Treatment of advanced digestive non-colon cancer with a weekly 24-h infusion of high-dose 5-fluorouracil modulated by folinic acid and cisplatin: an easy-to-use and well-tolerated combination

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The combination of 5-fluorouracil (5-FU) modulated by folinic acid (FA) and cisplatin is commonly used in advanced digestive non-colon cancers (ADNCC). In order to simplify treatment administration by avoiding cisplatin-related hydration, we investigated a weekly regimen of 5-FU/FA/cisplatin. Patients with ADNCC were treated with 5-FU 2.0 g/m^2, FA 500 mg/m^2 and cisplatin 25 mg/m^2 day 1, for 6 weeks with a 2-week rest, and were assessed for toxicity, tumor response and disease-free survival. Forty-three patients with measurable ADNCC were treated with this weekly regimen. Primary tumor sites were mainly esophagus ($n=17$), stomach ($n=12$) and pancreas ($n=9$). Results were as follows. Toxicity was mostly hematological, with 16% grade 3/4 neutropenia (seven of 43) and 4% febrile neutropenia (two of 43). Objective response (OR) was observed in 19 of 43 (44%) patients including four complete responses (9%) and 15 partial responses (35%). Another 18 patients (42%) experienced stable disease. Time to progression was 6.5 months. The median response and stable disease durations were 4.3 (range 3–34) and 5 (range 2–16) months, respectively. We conclude that weekly administration of 5-FU/FA/cisplatin is an active and well-tolerated regimen. Toxicity is manageable and allows chemotherapy on an outpatient basis without hydration program as required when cisplatin is used at the dose of 50 mg/m^2. *Anti-Cancer Drugs* 15:725–728 © 2004 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2004, **15**:725–728

Keywords: chemotherapy, gastric cancer, esophageal cancer, pancreatic cancer

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Received 20 January 2004 **Revised form accepted** 8 May 2004

Introduction

Most of the patients suffering from digestive non-colon cancers (DNCC), including esophageal, gastric, pancreatic, biliary tract carcinomas and cancers of unknown origin, will be diagnosed with locally advanced disease or will develop metastatic disease requiring systemic chemotherapy. The role of chemotherapy has been assessed in gastric cancer and pancreatic cancer. When patients receiving chemotherapy were randomly compared to those receiving best supportive care only, a benefit in survival and quality of life was demonstrated. [1–5]. Despite the emergence of new chemotherapeutic agents [5–8], cisplatin and 5-fluorouracil (5-FU)-based chemotherapy is the most common combination used in an advanced setting. Various schedules and doses of 5-FU/cisplatin have been used in the past 10 years. It is widely accepted that, at least in gastric cancer, they are equally active [8–14]. The continuous 5-day infusion of 5-FU ± FA, combined with cisplatin (FUP) is frequently used in advanced esophageal cancer, and seems to be moderately active in gastric [8,9], pancreatic [12] and biliary tract adenocarcinomas [13]. However, hematological and digestive toxicities may be severe [9]. In the same setting of diseases, the weekly 24-h infusion of high-dose 5-FU/FA associated with biweekly cisplatin was well tolerated, with only 10% grade 3/4 neutropenia and no grade 3/4 digestive toxicity. A 20% response rate was obtained in gastric cancer [15]. In order to simplify treatment administration by avoiding cisplatin-related hydration we investigated a weekly regimen of 5-FU/FA/cisplatin.

Patients and methods

Patients

From January 1998 to December 2001, a total of 43 patients suffering from an advanced DNCC were treated with a weekly combination of 5-FU/FA/cisplatin. Patients had to have measurable disease and could have received previous chemotherapy. Additional eligibility requirements include a WHO performance status (PS) ≤ 2, and a complete blood test evaluation with normal hematological, renal and hepatic function.

Treatment

Patients were treated with a weekly regimen of 5-FU 2.0 g/m^2, FA 500 mg/m^2 and cisplatin 25 mg/m^2 day 1, for

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6 weeks followed by a 2-week rest. Anti-emetic agents were given before each cisplatin administration and consisted of the combination of a 5-HT_3 antagonist combined with i.v. corticosteroids. The treatment was continued orally for 3 days after the end of chemotherapy. Chemotherapeutic doses were reduced if patients had severe digestive toxicity (nausea, vomiting, diarrhea), neutropenia, thrombocytopenia or renal toxicity (evaluated by isotopic clearance). In case of WHO grade 3/4 toxicities not resolved at the time of re-treatment, a 1-week delay was planned and the drug dosage reduced by 50%. The treatment was continued until progression of the disease, or major toxicity.

Toxicity

Hematological and non-hematological (cardiac, renal, hepatic, digestive) toxicities were graded according to the WHO scale. The toxicity was evaluated after each course of chemotherapy.

Evaluation of treatment

All patients were assessed by radiological investigations including computed tomography (CT) scan, ultrasonography and/or magnetic resonance imaging (MRI) every 2 months. The response was evaluated by measuring one or more target lesions including the primary tumor, metastatic disease and/or lymph node involvement. Patients were considered to achieve a partial response (PR) if their tumor masses regressed so that the product of their perpendicular dimensions was reduced by 50%. Minor response (MR) was defined as a reduction of 25–50% of the product of the largest perpendicular dimensions. Progressive disease (PD) was defined as an increase of 25% or more. Stable disease (SD) represents the group between 25% regression and 25% progression.

Table 1 Patient characteristics

Total	43
Sex F/M	14/29
Median age (years)	60
WHO PS	
0	15
1	18
2	10
Primary site of the tumor	
esophagus	17
pancreas	12
stomach	9
cholangiocarcinoma	3
unknown	2
Metastatic site	
locoregional	24
liver	15
lymph nodes	14
peritoneum	9
lungs	6
bones	1
brain	1
Previous treatment	14
chemoradiotherapy	10
chemotherapy	4
phase I	1
5-FU/cisplatin/gemcitabine	2
gemcitabine	1

Table 2 Treatment-related toxicities (%)

Toxicity	Grade 2	Grade 3	Grade 4
Hematological			
anemia	23	7	0
thrombocytopenia	7	7	0
neutropenia	2	9	5
febrile neutropenia	0	2	2
Non-hematological			
nausea/vomiting	5	0	0
diarrhea	5	2	0
renal insufficiency	5	2	0
neuropathy	5	0	0
mucositis	5	0	0
hand/foot syndrome	2	2	0

Results

Forty-three patients were treated from January 1998 to December 2001. There were 14 women and 29 men, median age was 60 years (range 30–79). Among the 43 patients, 17 had esophageal cancer (four adenocarcinomas and 13 squamous cell carcinoma), 12 had gastric cancer, nine had pancreatic cancer, three had a cholangiocarcinoma and two had an adenocarcinoma of unknown origin, but likely digestive. All patients had measurable disease. There were 22 locally advanced and 21 metastatic diseases. The metastases were mainly located in the liver (15 of 43), lymph nodes (14 of 43), peritoneum (nine of 43), lungs (six of 43), bones (one of 43) and brain (one of 43).

The PS was good with a majority of PS 0 and 1 (see Table 1). A total of 79 chemotherapeutic cycles were administered, with a median number of cycles per patient of 2. The treatment was administered as first-line chemotherapy in 39 of 43 patients and as a second-line therapy in four patients. Ten patients with stage III (UICC 1997) esophageal cancer were previously treated by neoadjuvant 5-FU/cisplatin-based chemo-radiotherapy.

Toxicity

The weekly 5-FU/cisplatin regimen was well tolerated. Six patients experienced a grade 3/4 neutropenia (14%), two neutropenic fever (5%), three severe anemia (7%) and six thrombocytopenia (7%). Grade II/III diarrhea occurred in three patients (7%) and nausea/vomiting in one (2%), but were well controlled by anti-diarrheic and anti-emetic agents. Renal insufficiency grade 2 and 3 were observed in two and one patients, respectively. No treatment-related death was observed (Table 2). No patient had hair loss and no ototoxicity was observed.

