PERGAMON

European Journal of Cancer 37 (2001) 1828–1832

European Journal of Cancer

www.ejconline.com

A weekly 24-h infusion of high-dose 5-fluorouracil (5-FU) + leucovorin and bi-weekly cisplatin (CDDP) was active and well tolerated in patients with non-colon digestive carcinomas

F.X. Caroli-Bosc[a,*], J.L. Van Laethem[b], P. Michel[a], F. Gay[b], A. Hendlisz[a], F. Forget[a], H. Bleiberg[a]

[a]*Gastroenterology Department, Institut Jules Bordet, Rue Héger-Bordet, 1-1000 Brussels, Belgium*
[b]*Gastroenterology Department, Erasme Hospital, Route de Lennik, 808-1070 Brussels, Belgium*

Received 13 November 2000; received in revised form 19 March 2001; accepted 11 May 2001

Abstract

In patients with non-colon digestive carcinomas, various schedules and doses of 5-fluorouracil (5-FU) and leucovorin combined with cisplatin (CDDP) have been used extensively. The present study explored the toxicity and activity of a weekly 24-h infusion of high dose 5-FU modulated by high dose leucovorin with bi-weekly CDDP. 59 patients with measurable disease were treated with a weekly infusion of high dose 5-FU (2 or 2.6 g/m^2) + leucovorin 500 mg/m^2 for 6 weeks and a bi-weekly dose of CDDP (50 mg/m^2). All patients had metastatic or locoregionally advanced disease and had a performance status $\leqslant 3$. All patients were evaluable for toxicity and 58 for response. Toxicity was different according to the schedule of 5-FU. Serious adverse events occurred most frequently when 5-FU was given at a dose of 2.6 g/m^2 with a high incidence of grade 3/4 neutropenia (16%) and febrile neutropenia (13%), and led to dose reductions in both CDDP and 5-FU in 13 patients (34%). For patients who started 5-FU at a dose of 2 g/m^2, no reduction in 5-FU was required, and only 4 patients required a dose reduction of CDDP (19%). Grade 3/4 neutropenia was seen in 10% of patients of this group and only 1 patient required hospitalisation for febrile neutropenia. Other grade 3/4 toxicities were rare in both groups. Renal toxicity was infrequent and mild and did not require dose adjustments. The overall response rate was 33%; 19 patients achieved a partial responses (PR). No patient had a complete response (CR). The median duration of response was 5.7 months (range 2–24 months) and the median survival was 7.9 months (range: 1–30, 95% confidence interval (CI): 7–9). The combination of weekly 24-h infusion of high dose 5-FU with leucovorin and bi-weekly cisplatin seems a well-tolerated and active treatment in non-colon digestive carcinomas. A dose of 2 g/m^2 of 5-FU seems to be recommended.

Keywords: Chemotherapy; Oesophageal cancer; Gastric cancer; Pancreatic cancer; Biliary tract cancer; Cancer of unknown primary site; Weekly 5-FU

1. Introduction

Non-colon digestive carcinomas have a poor prognosis mainly due to the aggressiveness of the disease. Thus, palliative chemotherapy appears to provide the best therapeutic approach for these patients. Existing chemotherapeutic options for patients with unresectable metastatic or locally advanced non-colon digestive carcinomas are of limited value. However, trials comparing best supportive care versus chemotherapy or chemoradiotherapy suggest that treatment has a positive effect on survival and quality of life for oesophageal [1,2], gastric [3–6], biliary [7] and pancreatic cancers [7,8]. Several new systemic agents like irinotecan, docetaxel, paclitaxel and gemcitabine, alone or in combination, are being investigated mainly in phase II studies but no reliable information is presently available. Today, 5-fluorouracil (5-FU) and cisplatin (CDDP) are the most commonly used drugs in combination regimens in the treatment of these tumours. One of the most commonly used chemotherapeutic schedules is 5-FU given as a continuous infusion (1 g/m^2/daily for 4 consecutive

* Corresponding author. Tel.: +32-2-541-3207; fax: +32-2-538-0858.
E-mail address: adenis@ulb.ac.be (F.X. Caroli-Bosc).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00180-0

days) [9,10]. Nevertheless, if this schedule constitutes a standard treatment for squamous cell carcinoma of the oesophagus, other schedules may be considered as standard treatments in gastric cancer. This is consistent with recent studies reported by Vanhoefer and colleagues [11] and Ross and colleagues [12]. Ardalan and coworkers have reported promising results in colorectal cancer, using a weekly 24-h infusion of high-dose 5-FU (2.6 g/m^2) with leucovorin (500 mg/m^2) [13]. In order to enhance the activity of this 5-FU-based regimen, CDDP has been added to the combination. We report on our experience with a 5-FU, leucovorin and CDDP regimen in terms of toxicity, tolerance and activity in patients with locally-advanced or metastatic non-colon digestive cancers.

2. Patients and methods

2.1. Eligibility criteria

The trial was performed at the Jules Bordet Institute Cancer Center and in the Gastroenterology Department of Erasme University Hospital (Brussels, Belgium). From January 1996 to December 1999, 59 patients were enrolled in this study. All have histologically confirmed digestive carcinomas. Additional eligibility requirements included the following: World Health Organization (WHO) performance status $\leqslant 3$, age less than 75 years, and a life expectancy of at least 12 weeks. Patients were also required to have adequate haematological and hepatic function at study entry (white blood cell (WBC) count greater than 4000×10^9/l, platelet count greater than 100×10^6/l, blood urea nitrogen level less than 10.7 mmol/l of urea, creatinine concentration less than 132.6 μmol/l, and total serum bilirubin level less than 25.65 μmol/l. All patients underwent a pretreatment evaluation consisting of medical history and a complete physical examination, haematological testing, serum chemistry, electrocardiogram, and radiological assessment using computed tomography (CT) scan of all measurable tumour lesions.

2.2. Systemic chemotherapy

A permanent intravenous (i.v.) port chamber was implanted in all patients. For all patients, 5-FU was given once a week at a dose of 2 g/m^2 at the Erasme Hospital (=treatment A) and at a dose of 2.6 g/m^2 at the Institut Jules Bordet (=treatment B) as a continuous 24-h infusion, preceded by 500 mg/m^2 of leucovorin given as a 2-h infusion for a total of 6 weeks. This was considered as one treatment cycle. CDDP was given at a dose of 50 mg/m^2 as a 30–60-min i.v. infusion every 2 weeks for a total dose of 150 mg/m^2 per cycle. Each cycle was followed by a 2-week rest period (Fig. 1). Antiemetic treatment consisted of the administration of a combination of 5-HT3 receptor antagonists (ondansetron 8 mg) plus dexamethasone (20 mg) before each administration of CDDP. When 5-FU was administered without CDDP, control of emesis was performed with metoclopramide (20 mg) plus dexamethasone (20 mg). Dose modifications and treatment delay were scheduled according to blood cell counts and clinical toxicities. A 1-week delay of treatment was planned in the event of WHO grade 3/4 toxicities that had not resolved by the next week of treatment, and the drug dosage was reduced by 50% or discontinued.

2.3. Toxicity evaluation and response criteria

Toxicity was classified according to the WHO guidelines [14]. Objective response evaluations followed the International Union Against Cancer recommendations [15]. A complete response (CR) was defined as the complete disappearance of all measurable disease for a duration of at least 4 weeks, and a partial response (PR) as a greater than 50% reduction of all measurable tumour sites. Stable disease (SD) was defined as a less than 50% reduction of tumour lesions and no progression of more than 25%. The treatment was continued until tumour progression (PD) or unacceptable toxicity occurred. Toxicity was evaluated before each course of therapy. Performance status (PS) was evaluated for all patients before starting the treatment and after each cycle using the WHO grading scale.

