Weekly treatment with irinotecan, folinic acid and infusional 5-fluorouracil (ILF) in patients with advanced gastric cancer

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Although 5-fluorouracil remains the mainstay of treatment for advanced gastric cancer (AGC), no standard chemotherapy regimen exists. Combinations of irinotecan with folinic acid and infusional 5-fluorouracil (5-FU) (ILF) have shown good efficacy with acceptable toxicity in patients with metastatic colorectal cancer. At present, only sparse data on ILF are available for AGC. Therefore we conducted a prospective study of this combination in 25 consecutive patients with metastatic gastric cancer. Median age was 63 years, 10 had received prior chemotherapy and 13 presented initially with peritoneal carcinosis. Treatment consisted of irinotecan 80 mg/m^2, folinic acid 500 mg/m^2 and infusional 5-FU 2.0 g/m^2 over 24 h, given weekly for 6 weeks followed by a 1-week rest. Grade 3/4 hematologic toxicity occurred in six patients (anemia = 4, neutropenia = 1 and leukopenia = 1). Non-hematologic toxicity consisted mainly of nausea/vomiting (grade 3/4 in six patients) and diarrhea (grade 3/4 in 10 patients). The overall response rate was 20% for first- and second-line treatment, with two complete and three partial responses. Another nine patients (36%) had stable disease, for a tumor control rate of 56%. Median time to progression was 4 months, median overall survival and survival for patients with tumor control was 7 and 13 months, respectively. We conclude that ILF is a feasible outpatient regimen with manageable toxicity that provides tumor control in a high proportion of patients with advanced gastric cancer, even among those with unfavorable prognostic features. *Anti-Cancer Drugs* **14:645–650 © 2003 Lippincott Williams & Wilkins.**

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Introduction

Despite the decline in the incidence and mortality of gastric cancer observed in Western industrialized countries over the last decades, this tumor still remains the second most frequent type of cancer worldwide, next to lung cancer only. In contrast to cancer of the stomach, the incidence of cancer of the proximal gastroesophageal junction is increasing in many Western countries. The prognosis of gastric cancer is generally poor because most tumors are diagnosed at an advanced stage. Cure can be achieved only when a complete surgical resection of the tumor and affected lymph nodes is possible. Even in these patients, local relapse and metachronic metastatic disease commonly occurs, which explains the disappointing 5-year overall survival of 10% [1].

A number of relatively effective chemotherapy regimens have been developed for the treatment of locally advanced or metastatic gastric cancer. 5-Fluorouracil (5-FU) appears to be the most active single agent, but combinations of 5-FU with other agents such as etoposide, cisplatin or epirubicin have proven to be more effective in terms of survival [1,2]. Interestingly enough, the survival advantage was paralleled by an improvement in quality of life and treatment appeared to be cost-effective. Randomized trials have also shown a significant gain in median survival with polychemotherapy versus best supportive care, further establishing the palliative role of chemotherapy in advanced disease. However, none of the chemotherapy regimens investigated thus far has been generally accepted as standard treatment [2–4].

Irinotecan (CPT-11), a camptothecin analog, has shown promising single-agent activity in patients with advanced gastric cancer [5–9]. Some of the combinations of irinotecan with other cytotoxic drugs, e.g. cisplatin, have demonstrated even higher antitumor activity, but sometimes also higher toxicity. For example, an early phase I–II study of irinotecan in combination with cisplatin given every 4 weeks to previously untreated patients resulted in an overall response rate (ORR) of 41% [9]. Diarrhea and neutropenia were the predominant toxicities [9]. A 2-weekly combination of irinotecan and cisplatin produced an even higher ORR (59%), and a median survival time of 10.5 months in previously untreated patients with advanced gastric cancer [10]. This regimen was relatively well tolerated even though grade 4 neutropenia occurred in 57% and grade 3 or 4 diarrhea in 20% of the patients.

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As a treatment for advanced colorectal cancer, combinations of irinotecan with 5-FU and folinic acid (FA) have shown clear synergistic activity in randomized trials [11,12]. The weekly administration of irinotecan 80 mg/m^2, high-dose FA (500 mg/m^2) and infusional 5-FU (up to 2.6 g/m^2 over 24 h) for 6 weeks followed by 1 week at rest was evaluated in a phase I study in patients with advanced colorectal cancer and showed a favorable toxicity profile consisting mainly of nausea and diarrhea, with a remarkable response rate of 64% [13]. More recently, this attractive synergistic regimen, with 5-FU given at a dose of 2 g/m^2 as a 22-h infusion, was investigated in a randomized phase II trial in patients with advanced gastric cancer and resulted in a higher response rate than irinotecan/cisplatin [14].