Activity

All patients were assessable for response to chemotherapy (Table 3). Nineteen patients (44%) achieved an objective

Table 3 Response to chemotherapy

	N	ORR [*N* (%)]	SD [*N* (%)]	PD [*N* (%)]
Esophagus	17	10 (59)	4 (24)	3 (17)
Stomach	12	7 (58)	5 (42)	0 (0)
Pancreas	9	2 (22)	4 (44)	3 (34)
Cholangiocarcinoma	3	0 (0)	2 (67)	1 (23)
Unknown origin	2	0 (0)	1 (50)	1 (50)
Overall response		19 (44)	16 (37)	8 (19)

response (OR), including four of 43 CR (9%) and 15 of 43 PR (35%). SD was observed in 18 of 43 (42%) and PD in six of 43 (14%). Gastric and esophageal cancer were the most chemosensitive tumors with 10 of 17 (59%) and seven of 12 (58%) OR, respectively. Squamous cell carcinoma (SCC) of the esophagus was particularly sensitive to chemotherapy with eight of 13 (61%) patients who responded to treatment, including three CR. Ten of the 13 patients with a SCC received previous neo-adjuvant radio-chemotherapy that included 5-FU/cisplatin before and after radiotherapy, of whom five responded to treatment. Two patients (4.6%) suffering from locally advanced pancreatic cancer had a PR.

Median time to progression (TTP) was 6.5 months (range 2–8). For gastric cancer it was 5.5 months (range 3–8).

Discussion

DNCC generally have a grim prognosis. Most of the patients have locally advanced or metastatic disease when they are diagnosed and palliative chemotherapy appears to be the only valuable option in their management [1–4]. Various 5-FU/cisplatin-based chemotherapies have been used in gastric, pancreatic and esophageal cancer. Despite an obvious activity illustrated by a significant level of ORs, the median survival time remains poor. In gastric cancer, where these combinations have been the most investigated, response rates vary from 20% for 5-FU/cisplatin (continuous infusion of 5-FU 1 g/m^2/day for 5 consecutive days and cisplatin 100 mg/m^2 1-h infusion with hyperhydration on day 2, every 29 days) [9], 43% for PELF (cisplatin 40 mg/m^2 i.v. days 1 and 5; epirubicin 30 mg/m^2 i.v. on days 1 and 5; leucovorin 200 mg/m^2 i.v. bolus on days 1–4; and 5-FU 300 mg/m^2 i.v. bolus, days 1–4, administered every 3 weeks) [10] and 45% for ECF (cisplatin 60 mg/m^2 i.v. day 1, repeated every 3 weeks; epirubicin 50 mg/m^2 i.v. day 1, repeated every 3 weeks; 5-FU 200 mg/m^2/day continuous i.v. for 3 weeks) [11]. However, the median survival times were 7.2, 8.1 and 8.9 months, respectively, i.e. not significantly different from that of 7.3 months previously obtained with FAMTX [16].

Although our study was not designed and has no statistical power to firmly assess the activity of our weekly 5-FU/FA/cisplatin regimen, our response rate of 44%, all DNCC tumors included, suggests that its activity is in the range of the previously reported, comparable, 5-FU/cisplatin-based regimens [9–11].

The toxicity of our regimen is moderate. The main toxicity encountered in our trial was hematological with 14% grade III–IV neutropenia. Digestive toxicities were low and no severe renal insufficiency was observed (Table 2). When compared to 5-FU/FA and the bi-weekly administration of cisplatin, neutropenia was seen in a higher proportion of patients (14 versus 10%) [15].

Conclusion

If one assumes that response rate is often concomitant to improvement in quality of life [2] and that the patients prefer a fully ambulatory treatment, we believe that our outpatient regimen that combines activity and moderate toxicity could be a reasonable alternative schedule. New palliative chemotherapy including taxanes and CPT-11 are currently under investigation. One may hope that these new approaches will significantly modify the grim prognosis of DNCC patients

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