2.4. Follow-up evaluation

The end-points of the study were feasibility, toxicity, response rate and time to treatment failure. The response assessment by CT scan was done after every cycle of treatment. Response duration was measured in weeks from the day of response documentation to either the day of disease progression or to death if the patient died without disease progression. Survival was calculated from the start of chemotherapy using the Kaplan–Meier method.

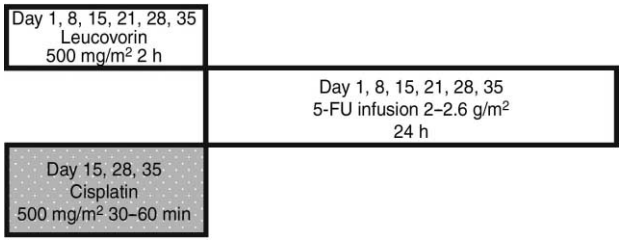

Fig. 1. Bi-weekly cisplatin and weekly leucovorin 5-FU by continuous infusion (one cycle = 8 weeks).

Table 1
Patients characteristics

Characteristics	No. of patients (%)
Men/women (total)	39/20 (59)
Median age (years) (range)	57.7 (30–75)
Primary site of tumour	
Oesophagus	10 (17)
Stomach	20 (34)
Pancreas	21 (36)
Biliary tract	4 (7)
Unknown	4 (7)
Extent of disease	
Locally advanced	18 (31)
Metastatic	41 (69)
Liver only	19 (46)
Lung only	3 (7)
Peritoneum only	11 (27)
Lymph nodes only	3 (7)
Liver + other(s)	5 (12)
Other(s) without liver	17 (41)
Histological subtypes	
Adenocarcinoma	54 (92)
Squamous cell carcinoma	5 (8)
Performance status	
0	17 (29)
1	31 (53)
2	7 (12)
3	4 (7)
Prior chemotherapy ± prior radiotherapy	7 (12)

3. Results

The study included 39 men and 20 women with a median age of 57.7 years (range 30–75 years). All were evaluable for toxicity, and 58 for response. Among the 59 patients, 10 had oesophageal cancer, 20 a gastric cancer, 4 a biliary tract cancer, 21 a pancreatic cancer, and 4 a cancer of unknown origin. 54 patients had histologically-confirmed digestive adenocarcinoma including oesophagus, gastric, biliary, pancreatic and unknown primary site carcinomas. 5 additional patients had squamous cell carcinoma of the oesophagus. For the gastric cancers, six tumours were localised to the cardia, eight to the antrum and six were linitis. 18 patients had a locally-advanced disease (12 pancreatic cancers and 6 oesophageal cancers) and 41 were metastatic. Of these, 36 patients had one organ involved, and 9 more than one tumour site. 7 patients had previously received neoadjuvant or adjuvant chemotherapy: 5 concomitant chemoradiotherapy with 5-FU/CDDP, 1 FAMTX (5-FU, doxorubicin, methotrexate), 1 ECF (epirubicin, cisplatin, 5-FU). Patients' characteristics are listed in Table 1.

3.1. Treatment regimen and modifications of dose

A total of 125 chemotherapy cycles were administered (median number of cycles per patient: 2; range, 0.3–6). For 21 subjects, 5-FU was started at a dose of 2 g/m^2, and for 38 it was started at a dose of 2.6 g/m^2. Table 2 shows the chemotherapy doses delivered per patient and the dose modifications made during the treatment courses. The mean chemotherapy dose given per patient was 27% g/m^2 for 5-FU (22 for treatment A, 33% for treatment B), and 284 mg/m^2 for CDDP (267 for treatment A, 300 for treatment B) for gastric cancers these doses were 2-fold those given for the other tumour. Toxicity led to a dose reduction of both CDDP and 5-FU in 13 patients (34%) when 5-FU was given at an initial dose of 2.6 g/m^2. The dose of chemotherapy was never less than 2 g/m^2 for 5-FU and 20 mg/m^2 for CDDP. Dose reductions were due to febrile neutropenia and diarrhoea in the majority of cases and were associated with a treatment delay of less than 1 week in all patients. For patients who started 5-FU at 2 g/m^2, no reduction in 5-FU was required, and 4 patients required a dose reduction for CDDP (19%).

