drugs and drug combinations as they are considered unable to sustain a possible toxicity related to the most commonly employed drugs. Based on the results of the most recent trials showing that chemotherapy may be useful also in elderly patients [31], the improved techniques of best support care and the availability of drugs such as GEM, taxanes, or oxaliplatin which have less toxicological profile, we believe that few of these patients should be excluded.

Our translational investigation has been designed on the basis of previous preclinical and clinical studies demonstrating a possible positive interaction of GEM with either 5-FU or oxaliplatin. GEM is a difluoro-2′,2′-deoxy-cytidine that requires activation through the synthesis of its phosphorylated metabolites and acts by inducing DNA damage, by blocking the DNA repair system and affecting the deoxy-nucleotide synthesis [32–34]. The rationale of our multi-drug combination resides on the knowledge that GEM, induces major alterations in the pharmacodynamics, pharmacokinetics, and anti-tumor activity of 5-FU [20–24, 27–29] and oxaliplatin [25, 30, 32–37] that may lead to positive anti-tumor results also in gastric cancer patients. We also found that GEM, used at concentrations potentially achievable in patients, is able to enhance the cytotoxic, and pro-apoptotic activity of oxaliplatin and FUFA combination. The anti-tumor effects in vitro of the GEM, oxaliplatin, and 5-FU

regimen designated as GOLF was far greater than those induced by the combinations of GEM/5-FU, oxaliplatin/GEM or oxaliplatin/5-FU (unpublished data). In parallel, other groups also showed that GEM can also have supra-additive anti-tumor activity when used in combination with oxaliplatin [32–37]. This effect, found in various tumor cell lines in vitro, has been explained on the ground that GEM blocks the nuclear mechanisms used by cancer cells to remove oxaliplatin adducts and to allow DNA repair [35–37] with consequent induction of apoptosis. In regard to the clinical rationale, previous studies have shown the potential benefit of oxaliplatin + FUFA (FOLFOX-6) also in gastric cancer patients [19]. So far, single agent GEM anti-tumor activity in patients with gastric cancer is unexplored; this drug in fact, has never been extensively studied in gastric cancer as well as in other common cancer like colon cancer on the basis of the first enthusiastic results obtained in NSCLC and pancreas carcinoma that allowed this drug to move very rapidly from phase I/II to phase III trials in these very refractory malignancies [32, 33, 37]. In our study however, the addition of GEM to 5-FU and oxaliplatin, has been considered on the bases of its bio-modulating activity on both drugs that may result in an enhanced anti-tumor activity. A previous study of our group has also shown the excellent safety profile of the GEM + FOLFOX-4 combination and the significant anti-tumor activity as second line of treatment in colon cancer patients [30]. In conclusion, the GEM + FOLFOX-4 combination seems to be promising for the treatment of advanced gastric carcinoma and deserves to be studied in neoadjuvant setting and larger phase III clinical trials in order to investigate its real impact on the survival of these patients.

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