At present, only sparse data on the irinotecan/FA/5-FU regimen (ILF) are available from European countries. Therefore, we started this open-label pilot study, to first evaluate feasibility, safety and efficacy of this regimen in patients with advanced gastric cancer, some also with poor prognostic features including peritoneal carcinosis and/or previous chemotherapy. We were particularly interested whether toxicity and efficacy of ILF is promising enough to warrant further investigation of ILF in a further randomized phase II study [15]. As we administered ILF on an outpatient basis, particular attention was also given to the prompt and aggressive management of delayed diarrhea with loperamide and hospitalization if necessary.

Patients and methods

Consecutive patients with histologically documented adenocarcinoma of the stomach or gastroesophageal junction and measurable progressive metastatic disease, age 18–80 years, minimum life expectancy of 3 months, Karnofsky performance status ≥ 60, and adequate hematologic, hepatic and renal function were recruited into this study. Patients with CNS metastases, bowel obstruction or ileus were excluded from the study. Before treatment, all patients gave written informed consent, and a subcutaneous subclavian port was inserted (Port A; Therex, Walpole, MA).

As previously described [12], treatment consisted of fixed doses of irinotecan 80 mg/m^2 given as a 1-h infusion and folinic acid 500 mg/m^2 as a 2-h infusion, followed by a 24-h infusion of 5-FU at a dose of 2.0 g/m^2. Therapy was administered weekly for 6 weeks followed by 1 week off treatment. To prevent expected toxicities, patients were carefully informed about the potential risk of delayed diarrhea and neutropenia, and the need for early intervention with loperamide [16] and metoclopramide, prophylactic antibiotics or hospitalization and parenteral rehydration in case of refractory diarrhea lasting more than 48 h [17]. Atropine was given as needed for irinotecan-related cholinergic symptoms [18]. Antiemetic agents were administered at the discretion of the treating physician. Treatment was continued until one of the following occurred: disease progression, unacceptable adverse effects or withdrawal of patient's consent.

To obtain data about the feasibility, safety and efficacy of the ILF regimen, 25 subjects seemed to be sufficient to later perform a large randomized phase II study [15]. If more than 50% tumor control or a response rate of 20% were found in these patients, a subsequent randomized phase II trial was considered. Primary end points were the toxicity and efficacy of the regimen; secondary end points were time to progression and overall survival. The overall objective response rate [ORR = complete responses (CRs) and partial responses (PRs)] to therapy was assessed by clinical findings and computed tomography (CT) and was documented according to WHO guidelines. A CR was defined as complete disappearance of all evidence of cancer. A PR was defined as a reduction in the sum of the products of the biperpendicular diameters of all measurable lesions by at least 50%. Progressive disease (PD) was defined as an increase in the sum of the products of the greatest biperpendicular diameters of all measurable lesions by at least 25% or the appearance of new lesions. Stable disease (SD) was defined as any reduction or increase in measurable lesions which did not meet the criteria for PR or PD. Additional end points included the tumor control rate (CR + PR + SD), time to progression, and frequency and severity of toxicities. Safety assessments and complete blood counts were performed weekly. Toxicity was graded according to NCI–CTC criteria. In case of any toxicity grade 2 except hand–foot syndrome or alopecia, the next planned doses of ILF were delayed for a maximum of 1 week (or to resolution of diarrhea for at least 5 days). In case of toxicity grade 3/4 or if improvement from grade 2 to 1 (or resolution of diarrhea) was not reached by 2 weeks, the following chemotherapy doses were reduced by 20%. If grade 3/4 toxicity did not improve by 2 weeks, treatment was discontinued.

Statistical analysis including survival analysis was performed with the SPSS software package. All data assessed up to 1 January 2003 were included in the statistical analyses. Survival ('time to death') was measured from the time of diagnosis of metastatic disease to the date of death or last follow-up. Progression-free survival was calculated from treatment onset to the time of progression, patient withdrawal or death of any cause. All patients were included in analyses of toxicity and survival, and those who completed at least two chemotherapy cycles were evaluable for response. All parameters were evaluated by appropriate descriptive statistics. Survival time and progression-free survival were evaluated using

Kaplan–Meier methods. Analyses were considered as explorative analyses.

Results

Between May 2000 and April 2002, 25 consecutive patients with metastatic adenocarcinoma of the stomach (20 patients) or proximal gastroesophageal junction (five patients) were enrolled into the study. The baseline characteristics of the patients are shown in Table 1. Median age was 63 years (range 34–79). Seventeen patients had previous surgery and 10 patients received prior chemotherapy, all of them with a 5-FU-based regimen. The majority of patients had one or more clinical features indicating poor prognosis: 80% of the patients had two or more metastatic sites, 52% had peritoneal involvement and 68% reported a weight loss of more than 5 kg. Twenty-five patients were evaluable for toxicity and response, respectively.

The patients received a total of 101 chemotherapy cycles (median 3 per patient) including 486 weekly treatments (median 13 per patient). Treatment was delayed at least once during the course of chemotherapy in 18 patients and a dose reduction was required in 12 patients. The most common causes for discontinuation of study treatment were disease progression, clinical deterioration or death (20 patients). Treatment was discontinued due to severe toxicity in four patients (hand–foot syndrome = 1 patient, diarrhea = 1 patient, neutropenia = 2 patients) and another four patients refused to continue study treatment. After withdrawal from the study, a further treatment option was offered to nine patients, consisting mainly of cisplatin or taxanes.

Data on toxicity for all patients are shown in Tables 2 and 3. Hematologic toxicity was mild to moderate in the majority of patients. One patient (4%) had grade 3 leukopenia, one patient (4%) had grade 3 neutropenia and four patients (16%) had grade 3 or 4 anemia. Mild to moderate thrombocytopenia occurred in four patients (16%). The predominant non-hematologic toxicity was delayed diarrhea that reached grade 3/4 in 10 patients (40%). Six patients (24%) had grade 3/4 nausea and vomiting, and seven patients reported severe pain that was probably related to the underlying disease. Other non-hematologic toxicities were generally mild to moderate, and included asthenia, cholinergic syndrome, constipation, fever, mucositis and alopecia. No toxic death occurred. Hospital admission for treatment-related toxicity was required in 11 patients (nine for anemia and two for diarrhea) and 17 patients with diarrhea received at least one course of loperamide which was successful in 13 patients. One patient received additional budesonide. No thrombotic complications were seen.

The response data are shown in Table 4. The ORR achieved with the ILF regimen was 20%, with two CRs and three PRs. In addition, nine patients (36%) had SD

Table 1 Patient characteristics

Characteristic	All patients	First line	Second line
No. patients	25	15	10
Gender (male/female)	19/6	10/5	9/1
Median age, years (range)	63 (34–79)	59 (38–78)	64.5 (34–79)
Primary tumor site			
stomach	20	15	5
distal esophagus or cardia	5	0	5
Metastatic sites			
liver	13	6	7
peritoneum	13	10	3
lymph nodes	15	9	6
other sites	10	7	3
No. of metastatic sites			
1	5	2	3
2	13	8	5
≥ 3	7	5	2
Previous treatment			
surgery only	11	11	0
surgery + chemotherapy	6	0	6
chemotherapy only	4	0	4
No treatment	4	4	0

Table 2 Hematologic toxicity (no. of patients)

	WHO Grade				
	0	1	2	3	4
Leukopenia	15	7	2	1	0
Neutropenia	19	3	2	1	0
Anemia	5	7	9	2	2
Thrombocytopenia	21	3	1	0	0

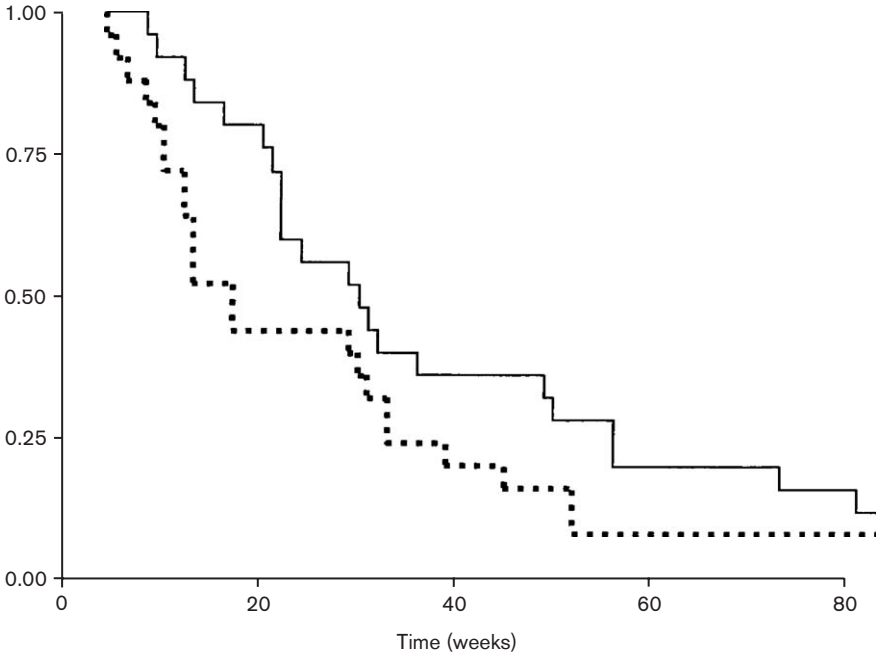
Table 3 Non-hematologic toxicity (no. of patients)

	WHO Grade				
	0	1	2	3	4
Nausea/vomiting	4	10	5	5	1
Diarrhea	2	4	9	9	1
Alopecia	21	2	0	2	0
Cholinergic syndrome	15	10	0	0	0
Fever	20	4	1	0	0
Mucositis	21	3	1	0	0
Constipation	16	6	3	0	0
Asthenia	7	18	0	0	0
Pain	8	5	5	7	0

Table 4 Response

No. of patients (%)	All patients ($n=25$)	First-line ($n=15$)	Second-line ($n=10$)
CR	2	1	1
PR	3	2	1
ORR (CR + PR)	5 (20%)	3 (20%)	2 (20%)
SD	9	5	4
Tumor control rate (CR + PR + SD)	14 (56%)	8 (53%)	6 (60%)
PD	11	7	4

Fig. 1



Progression-free and overall survival of all patients are depicted according to Kaplan–Meier depicted as dotted and linear lines, respectively.

Table 5 Survival by prior chemotherapy and peritoneal involvement

	Median time to progression (weeks)	Median survival (weeks)
All patients ($n=25$)	17	30
Prior chemotherapy		
yes ($n=10$)	23	30
no ($n=15$)	13	30
Peritoneal carcinosis		
yes ($n=13$)	11	23
no ($n=12$)	31	43.5

for a tumor control rate of 56%. Disease progression occurred in 11 patients (44%). Median time to progression was 17 weeks (4 months) and median overall survival was 30 weeks (7 months) (Fig. 1). Median survival of those patients who had tumor control was 56 weeks (13 months). The survival outcome of patients with or without previous chemotherapy was similar, mainly due to the large number of untreated patients with initially diagnosed peritoneal carcinosis (Table 5). Patients with peritoneal carcinosis tended to fare worse than those without peritoneal involvement. The median time to progression and median survival for 13 patients with peritoneal carcinosis was 11 and 31 weeks versus 23 and 43.5 weeks for patients without peritoneal involvement, respectively. At the time of evaluation, 21 patients had died and four were still alive with SD.

Discussion

Treatment for advanced or metastatic gastric cancer remains unsatisfactory. No clear advantage has been demonstrated in randomized studies for any one of the newer chemotherapy regimens studied thus far, with relatively poor response rates and survival times reported in most clinical trials [2–4]. Therefore no generally accepted treatment standard exists. Although it has been shown that chemotherapy improves survival to a statistically significant extent compared with best supportive care alone, the survival advantage appears marginal from a clinical perspective and it remains unclear which toxicity burden is reasonable for the individual patient in view of the generally limited life expectancy.

In our study we evaluated a weekly chemotherapy regimen that combines irinotecan with the high-dose folinic acid and 24-h infusional 5-FU schedule advocated by the German Association of Medical Oncology (AIO). This specific regimen (together with a biweekly combination of irinotecan with the 5-FU/FA schedule according to de Gramont) was evaluated in a phase III study as palliative treatment for patients with advanced colorectal cancer and was found to be superior to 5-FU/FA alone in terms of response rate, time to progression and overall survival [12]. Therefore, we considered it worthwhile to investigate the efficacy and tolerability of the ILF regimen also in patients with advanced gastric cancer.

Our study population was a consecutive patient series enrolled with a minimum of selection criteria. It thus included patients with poor prognostic features who are typically seen in clinical practice, but are often excluded from clinical trials. For example, our patients had a median age of 63 years, which is higher than in most clinical studies conducted in this setting. Moreover, the majority of the patients (17 out of 25) had a history of significant weight loss (above 5 kg) as an indicator of poor performance status. All patients had metastatic disease, 13 had peritoneal carcinosis and 10 had received previous palliative chemotherapy with a 5-FU-based regimen. Approximately one-third of the patients had no prior surgery because of primary advanced disease. Inoperable disease is known to be associated with a poor prognosis because these patients are at an increased risk of perforation and bleeding [19]. Furthermore, none of the patients in our study received i.v. nutrition, but some of them required placement of a percutaneous enteral gastrostomy (PEG) tube to ensure appropriate nutrition [20].

In view of the unfavorable patient characteristics, the treatment results observed in our study with the ILF regimen appear promising. Tumor growth was controlled in more than half of the patients, median time to progression was 4 months and median overall survival was 7 months. Remarkably, median survival of the patients achieving control with ILF was 13 months. These data compare favorably with those reported for etoposide + 5-FU/FA (ELF) or cisplatin-based regimens [4,21]. For example, median survival times of 6.7–7.2 months were reported in the phase III study of the EORTC with the regimens ELF, FUP (infusional 5-FU + cisplatin) and FAMTX (high-dose methotrexate + 5-FU + doxorubicin) among patients with no prior chemotherapy [3]. In a randomized phase II study presented at the ASCO 2001 meeting, the same ILF regimen as used in our study was compared with an irinotecan–cisplatin combination [14]. In the first-line setting, and in a patient population with substantially more favorable characteristics compared with our study, the objective response rate with ILF was 42%, with a further 42% achieving stable disease [14]. The irinotecan + cisplatin combination was less effective, with an ORR of 28% and SD in 41% of the patients. These results underline the true potential of the ILF regimen for the treatment of advanced gastric cancer, which has recently also been confirmed in a randomized phase II study of our group whose results were presented at the ASCO 2003 meeting [15].

Patients with advanced gastric cancer who present with peritoneal carcinosis generally have a particularly poor prognosis [22,23]. This clinical experience is also reflected in our study data. Median time to progression among patients without peritoneal carcinosis was nearly 3 times and median survival 2 times longer than among patients presenting without peritoneal involvement. However, we also observed a remarkable exception to that rule in a patient who derived long-lasting benefit from treatment with the ILF regimen. This man aged 65 developed laparoscopically and histologically confirmed peritoneal carcinosis after resection of his gastric adenocarcinoma. His initial Karnofsky index of 70 improved under treatment with ILF. He received 7 cycles of chemotherapy and was still progression-free at 89 weeks. A second laparoscopy was attempted but failed due to the presence of intra-abdominal adhesions. Therefore, his response to treatment was classified as SD. The patient is still alive 123 weeks after start of treatment.

The main non-hematologic toxicity of irinotecan is delayed diarrhea. This potentially life-threatening complication requires prompt patient-initiated therapeutic intervention with high-dose loperamide as soon as the first loose stool occurs (2 mg every 2 h for at least 12, but no longer than 48 h). The incidence and severity of diarrhea in our study was similar to that seen with the ILF regimen in patients with advanced colorectal cancer [17] and most patients responded well to treatment with loperamide. Hospitalization for treatment of severe diarrhea was needed in only two patients and no patient died of this complication. Therefore, diarrhea was not a major clinical problem during treatment with the ILF regimen, all the more if we take into consideration that patients with peritoneal carcinosis are exposed to an increased risk of diarrhea independent of treatment.

In conclusion, the results obtained in our study with the combination of irinotecan and 5-FU/folinic acid are promising enough to warrant further evaluation of this regimen for the treatment of advanced gastric cancer, including randomized comparisons with more established chemotherapy regimens [15]. Even in a population of patients with poor prognostic features including peritoneal carcinosis and/or previous chemotherapy, at least half of the patients can be expected to achieve tumor control with ILF chemotherapy, and every second responder will survive for more than a year.

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