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Clinical report

Results of leucovorin and doxifluridine oral regimen in the treatment of metastatic colorectal cancer

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We conducted a multicentric phase II study on advanced colorectal cancer to determine the efficacy and toxicity of oral treatment with leucovorin (LV) plus doxifluridine (5′DFUR), a novel fluoropyrimidine derivative with proven antitumor activity in different experimental models. Thirty-six outpatients with measurable disease entered the trial and received orally LV 20 mg in the morning and in the afternoon, and 2 h later 5′-DFUR 500 mg/m^2 every 2 days for 3 months. Thirty-four evaluable patients underwent a total of 408 weeks of treatment. The response rate was 35%, with two complete remissions and 10 partial responses. The median survival of patients who responded to treatment (responders) was 17.1 months (range 4–32), which was significantly longer ($p < 0.001$) than the 6.5 months (range 2–11) of the patients who did not respond (non-responders). Therefore, after 4–8 weeks of treatment, 14 patients (41%) had an improvement in their performance status and/or stabilization of pain. General toxicity was usually mild, myelo and gastrointestinal toxicity were moderate, and there was no evidence of relevant neurological toxicity. These results show that a home therapy with oral LV–5′DFUR is a safe and effective treatment regimen for metastatic colorectal carcinoma. [© 1998 Lippincott Williams & Wilkins.]

Key words: Doxifluridine, leucovorin, metastatic colorectal cancer, oral therapy.

Introduction

The treatment of metastatic colorectal carcinoma presents a difficult challenge to the oncologist; despite the therapeutic progress, over 50% of patients diagnosed with colorectal cancer still die of metastatic disease.[1] Hepatic metastases are the major cause of death and morbility; half of these patients develop recurrent disease and liver is the main site in 60% of these recurrences.[2] Out of this 60% only 25% of patients are eligible for resection (unilobar liver metastasis or solitary lesion). Most patients with recurrent disease are suitable for chemiotherapeutic regimen.

Current treatments for metastatic colorectal carcinoma are inadequate. Therapy with 5-fluorouracil (5-FU), the only active single agent, results in objective remissions in only 3–20% of patients, with few complete responses, few durable remissions and no improvements in overall survival.[3,4] Studies combining 5-FU with biochemical modulators, either leucovorin (LV) or interferon, improved the response rate to 20–40%.[5–7] Nevertheless, the median survival time of these patients does not exceed 12 months and the percentage of patients who really benefit from these treatments cannot be considered satisfactory.[8] Consequently efforts have been made towards finding 5-FU derivatives with better antitumor activity and less toxicity. Doxifluridine (5′-deoxy-5-fluorouridine) (5′DFUR), synthesized by Cool *et al.* in 1976,[9] is a new fluoropyrimidine derivative with significant antitumor activity in animal models.[10,11] Its molecular structure consists of a 5-FU molecule attached to a pseudopentose. Due to the missing hydroxyl group in the 5′ position, this compound cannot be directly metabolized in DNA or RNA synthesis, but may serve as a 5-FU prodrug in the cell following cleavage by a pyrimidine phosphorylase.[12] In man, 5′DFUR has been found to be active in breast, stomach, colorectal, and head and neck cancers.[13] Furthermore, the drug may be administered orally with very low general and gastrointestinal toxicity.[8]

In order to achieve a high response rate together with a low treatment-related toxicity we employed an

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oral LV plus 5'DFUR regimen to obtain the same effects of 5-FU continuous infusion that has recently proved its efficacy in the treatment of metastatic colorectal cancer.[14]

Patients and methods

Patients

Between September 1994 and May 1997, we recruited 36 patients with metastatic or surgically unresectable colorectal carcinoma. All of them signed their informed consent. Eligibility criteria included histologically proven metastatic or surgically unresectable adenocarcinoma with measurable or assessable disease serving as an indicator of response to treatment, patient age younger than 75 years, life expectancy of at least 6 months, Karnofsky performance status $\geqslant 40$,[15] no previous treatment for 6 months, and adequate hematologic (leukocyte count $\geqslant 4000/\mu l$, hemoglobin level $\geqslant 10$ g/dl, platelet count $\geqslant 150\,000/\mu l$), hepatic (serum bilirubin level $\leqslant 1.5$ mg/dl) and renal function (serum creatinine level $\leqslant 1.5$ mg/dl). Patients with ascites, pleural diffusion, bone metastases as the single lesion or active CNS disorder or known cerebral metastases, uncontrolled infections or metabolic disease, were considered ineligible.

The main characteristics of the 34 evaluable patients are summarized in Table 1.

Table 1. Clinical characteristics of patients

Enrolled patients	36 (27M/9F)
Evaluable patients	34 (26M/8F)
Median age [years (range)]	60 (41–74)
Pretreatment	
adjuvant chemotherapy (LV–5-FU)	18
first-line chemotherapy (LV–5-FU)	10
untreated before	6
Performance status (Karnofsky)	
40–60	5 (15%)
60–80	13 (38%)
80–100	16 (47%)
Primary tumor site	
colon	27
rectum	7
Disease site	
locoregional	7 (21%)
liver	18 (53%)
lung	5 (15%)
lymph nodes	4 (11%)

Treatment

Patients received orally LV 20 mg in the morning and in the afternoon, and 2 h later 5'DFUR 500 mg/m^2 every 2 days for 3 months. In responders and stable disease patients, treatment was extended for 6 months.

5'DFUR 500 and 750 mg tablets were kindly supplied by Roche (Milan, Italy).

No antiemetic prophylaxis was prescribed. The assessment of drug intake was done both by questioning patients at each visit and by accurate drug monitoring.

Evaluation of response and toxicity

The response rate was assessed every 4 weeks. Response, response duration, survival time and treatment-related toxicity were defined according to the World Health Organization (WHO) criteria.[15] *Complete response* (CR), the complete disappearance of all evaluable signs of the tumor in two consecutive observations not less than 4 weeks apart. *Partial response* (PR), more than 50% decrease in the cross-sectional areas of the measurable lesions. *Stable disease* (SD), less than 25% change in the extent of the disease and no appearance of new lesions. *Progressive disease* (PD), more than 25% increase in these measurements and/or the appearance of new lesions.

In the presence of CR, PR or SD patients were treated for a maximum of 6 months (two periods of 3 months of treatment and an interval of 1 month with no treatment). In the presence of PD, patients were treated until they progressed.

Results

Thirty-four of the 36 patients who entered this study had an adequate trial, and were assessable for both response and toxicity. One patient refused to continue the therapy during the first week and another died of cerebral hemorrhage during the second month of treatment.

The 34 evaluable patients underwent a total of 408 weeks of treatment. Responses became apparent after a median of 6 weeks (range 4–8) and are summarized in Table 2. Of these, two (6%) were CRs and 10 (29%) PRs, with a total response rate of 35% [95% confidence limits (CI): 27–50]. No evidence was found as to a preferential site of response. SD was seen in 14 patients (41%) and PD in 8 (24%). The median survival

Table 2. Tumor response by dominant measureable site

Localization	No.	CR	PR	SD	PD
Locoregional	7	–	3 (42)	2 (29)	2 (29)
Liver	18	1 (6)	5 (28)	7 (39)	5 (27)
Lung	5	–	2 (40)	2 (40)	1 (20)
Lymph nodes	4	1 (25)	–	3 (75)	–

Pecentages in parentheses.

Table 3. Toxicity of LV–5′DFUR oral regimen

Side effect	No. of patients at toxicity grade[a]				
	0	1	2	3	4
Nauseas/vomiting	10 (29)	12 (36)	10 (29)	2 (6)	–
Diarrhea	9 (26)	6 (18)	12 (35)	7 (21)	–
Mucositis	11 (32)	15 (44)	4 (12)	4 (12)	–
Gastric pain	15 (44)	17 (50)	2 (6)	–	–
Myelosuppression	12 (35)	17 (50)	5 (15)	–	–
Neurological	13 (38)	17 (50)	4 (12)	–	–

[a]According to WHO criteria.[15]
Percentages in parentheses.

duration of responders was 17 months (range 7–32), which was significantly longer ($p < 0.001$) than the 7 months (range 2–11) of non-responders, while the median duration of SD was 13 months (range 5–28). No evidence was found of any significative difference in these parameters between pretreated and previously untreated patients. Moreover, after 4–8 weeks of treatment, 14 patients (41%) had an improvement in their performance status and stabilization of pain.

Toxicity

Treatment was well tolerated and both the acute and cumulative side effects were manageable and reversible. Toxicities are summarized in Table 3. As reported by others,[14] the main toxicity was gastrointestinal and tended to be cumulative after 2 months of treatment. However, no patient had severe stomatitis or diarrhea (WHO toxicity grade >3). None required hospitalization for severe myelosuppression. Infections (mainly pulmonary) experienced by five patients were all manageable on an outpatient basis. Nausea and vomiting were not major problems, and hepatic, renal and neurologic toxicity were not remarkable. No significant differences were found in terms of tolerability between previously untreated and pretreated patients.

Discussion

In chemotherapy of metastatic colorectal cancer, the response rate in 5-FU-based regimens is generally about 20%. Recently, an intensive chemotherapeutic protocol has been developed that proved to be effective in 35% of cases, but associated with a higher incidence of drug toxicity: 18% of patients experienced severe or life-threatening leukopenia.[16] Biochemical modulation of 5-FU with LV, PALA or interferon seems to yield promising results, although only the combination of 5-FU with LV has proved superior to 5-FU alone in prospective randomized trials.[17] Based on these results, attempts were made to improve the therapeutic benefit of 5-FU alone or 5-FU plus LV: route, schedule and the use of prolonged or continuous i.v. infusion were modified, in order to obtain a higer dose per unit of time and the lack of myelotoxicity.[18,19] These regimens have improved the objective response rate, and sometimes the quality of life and survival of patients, even if more effective agents are clearly needed. 5′DFUR is a prodrug of 5-FU, selectively activated by tumor cells.[20] Clinical studies have shown that the side effects of 5′DFUR differed after i.v. or oral administration, while preclinical studies suggest that the oral route was the most promising way of administration. Clinical data indicated that 5′DFUR is well tolerated when administered orally and frequently has a better therapeutic efficacy than 5-FU if used on an adeguate schedule. In this trial we evaluated the real efficacy and tolerability of the LV–5′DFUR oral regimen. We used this treatment protocol to reproduce the action of a biological modulator (LV) and the continuous infusion regimen of fluorinated pyrimidines through an oral route. