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ORIGINAL ARTICLE

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Bi-weekly chemotherapy with cisplatin, epirubicin, folinic acid and 5-fluororacil continuous infusion plus g-csf in advanced gastric cancer: a multicentric phase II study

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Abstract *Background*: It has been demonstrated that the 3-weekly PELF regimen is superior to FAM and FAMTX in advanced gastric cancer. The aim of this multicentric phase II study was to evaluate the efficacy and tolerability of a PELF regimen, given every 2 weeks as a first-line therapy in patients with unresectable or metastatic gastric carcinoma. *Methods*: Fifty-nine patients were treated with the following schedule: cisplatin (40 mg/m^2, day 1), epirubicin (30 mg/m^2, day 1), 5-fluorouracil (400 mg/m^2 bolus, followed by 600 mg/m^2, 22 h continuous infusion, day 1 and 2) and folinic acid (100 mg/m^2, 2-h infusion, day 1 and 2). G-CSF (5 μg/kg) was administered on day 6, 8, 10, and 12. Cycles were repeated every 2 weeks for a maximum of twelve courses. *Results*: Of the 52 evaluable patients, three (5.8%) complete responses, and 15 (28.8%) partial responses were observed, for an overall response rate of 34.6%. The median duration of response was 8 months. Nineteen patients had stable disease and 15 progressed on therapy. At a median follow-up of 12 months, the median time to progression was 8 months and the median survival duration was 13 months, with a 1-year survival rate of 53.5%. Grade 3 or 4 observed toxicities were: neutropenia in 26 patients (44%), thrombocytopenia in four patients (6.7%), and mucositis in seven patients (11.9%). *Conclusions*: The bi-weekly PELF regimen seems to be feasible with an acceptable toxicity profile and an activity comparable to the 3-weekly schedule.

Keywords Advanced gastric cancer · Chemotherapy · PELF · Bi-weekly

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Introduction

Locally advanced, recurrent or metastatic gastric cancer remains one of the major causes of cancer death worldwide. Although several active regimens have been investigated in the last decade, the median survival is still really poor, ranging from 6 months to 8 months [1]. The Italian Oncology Group for Clinical Research (GOIRC) developed in 1994 a cisplatin, epirubicin, fluorouracil and folinic acid regimen (PELF), which seemed to be a feasible and active combination in advanced gastric cancer [2]. Two randomized trials comparing PELF with FAM (fluorouracil, doxorubicin and mitomycin-C) [2] and FAMTX (fluorouracil, doxorubicin and methotrexate) [3] have been conducted. These two latter regimens were considered as standard in 1980s and 1990s, respectively. It has been reported that the PELF is sig-

nificantly more effective than both control arms in inducing objective responses (43% vs. 15%, $P = 0.001$ vs. FAM; 39% vs. 22%, $P = 0.009$ vs. FAMTX) without any differences in overall survival (OS) (8.1 vs. 5.6 months, $P = 0.24$ vs. FAM; 7.7 vs. 6.9, $P = 0.19$ vs. FAMTX) and time to progression (TTP) (4.7 vs. 2.6 months, $P = 0.58$ vs. FAM; 5.9 vs. 3.5, $P = 0.34$ vs. FAMTX). No significant differences in toxicity were observed between PELF and FAMTX, but PELF combination was more toxic compared with FAM (WHO grade 1–4, nausea/vomiting $P = 0.03$, diarrhea $P = 0.01$). In a phase II study, a weekly intensive PELF regimen with G-CSF support has also been investigated. An overall response rate (ORR) of 62% was achieved, without any additional toxicity compared with the 3-weekly schedule [4].

The increase of 5-fluoruracil dose intensity, achieved with the adjunction of continuous infusion (De Gramont schedule), has been found to be associated with an improvement of activity in colorectal cancer [5]. This schedule has also been investigated alone [6] and in combination with cisplatin [7] or cisplatin plus mitomycin-C [8] in advanced gastric cancer. Based on these results, we conducted a phase II study in order to evaluate the tolerability and the activity of bi-weekly PELF regimen, including an infusional fluorouracil administration according to De Gramont schedule.

Materials and methods

Patient selection

The protocol was conducted according to the guidelines of the Helsinki declaration. Patients with previously untreated, locally advanced or metastatic, histologically confirmed, gastric adenocarcinoma were eligible for the study. Patients were also required to have no previous chemo- or radio-therapy, age≥18, WHO Performance Status (PS) ≤ 2, adequate hepatic (serum bilirubin < 1.5 mg/dl; AST, ALT < 1.5 times the upper limit of normal), renal (serum creatinine < 1.5 mg/dl or estimated creatinine clearance > 50 cc/min), and bone marrow function (hemoglobin > 9 g/dl; ANC $> 1{,}500$ cells/μl; PLT $> 100{,}000$ cells/μl); absence of symptomatic brain metastases, and no other second malignancies. Patients were required to have bi-dimensional measurable disease, possibly at CT scan. Patients with non-measurable disease were not included for response evaluation, but they were assessed for toxicity and survival analysis. A written informed consent of all patients according to the rules and regulations of the individual participating institutions was obtained.

Chemotherapy

The regimen consisted of cisplatin (DDP) 40 mg/m^2 intravenous (i.v.) day 1, epirubicin (Epi) 30 mg/m^2 i.v. day 1, folinic acid (FA) 100 mg/m^2 i.v. day 1 and 2 as a 2-h infusion, followed by 5-fluorouracil (5-FU) 400 mg/m^2 bolus i.v. and 5-FU 600 mg/m^2 i.v. in continuous infusion of 22 h, day 1 and 2. To receive continuous infusion, patients were required to implant a central venous port-a-cath, connected with external delivery devices. No anti-thrombotic prophylaxis was suggested; anti-thrombotic therapy was allowed during treatment. Chemotherapy was recycled every 2 weeks. As a planned part of treatment, patients had to receive G-CSF support 5 μg/kg subcutaneously injection on day 6, 8, 10 and 12 after each chemotherapy administration [9]. Adequate pre-DDP hydration according to investigational center practice was used. Acute antiemetic treatment consisted in dexamethasone 12 mg i.v. and 5 HT-3 antagonists before DDP infusion. Delayed antiemetic treatment was delivered according to physician's practice. Treatment was planned for 12 courses and interrupted if unacceptable toxicity or disease progression occurred, or on patient refusal.

Evaluation of toxicity and response

Treatment toxicity was evaluated following the National Cancer Institute Common Toxicity Criteria (NCI–CTC version 2.0). In the event of toxicity, chemotherapy administration was delayed by a week or until full recovery in case of WBC $< 3{,}000$/mcl, ANC $< 1{,}500$/mcl, platelet count $< 100{,}000$/mcl. Patients who experienced febrile neutropenia or sepsis, requiring intravenous antibiotics received a dose reduction of 25%. For grade 4 events, a 25% reduction of the dose was required. Grade 4 gastrointestinal toxicity required hospital admission for intravenous hydration. Grade 3 or 4 peripheral neuropathy required interruption of all therapy until adverse effects had resolved (to a maximum of grade 1).

Overall response rate (ORR) was recorded according to the World Health Organization (WHO) criteria [10], and was planned to be performed after 6 cycles (12 weeks), at the end of chemotherapy and every 3 months during follow-up. Clinical response were assessed using the following criteria: (1) complete response (CR), the disappearance of all lesions, symptoms and biochemical changes related to gastric cancer for a period of > 4 weeks during which no new lesions appeared, (2) Partial response (PR), a reduction of $> 50\%$ in the sum of the products of perpendicular diameters of all measured lesions lasting > 4 weeks during which no new lesions appeared and no existing lesions increased in size, (3) Stable disease (SD), a reduction of $< 50\%$ or an increase of $< 25\%$ in the sum of the products of two perpendicular diameters of all measured lesions lasting > 4 weeks during which no new lesions appeared, (4) Progressive disease (PD), an increase of $> 25\%$ in the product of two perpendicular diameters of any measured lesion over the dimensions at study entry, or the appearance of new areas of malignant disease.

Statistical design

The primary end-points of this multicentric phase II study were to evaluate the safety and the activity (ORR) of the combination of DDP, Epi, FA and 5-FU bolus and continuous infusion in a bi-weekly schedule. Time to progression (TTP) (time expressed in months between the first day of protocol treatment and the day of disease progression) and overall survival (OS, time expressed in months between the first day of chemotherapy infusion and death or last follow-up) were considered as secondary end-points. All patients enrolled received at least one treatment cycle and were considered the intention-to-treat population (ITT). This population was evaluated for the activity and safety analysis. This study followed the optimal two-stage design as described by Simon [11]. The trial was designed to demonstrate with 90% probability, an ORR ranging between 20% and 35% at the significant level of 5%. To reach this goal, at the first stage 31 patients were needed with at least six responses, and at the second stage, with a sample size of 53 patients, 15 responses were needed.

Results

Between April 2001 and October 2003, 59 consecutive patients were enrolled onto this study by coinvestigators from four Medical Oncology Centers. Patients characteristics are listed in Table 1: the median age at diagnosis was 62 (range, 31–80 years), 42 (71.2%) were male, most of the enrolled patients were in good performance status as PS was 0–1 in 53 (89.8%), 28 (47.5%) underwent surgery for palliative (13) or curative (15) intent. Patients undergone palliative surgery started chemotherapy after a median time of 2 months (range, 1–3), while patients undergone curative surgery after 5 months (range, 1–53). Only 5% of patients (three) had locally advanced disease, and five patients had non-measurable disease (8.5%). At June 2004, the median follow-up from the treatment beginning was 12 months (range, 2–34).

Table 1 Patient characteristics

	No. of patients (total: 59)	Percent
Age		
Median (range)	62 (31–80)	
Gender		
Male	42	71.2
Female	17	28.8
Performance status (WHO)		
0	38	64.4
1	15	25.4
2	6	10.2
Stage		
III	3	5.1
IV	56	94.9
Site of metastasis		
Liver	29	49.1
Lymph-nodes	25	42.4
Peritoneum	11	18.6
Lung	6	10.2
Other	9	15.2
No. of organ involved		
1	19	32.2
2	22	37.2
≥3	13	22
Prior surgery		
None	31	52.5
Curative/palliative	28	47.5
Assessability of disease		
Measurable	54	91.5
Non-measurable	5	8.5

Toxicity

Fifty-nine patients received a total of 483 cycles, with a median of eight per patient (range, 2–12), and were evaluated for toxicity. In particular, 30 patients received not more than eight cycles: of these, 18 stopped treatment for PD (three were not evaluable for response), two patients interrupted therapy for serious adverse events onset (thrombosis of sinus cavernosus and CNS cerebrovascular ischemia), one patient died before response evaluation after the sixth cycle, and nine patients discontinued chemotherapy for grade 3 and 4 toxicity. Toxicity results for patients and cycles are listed in Table 2. Thirty-seven patients (63%) underwent a long treatment without any dose modification. Twenty-two patients (37%) underwent a dose modification for toxicity. Median relative administered dose was 0.92. We observed mainly haematological toxicities. Thirteen patients experienced grade 4 neutropenia (22%), 13 patients experienced grade 3 neutropenia (22%), and four patients had grade 3 thrombocytopenia (6.8%); two (3.4%) and three (5.1%) patients had grade 3 febrile neutropenia and anemia respectively. Non-haematological toxicities were uncommon and moderate with only one neurorotoxicity of grade 2 (moderate pain interfering with function) after nine cycles, with DDP administration suspension. Five patients (8.5%), two (3.4%) patients experienced grade 3 and 4 mucositis respectively. Other relevant toxicities were grade 3 vomiting (three patients, 5.1%) and grade 3–4 asthenia (two patients, 3.4%, and one patient, 1.7%). Only one patient experienced grade 3 cardiotoxicity (medication-controlled atrial fibrillation). Three adverse events considered as grade 3 neurological and vascular toxicity were observed: two patients experienced an episode of CNS cerebrovascular ischemia (TIA, transitory ischemic attack), followed by complete clinical recovery; one patient with thrombosis of sinus cavernosus stopped chemotherapy and underwent specific anti-coagulant treatment. The onset of these events is still unclear, eventually due to a cancer-related hypercoagulable state or to the effect of chemotherapy. One chemotherapy-related death occurred in a patient, who experienced a fatal heart attack one day after the end of the eighth cycle.

Table 2 WHO common toxicity criteria in 59 patients and 483 courses

	Grade							
	1		2		3		4	
	Patients/courses	Percent	Patients/courses	Percent	Patients/courses	Percent	Patients/courses	Percent
Hematologic toxicity								
Anemia	9/21	15.3/4.3	10/22	16.9/4.6	3/3	5.1/0.6	–	–
Leucopenia	17/27	28.8/5.6	15/12	25.4/2.5	10/6	16.9/1.2	–	–
Neutropenia	1/6	1.7/1.2	7/22	11.9/4.6	13/29	22/6	13/13	22/2.7
Thrombocitopenia	7/25	11.9/5.2	5/7	8.5/1.4	4/5	6.8/1	–	–
Nonhematologic toxicity								
Nausea	11/38	18.6/7.9	10/13	16.9/2.7	2/2	3.4/0.4	–	–
Vomiting	5/16	8.5/3.3	7/10	11.9/2.1	3/5	5.1/1	–	–
Diarrhea	9/11	15.3/2.3	2/2	3.4/0.4	1/1	1.7/0.2	–	–
Mucositis	2/13	3.4/2.7	5/13	8.5/2.7	5/6	8.5/1.2	2/2	3.4/0.4
Neurotoxicity	1/1	1.7/0.2	2/4	3.4/0.8	–	–	–	–
Asthenia	12/29	20.3/6	6/8	10.2/1.7	2/2	3.4/0.4	1/1	1.7/0.2

Table 3 Overall response rate (ORR)

	Patients	I.T.T. 59 (95% CI)	Evaluable 52[a] (95% CI)
Complete response (CR)	3	5.1% (0–10.7%)	5.8% (0–12.1%)
Partial response (PR)	15	25.4% (14.3%–36.5%)	28.8% (16.5%–41.2%)
Stable disease (SD)	19	32.3% (20.3–44.1%)	36.5% (23–49.6)
Progressive disease (PD)	15	25.4% (14.3–36.5%)	28.8% (16.5–41.2%)
Overall response rate (ORR)	18	30.5% (18.8–42.3%)	34.6% (21.7–47.5%)

[a]Patients excluded: five owing to non-measurable disease, one lost to follow-up and another patient dead for non-chemotherapy-related before response evaluation
I.T.T.: intention to treat; CI: confidence intervals

Response and survival

Activity results are listed in Table 3. Out of 59 patients 52 were evaluable for tumor response; seven patients were excluded from the ITT population for the following reasons: non-measurable disease in five patients, one patient was lost to follow-up and another patient for death, not related to chemotherapy before response evaluation. Objective tumor response was achieved in 18 patients, with an ORR of 30.5% (95% CI 18.8–42.3%) in the ITT analysis; three patients reached CR (5.1%, 95% CI, 0–10.7%). In the evaluable patients analysis, objective tumor response was 34.6% (95% CI 21.7–47.5%), and CR was obtained in 5.8% of patients (95% CI, 0–12.1%). Median response duration was 8 months (range, 1–13). None of the patients who achieved response underwent surgery (one patient with PR actually refused surgical treatment). Twenty-two patients (37.3%) received second-line chemotherapy: of them, two patients achieved CR in the first-line treatment, four patients PR, five patients had SD, while six patients showed progression and five patients were not evaluable for response. Median TTP and OS were 8 months (95% CI 5–11) and 13 months (95% CI 10–17) respectively. One-year TTP was 27.3%, and 1-year OS was 53.5%.

Discussion

To-date, no guidelines or consensus exist about the up-front treatment of advanced/metastatic gastric cancer patients. Based on randomized trials, three different regimens are commonly used: the combination of DDP, Epi, and 5-FU protracted infusion (ECF), standard in most of the European countries and US [12], the combination of DDP and 5-FU continuous infusion (CF), control arm in most of US trials [13], and the DDP, Epi and 5-FU modulated by FA (PELF) considered the reference regimen in Italy [2, 3]. In addition, Irinotecan-DDP is a fairly common utilized regimen [14]. We designed a multicentric phase II study, administering PELF as a bi-weekly schedule to obtain the 5-FU intensification.

The 3-weekly PELF schedule has demonstrated to be more active than the standard 1980s and 1990s regimens such as FAM and FAMTX, in terms of response rate, with a non-significant favorable trend in TTP and OS [2, 3]. To increase the activity and efficacy of this combination, a phase II study has investigated the intensification of all drugs in a weekly approach with G-CSF support, with promising results [4]. In our study, the intensification of 5-FU has been reached combining 5-FU bolus plus 5-FU continuous infusion as developed by De

Gramont et al. [5]. As described in advanced colorectal cancer, the combination of those two different modalities of 5-FU administration permits to improve activity and tolerability of such a drug. These clinical results have biologic roots, due to two different mechanisms of action: bolus 5-FU seems to interfere mainly with mRNA synthesis, while 5-FU continuous infusion does act in DNA synthesis pathway [15]. This 5-FU schedule allowed increasing the 5-FU dose intensity from 400 mg/m^2/week, as in a 3-weekly PELF regimen, to 1,000 mg/m^2/week, in our trial design. This 5-FU schedule has been investigated in a three published phase II study, alone [6] or in combination with DDP [7] and DDP plus mitomycin-C [8]; the results of these trials were encouraging in terms of both safety profile and activity.

Notwithstanding these promising perspectives, PELF administered as a bi-weekly schedule has demonstrated to have questionable activity and a toxicity profile less tolerable then expected in our subset of patients. In particular, the observed myelotoxicity (severe neutropenia) can be actually referred to the adjunction of bolus 5-FU, which is virtually absent in the infusional 5-FU administration. The ORR was 30.5% in the ITT population, and 34.6% considering only evaluable patients. CR rate was 5.1% and 5.8%, respectively. Although these response rates resemble those reported in two previously randomized trials using 3-weekly PELF as experimental arm [2, 3], it should be taken into account that a phase II trial could overestimate the obtained results by selection biases. Though not comparable, the slight difference in response rates in favor of a 3-weekly PELF, when indirectly compared with our schedule could be related to the relatively higher DDP and Epi dose intensity. In fact, higher response rates (62%) have actually been observed when DDP and Epi were strongly intensified in a weekly schedule plus G-CSF supply [4]. Even though the bi-weekly intensification of PELF did not show remarkable activity, the rate of patients showing SD (32.2% in ITT population, 36.5% in evaluable patients) and the median duration of response (8 months; range, 1–13) was encouraging. Furthermore, comparing indirectly our results with those coming from the phase II weekly schedule, we observed more patients with SD with a comparable duration of response [4].

In spite of the G-CSF use, hematological toxicity was not completely manageable. The G-CSF supply was considered necessary in order to switch from a 3-weekly to a 2-weekly schedule, but on every-other-day G-CSF administration, not considered as a standard option, was not able to avoid the neutropenic toxicity [9, 16, 17]. The conventional daily G-CSF administration would likely decrease the neutropenia rate. In our study, none of the patients experienced grade 4 leucopenia and febrile neutropenia. Grade 3 and 4 neutropenia were each observed in 22% of the cases, and grade 3 leucopenia occurred in 16.9% of patients. Grade 3 febrile neutropenia was seen in two patients (3.4%). However, no chemotherapy-related deaths due to hematological toxicity occurred. Grade 3 and 4 leucopenia with 3-weekly PELF is widely different in the randomized trials, which occurred in 7% and 2.5% respectively [2], 28.7% and 13.8% [3] of patients; no reasons are given in the last randomized trial to justify this data. An exhaustive overview of neutropenia and febrile neutropenia rates across randomized and weekly phase II studies is not actually possible, since these papers lack these data [2, 4] . The main grade 3–4 non-hematological toxicities were mucositis, nausea/vomiting and diarrhea. The gastrointestinal toxicity outline featured by mucositis (12.7%) rather than nausea/vomiting (grade 3 9.1% only) and diarrhea (grade 3 1.8% only) would likely be related to the adjunction of infusional 5-FU, which confers a different toxicity profile compared with bolus alone [5]. The two recorded vascular adverse events (1 TIA, 1 sinus cavernosus thrombosis) are not clearly to be considered as chemotherapy related; their onset could be due to the non-routinary use of anti-thrombotic prophylaxis in patients with implanted central venous access device.

In the efficacy analysis, at a median follow-up of 12 months, promising results were observed in median TTP (8 months) and in median OS (13 months). In our subset of patients, 27.3% of them were progression-free at 1 year of follow-up; more than half of the patients (53.5%) were alive at 1 year of follow-up. Even though the phase II data studies might be affected by the patient selection bias, our results in terms of 1-year survival seem promising. Caution should be applied in the interpretation of these results; we are not able to justify these outcomes only with 22 of patients receiving further treatment, because the impact on survival of second-line chemotherapy in advanced gastric cancer is still under debate. However, we cannot rule out the influence of a better administration of 5-FU (bolus plus continuous infusion) on TTP and survival results. Despite the lower response rate than those obtained with new drugs [18–21], these outcomes could also be influenced by the high rate of SD and by the relatively favorable characteristics of the patients before treatment.

New treatment regimen with novel cytotoxic drugs such as irinotecan, oxaliplatin and taxanes, or biologic agents such as epidermal growth factor antibodies and antiangiogentetics, might improve the efficacy of treatment in patients with metastatic gastric cancer [18, 21]. Phase III trial with new agent combinations are required to verify the real activity of new drugs.

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