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Short Communication

Doxifluridine in Colorectal Cancer Patients Resistant to 5-Fluorouracil (5-FU) Containing Regimens

E. Bajetta,[1] M. Di Bartolomeo,[1] L. Somma,[1] M. Del Vecchio,[1] S. Artale,[1] F. Zunino,[2] P. Bignami,[3] E. Magnani[1] and R. Buzzoni[1]

[1]Division of Medical Oncology B; [2]Division of Experimental Oncology B; and [3]Division of Surgical Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy

Doxifluridine(5-dFUR) is a fluoropyrimidine derivative, which is preferentially converted to 5-fluorouracil (5-FU) within tumour tissues. Although the activity of 5-FU in metastatic colorectal cancer is well recognised, resistance to this agent is frequently observed and remains its major limitation. The aim of this phase II study was to evaluate the activity of oral and i.v. 5-dFUR in metastatic or locally advanced colorectal cancer patients, who had been previously treated with a 5-FU containing regimen in either an adjuvant or metastatic setting. We treated 48 patients who, on the basis of tumour progression during, or within 8 weeks of the discontinuation of 5-FU therapy, were considered 5-FU resistant, 14 of the patients received 5-dFUR 3000 mg/m^2 as a 1-h i.v. infusion, combined with L-leucovorin 25 mg/dose on days 1–5, every 3 weeks; the remaining 34 received oral 5-dFUR 1200 mg/m^2 for 5 days followed by 5 days off. Oral L-leucovorin 25 mg/dose was administered 2 h before 5-dFUR. On the basis of WHO criteria, 4/14 (29%, 95% CI 4–51) partial responses were noted in the i.v. treated patients, and 4/34 (12%, 95% CI 1–23) in those treated orally. The radiological examinations documenting the response were a CT scan in 4 cases, ultrasound in 2 and NMR in 2. The median response duration was 6 months (range 3–11+), whereas the median time to treatment failure was 4 months (range 2–17). The responses were achieved in cases previously treated with a median of 9250 mg/m^2 (range 5500–18650) of 5-FU. No CTC-NCI grade 4 toxicity was observed, although grade 3 diarrhoea occurred in 5 of the orally treated and in 3 of the intravenously treated patients. This is the first report documenting the efficacy of 5-dFUR in patients resistant to 5-FU therapy, and suggests that there is an absence of complete cross-resistance between these two fluoropyrimidines.

Key words: colorectal cancer, fluoropyrimidine, doxifluridine

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INTRODUCTION

DOXIFLURIDINE (5-deoxy 5-fluorouridine; 5-dFUR) is a fluoropyrimidine derivative first synthesised by Cook [1]. It cannot be phosphorylated and assimilated into nucleic acid unless it is first metabolically converted into 5-fluorouracil (5-FU) by the action of uridine phosphorylase. 5-dFUR cytotoxicity seems to depend on its cellular presence, and is probably restricted to those cells which have a high degree of uridine phosphorylase activity. Bollang and Hartmann have found that the drug has a better therapeutic index than other fluoropyrimidines such as 5-FU and fluxuridine (FUDR) [2, 3]. The low level of uridine phosphorylase activity in bone marrow explains the absence of 5-dFUR myelosuppressive toxicity.

The systemic availability of unchanged drug after oral 5-dFUR administration ranges from 50% to 80% (depending on the dose schedule), which is much higher than that of 5-FU [4]. Clinical trails of the oral formulation, carried out in Japan, have demonstrated its therapeutic efficacy and mild toxic effects in patients with advanced gastrointestinal carcinomas, and this led to its commercial approval [5, 6].

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Correspondence to E. Bajetta.
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Different schedules have also been extensively tested in patients with advanced colorectal carcinoma [7–9].

The efficacy of 5-dFUR in colorectal cancer patients has been documented in three clinical trials carried out at the Istituto Nazionale Tumori of Milan [10–12]. The first was a randomised phase III study comparing intravenous 5-dFUR and 5-FU, and demonstrated the better activity of the former; the second was a phase II study that confirmed the efficacy and tolerability of the association of the oral formulation and leucovorin in both pretreated and untreated patients; the third was a randomised, non-comparative phase II trial that separately evaluated the activity of two schedules of oral or intravenous (i.v.) 5-dFUR plus leucovorin in the treatment of advanced colorectal cancer [10–12]. Despite the availability of a wide range of chemotherapeutic agents, only a few single drugs have so far been found to be significantly active against colorectal cancer. 5-FU is the most widely-used drug for advanced colorectal cancer and, when given as first-line treatment in randomised investigations, has led to an objective response rate of 10–20% [13, 14]. The biochemical modulation of 5-FU by leucovorin has improved response rates, but its impact on survival is minimal [15]. Nevertheless, while the majority of patients do not respond or progress after achieving a brief benefit, this combination still represents the standard treatment of advanced colorectal cancer. The failure of conventional chemotherapy to provide lasting disease remission has prompted investigations to seek alternative treatment strategies.

The results of only one trial have provided evidence of the efficacy of 5-dFUR in patients previously treated with 5-FU [16]. On the basis of this background, the present study investigated the role of 5-dFUR in a selected group considered 5-FU resistant among 118 5-FU pretreated consecutive patients.

PATIENTS AND METHODS

Patient population

Between April 1992 and December 1994, a randomised non-comparative phase II study was conducted in order to evaluate the efficacy of 5-dFUR in 118 consecutive metastatic colorectal cancer patients who had been previously treated with a 5-FU containing regimen in either an adjuvant or metastatic setting. The patients, all of whom had histologically proven adenocarcinoma of the colon or rectum, and had been pretreated with chemotherapy regimens containing bolus or continuous infusions of 5-FU, were randomised to receive for their metastatic disease either oral or i.v. 5-dFUR. The present report describes a selected group of patients who were considered to be 5-FU resistant if clear and documented tumour progression occurred during 5-FU therapy or within 8 weeks of the last 5-FU administration in either an adjuvant or metastatic setting. Progression had to be demonstrated by two successive imaging investigations (CT scan or ultrasound), separated by an interval of no longer than 6 months, and showing a more than 25% growth of the target lesions or the appearance of new lesions. The patients had to have been treated with no more than two chemotherapy programmes involving 5-FU (including intra-arterial hepatic infusion), one of which had to have been given as adjuvant therapy.

The patients had to have measurable lesions; be $\leq$75 years of age; have an ECOG performance status $\leq$2; a WBC count $\geq$4000/mm^3; a platelet count $\geq$100000/mm^3; normal renal function; and a total bilirubin level of $\leq$3 mg/dl. Cases with uncontrolled infections or metabolic disease, active CNS disorders or known cerebral metastasis, and those who had received prior radiotherapy on the measurable lesions, were excluded from the analysis.

Treatment and study design

Oral 5-dFUR was given at a dose of 1200 mg/m^2 for 5 consecutive days (followed by 5 days off), with L-leucovorin 25 mg/dose being administered 2 h before and the i.v. dose was 3000 mg/m^2 in a 1-h daily infusion for 5 consecutive days every 21 days, again with a L-leucovorin 25 mg/dose. The first response evaluation was made after five cycles of oral and three cycles of i.v. therapy. In the case of documented stable disease or an objective response, a further four and two cycles were given, respectively. It was also planned to deliver another four and two cycles to the patients with a confirmed objective remission, thus meaning that a maximum of 13 cycles were administered to the oral group and seven to those treated i.v. The patients with disease progression were considered suitable for supportive care.

Assessment of response and toxicity

The pretreatment evaluations included complete blood chemistry, renal and hepatic function tests, chest X-ray, abdominal ultrasound or computed tomography (CT) scan, ECG, and any other appropriate procedure, all of which were performed during the month preceding the start of treatment and repeated at the times of re-evaluation. Responses were defined as follows: a complete response (CR) as the disappearance of all known disease, determined on two successive occasions, at an interval of at least 4 weeks; a partial response (PR) as a >50% decrease in the cross-sectional areas of the measurable lesion; stable disease (SD) as a <25% change in the extent of the disease, with no appearance of new lesions; and progressive disease (PD) as a >25% increase in the area of measurable disease, or the appearance of new lesions. The occurrence of pleural effusion or ascites was also considered as PD in the presence of positive cytology. The response evaluations were reviewed by an independent Oncologist Review Board.

Side-effects were graded according to the Common Toxicity Criteria (CTC-NCI) of Bethesda's National Cancer Institute [17] and evaluated at the beginning of each cycle. In the case of grade 3 leuko-thrombocytopenia, diarrhoea or mucositis, the therapy was discontinued until recovery and then restarted at 50% of the dose. In the case of grade 4 toxicity, or grade 3 toxicity at two consecutive evaluations, the therapy was definitively stopped.

RESULTS

The present study is based on 48 patients considered to be 5-FU resistant who were fully evaluable for response and toxicity; all had been previously treated with adequate doses of 5-FU (not less than 5500 mg/m^2). Thirty-four of the enrolled patients were treated with oral 5-dFUR and L-leucovorin; 14 received i.v. 5-dFUR and L-leucovorin. Their main characteristics are shown in Table 1. Recto-sigmoid cancer (63%) was the most frequent primary site, colon cancer being evident in 37%; 69% of the cases had liver metastases, with this being the only metastastic site in 37%.

Table 1. Main characteristics of 5-FU-resistant patients

	No. of patients
Total entered	48
Male/female	26/22
Median age (range; years)	56 (30–75)
PS (ECOG): 0–1/2	35/13
Disease status	
Local relapse	4
Metastatic	40
Metastatic plus local relapse	4
Sites of metastases	
Liver	33
Lung	18
Lymph nodes	9
Liver involvement	
>30%	4
≤30%	29
Primary tumour	
Colon	18
Recto-sigmoid	30

Abnormal levels of lactic dehydrogenase were documented in 16 patients (median 864 U/l; range 463–1620 U/l; normal value: 230–460 U/l); CEA levels were measured in 35 patients and were high in 30 (range 22–4800 μ/ml; normal value 0–5 μ/ml).

15 of the patients had received 5-FU as adjuvant treatment (4 had received 5-FU alone and 11 5-FU 370 mg/m^2 plus leucovorin 100 mg/m^2, as a bolus injection for 5 days every 21); the remaining 33 had received palliative treatment for metastatic disease, using the same combination. Only 3 cases had received 5-FU or FUDR as an intra-arterial hepatic or intraportal infusion. 4 of the patients had been pretreated with two treatment lines.

Response

A total of 8 patients responded (4 in each group), 29% in the i.v. group (95% CI 4–51) and 12% in the oral group (95% CI 1–23). CT scan, ultrasound and NMR revealed a partial response in 4, 2 and 2 patients, respectively. Figure 1 shows disease regression after three cycles of i.v. 5-dFUR. There were 5 cases of SD and 35 of PD. The median response duration was 6 months (range 3–11+), and the median time to treatment failure 4 months (range 2–17). All the responsive patients had had progressive disease when treated with 5-FU plus leucovorin bolus after a median total dose of 9250 mg/m^2 (range 5500–18650). The partial responses were more frequent in the patients whose primary site was the colon (22%) than in those in whom it was the rectosigma (13%). The liver and lymph nodes were the most responsive sites, responding in, respectively, 18% and 22% of the patients. No activity was observed on lung metastasis. Of the 4 patients with >30% liver involvement, only one benefited from the therapy. The baseline lactic dehydrogenase level was high in 2 of the responsive patients (677 and 881 U/l), in both of whom a reduction was observed. In the 30 patients with high baseline CEA levels, no notable modification was observed during the treatment.

Side-effects

All the patients completed the treatment programme. No CTC-NCI grade 4 side-effect was observed. The main toxicity was diarrhoea, CTC-NCI grade 3 being reported in 5 of the orally-treated and in 3 of the i.v.-treated patients. The other mild–moderate toxicities included mucositis, which was more frequent in the i.v. group.

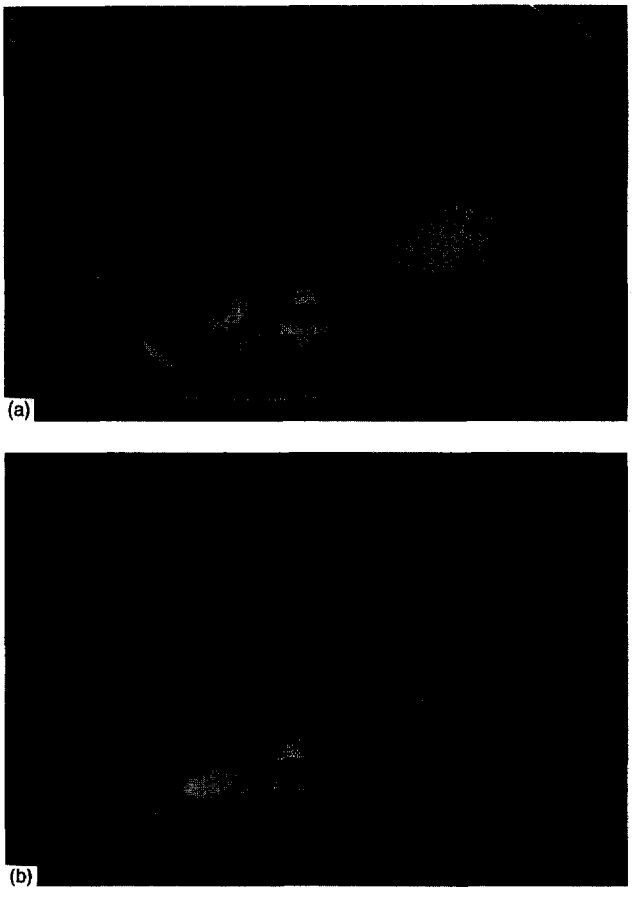

Figure 1. CT scans before (a) and after (b) chemotherapy, showing a marked reduction in liver metastases.

DISCUSSION

Although 5-FU is considered the mainstay of colorectal cancer therapy, many patients do not respond at all and, of those who do, few are complete responders and the duration of their response is generally short. An effective second-line chemotherapy would therefore be very useful.

Our experience suggests that 5-dFUR can be considered a valid alternative in patients failing to respond to 5-FU. The biochemical basis of fluoropyrimidine resistance has been extensively studied, and it has been shown that, before exerting its action, the drug is first transported into the cells and then metabolised by three major routes: anabolism to fluorouridine trisphosphate (FUTP), with the consequent inhibition of DNA and RNA synthesis; anabolism to fluorodeoxyuridine-monosphosphate (5-FdUMP) combined with thymidylate synthase; and catabolism by means of dihydrouracil dehydrogenase, with subsequent degradation of fluoro-β-alanine [18, 19].

One or more of these may be operative at any one time, depending on the drug (5-dFUR or 5-FU) and its schedule of administration. It has been documented that the RNA effect is related to pulse administration, and that thymidylate synthase inhibition and the DNA effect are related to prolonged 5-FU exposure. Moreover, there is evidence that

continuous exposure to 5-FU eradicates the cells that are resistant to short pulses [20, 21].

The incomplete cross-resistance between 5-dFUR and 5-FU can only be partially explained in terms of their pharmacokinetics. The activity of 5-dFUR is partially due to its intratumoral activation and the consequent inhibition of DNA and RNA synthesis, and partially due to the fact that its conversion to 5-FU ensures greater tumour cell exposure. In a previous study, we assessed the pharmacokinetic parameters of 5-dFUR and 5-FU in 20 patients receiving oral 5-dFUR, and found that the plasma concentrations of 5-dFUR and 5-FU remained relatively constant during treatment [11, 22]. These data may explain the efficacy of 5-dFUR after 5-FU pulse exposure, as the pro-drug continuously exposes tumour cells to 5-FU.

Another possible explanation is that the therapeutic index of 5-dFUR is up to 14 times better than that of 5-FU and other fluoropyrimidines, such as FUDR [2]. The reason for the antitumour activity and the low degree of myelotoxicity of 5-dFUR is documented by various investigations on cell metabolism, some of which have found a higher concentration of 5-FU in tumour cells after the administration of 5-dFUR than after the administration of 5-FU itself [23].

To the best of our knowledge, this is the first report proving the incomplete clinical cross-resistance between of 5-dFUR and 5-FU. In 1985, Taguchi and associates observed some activity of oral 5-dFUR in patients affected by breast cancer pretreated with 5-FU, but these cases were not defined as being 5-FU resistant [11].

Our results suggest that, although the response to 5-FU is not defined for all of the patients in this study, the median 5-FU dose administered to our 5-dFUR-responsive cases was 9250 mg/m^2 (about five cycles). This, together with the biological behaviour of colorectal cancer, indicates that the mechanism of resistance is *de novo*. The efficacy of 5-dFUR in colorectal cancer patients has also been documented by preclinical studies of human colon cancer models, in which 5-dFUR has been found to be more effective than 5-FU [24]. In addition, the good tolerability of both i.v. and oral 5-dFUR administration supports the use of this drug as a second-line treatment, and maintaining the quality of life through the use of the oral schedule became our goal in palliative treatment.

Further studies are required to define the optimal oral 5-dFUR schedule in order to improve its efficacy as a first-line treatment of colorectal cancer.

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