3.2. Toxicity

Toxicity was different according to the dose of 5-FU given (Table 3). Severe toxicities occurred most frequently when 5-FU was given at the dose of 2.6 g/m^2. Indeed, neutropenia (grade 3/4) occurred in 16% of patients given treatment B compared with 10% of those given in treatment A.

Hospitalisation for febrile neutropenia occurred in 13% of the patients given treatment B and 45% of those given treatment A. One toxic death was reported in the treatment B group. Non-haematological toxicities were also more frequent in the treatment B group which apart from the 5% of patients who experienced grade 3/4

Table 2
Data from doses of chemotherapy

Treatment	No. of patients	Median cycles (No. of patients)	Median dose of CDDP/patient (mg/m^2)	Dose reduction for CDDP *n* (%)	Median dose of 5-FU/patient (g/m^2)	Dose reduction for 5-FU *n* (%)
A[a]	21	2 (1–4)	269 (100–600)	4 (19)	22 (10–60)	0
B[b]	38	2.2 (0.3–6)	300 (75–900)	13 (34)	33 (5–90)	13 (34)

F-FU, 5-fluorouracil; CDDP, cisplatin.
[a] 5 stomachs, 16 pancreas.
[b] 15 stomachs, 5 pancreas, 10 oesophagus, 4 biliary tumours, 4 unknown site.

Table 3
Toxicity observed in patients receiving different doses of 5-FU

	Treatment A (2 g/m^2) $n=21$		Treatment B (2.6 g/m^2) $n=38$	
Grade (%)	1/2	3/4	1/2	3/4
Neutropenia	19	10	29	16
Febrile neutropenia	0	5	0	13
Anaemia	33	0	79	3
Thrombocytopenia	0	5	16	3
Nausea	38	0	3	8
Vomiting	29	0	37	5
Mucositis	14	0	0.5	0
Hand–foot syndrome	0	0	8	0
Diarrhoea	19	0	42	5
Neuropathy	14	0	13	3
Renal insuffiency	24	0	13	0
Alopecia	5	0	8	0

5-FU, 5-fluorouracil.

thrombocytopenia, did not occur in the treatment A group (Table 3). No complication with permanent i.v. port chambers was observed in this study.

3.3. Activity

58 patients were evaluable for response. Response to the therapy is summarised in Table 4. Considering the diversity of the tumour type and the small number of cases, responses are not given by treatment arm. Treatment efficacy was evaluated every 2 months after each cycle. One patient was excluded from the analysis for response because he died before the first evaluation. Of the 58 patients with measurable disease, no patient reached a CR, 19 had a PR (32.2%), 25 had a SD (42.4%), and 14 patients had a PD (23.7%). The mean duration of response was 5.7 months (range 2–24 months) and the mean duration of stable disease was 5.3 months (range 2–12 months). The 24-month response duration occurred in a patient with a well-differentiated gastric adenocarcinoma. The median survival duration for the whole population of 59 patients was 7.9 months (95% confidence interval (CI): 7–9). Responses were observed at several disease sites including the primary tumour, the liver, the lung, the peritoneum and lymph node metastases. Median time to response was 2 months, after one cycle (range 2–4 months).

At baseline, median PS was evaluated at 1 (range 0–3). The PS was improved in 12 patients (20%), and stable in 37 patients (63%) for a mean duration of 5 months. The improvement was apparent after a median time of 2 months and lasted for a median of 4.4 months.

4. Discussion

The majority of patients with non-colon digestive cancer have advanced and inoperable tumours at the time of diagnosis. The aim of chemotherapy in this situation is usually palliation. Despite its limited activity as a single agent, 5-FU remains the most used chemotherapeutic agent for advanced gastrointestinal tumours. As dose-intensity may be an important parameter for activity, 2-weekly doses of 5-FU have been investigated: 2.6 g/m^2 which is the recommended dose used in colorectal cancer [11] and 2 g/m^2, both given with 500 mg/m^2 of leucovorin. Combination with cisplatin has been shown to be synergistic [16]. The 5-FU schedule that has been used in the present study has been developed by others in gastric cancer studies [17]. This study was designed with the main objective of identifying the toxicity of the combination in a wide variety of primary digestive tumours.

Although the study was not randomised, toxicity was higher in treatment B than in treatment A (Table 3). A dose of 2 g/m^2 of 5-FU appears to be a well-tolerated regimen for patients with advanced non-colon gastrointestinal tumours. It is associated with moderate toxicity and can be performed on an out-patient basis. A median of two cycles was administered per patient. For gastric cancers, the median doses of 5-FU and cisplatin given per patient was 2-fold those given for the other tumours. The most important dose reductions were observed for the oesophageal cancers probably due to their poor general status. The bi-weekly administration of 50 mg/m^2 can be recommended for CDDP, the most important dose reductions were observed for the oesophageal cancer, without severe additional toxicities when 5-FU was started at a dose of 2 g/m^2. Only 4 patients (19%) had a progression reduction in dose

Table 4
Antitumour activity

Tumour site	n	(%) Overall response rate	Median duration of response (months) (range)	(%) stable disease	Median duration of stable disease (months) (range)	(%) Progressive disease	Median survival (months)
Oesophagus	10	40	4.8 (2–10)	30	6.3 (6–7)	30	10.6 (1–24)
Stomach	20	50	7.3 (3–24)	40	5.5 (3–9)	10	10.5 (3–30)
Biliary tract	4	0		25	6	75	3.9 (1–8)
Pancreas	21	24	5 (4–7)	52	4.7 (2–10)	24	8.2 (2–15)
Unknown	4	0		50	9 (8–10)	50	6.2 (2–12)
Overall	58	33	5.7 (2–24)	43	5.3 (2–12)	24	7.9 (1–30)

down to 20 mg/m^2 that was related to haematological toxicities. Renal toxicity was particularly low and was not responsible for dose-reductions in this study.

In our study, we obtained a 33% overall response rate in 58 evaluable patients and a median duration of response of 5.7 months (range 2–24 months). An additional 43% of patients showed SD lasting for a median of 5.3 months (range, 2–12 months). If we consider each type of tumour, the overall response rate is 50% for gastric cancer, 40% for oesophageal cancer, and 24% for pancreatic cancer. These results are comparable to those previously reported for gastric cancer [9,10,17,18], oesophageal cancer [19,20], and pancreatic cancer [21,22]. The results were poor for biliary tumours and cancers with an unknown primary site, but no conclusion can be drawn due to the small number of patients included in these groups [23,24]. The overall median survival was 7.9 months and was comparable to data reported in the literature except for biliary tumours.

Although the numbers are small, there was no difference in response nor in survival between the groups given 2.6 or 2.0 g/m^2 of 5-FU (data not shown).

The good clinical activity and the good tolerance of this regimen is further demonstrated by an increase in the PS in 20% of the patients and a stabilisation in 63% for a mean duration of 5 months [2–12]. This improvement in PS was apparent after a median period of time of 2 months and lasted a median duration of 4.4 months [3–12].

5. Conclusions

The present trial, performed on 59 patients, shows the good tolerance of the regimens used as well as the activity of a schedule consisting of a weekly 24-h infusion of high-dose 5-FU and leucovorin combined with a bi-weekly dose of CDDP. Our study suggests that 2.0 g/m^2 of 5-FU is the recommended dose to be used in non-colon digestive carcinomas.

References

1. Herskovic A, Martz K, Al-Sarraf M, *et al*. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992, **326**, 1593–1598.
2. Coia LR, Soffen EM, Schultheiss TE, Martin EE, Hanks GE. Swallowing function in patients with esophageal cancer treated with concurrent radiation and chemotherapy. *Cancer* 1993, **71**, 281–286.
3. Murad AM, Santiago FF, Petroianu ?, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993, **72**, 37–41.
4. Glimelius B, Hoffman K, Haglund U, Nyren O, Sjoden PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994, **5**, 189–190.
5. Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995, **71**, 587–591.
6. Glimelius B, Ekstrom K, Hoffman K, *et al*. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997, **8**, 163–168.
7. Glimelius B, Hoffman K, Sjoden PO, *et al*. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996, **7**, 593–600.
8. Cascinu S, Graziano F, Catalano G. Chemotherapy for advanced pancreatic cancer: it may no longer be ignored. *Ann Oncol* 1999, **10**, 105–109.
9. Kim NK, Park YS, Heo DS, *et al*. A phase II randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. *Cancer* 1993, **71**, 3813–3818.
10. Rougier P, Mahjoubi M, Lasser P. Neoadjuvant chemotherapy in locally advanced gastric carcinoma. A phase II trial with combined continuous intravenous 5-fluorouracil and bolus cisplatinum. *Eur J Cancer* 1994, **30A**, 1269–1275.
11. Vanhoefer U, Rougier P, Wilke HJ, *et al*. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000, **18**, 2648–2657.
12. Webb A, Cunningham D, Scarffe H, *et al*. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997, **15**, 261–267.
13. Ardalan B, Chua L, Tian EM, *et al*. A phase II study of weekly 24-hour infusion with high-dose 5-fluorouracil with leucovorin in colorectal carcinoma. *J Clin Oncol* 1991, **9**, 625–630.
14. Miller AB, Hoogstraten B, Staquet M. Reporting results of cancer treatment. *Cancer* 1981, **147**, 207–214.
15. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment* (WHO Offset Publication No. 48). Geneva, Switzerland, World Health Organization, 1979.
16. Leichman L, Berry BT. Cisplatin therapy for adenocarcinoma of the stomach. *Semin Oncol* 1991, **18**, 25–33.
17. Chen JS, Liu HE, Wang CH, *et al*. Weekly infusion of high-dose 5-fluorouracil and leucovorin in patients with advanced gastric cancer. *Anti-Cancer Drugs* 1999, **10**, 355–359.
18. Lacave AJ, Baron FJ, Anton LM, *et al*. Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer: a phase II trial. *Ann Oncol* 1991, **2**, 751–754.
19. Bleiberg H, Conroy T, Paillot B, *et al*. Randomized phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced sqamous cell esophageal cancer. *Eur J Cancer* 1997, **33**, 1216–1220.
20. Enzinger PC, Ilson DH, Kelsen DP. Chemotherapy in esophageal cancer. *Semin Oncol* 1999, **26**, 12–20.
21. Rougier P, Zarba J, Ducreux M, *et al*. Phase II study of cisplatin and 120-hour continuous infusion of 5-fluorouracil in patients with advanced pancreatic carcinoma. *Ann Oncol* 1993, **4**, 333–336.
22. André T, Lotz JP, Bouleuc C, *et al*. Phase II trial of 5-fluorouracil, leucovorin and cisplatin for treatment of advanced pancreatic adenocarcinoma. *Ann Oncol* 1996, **7**, 173–178.
23. Ducreux M, Rougier P, Fandi A, *et al*. Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. *Ann Oncol* 1998, **9**, 653–656.
24. Hainsworth JD, Greco FA. Management of patients with cancer of unknown primary site. *Oncology* 2000, **14**, 563–573.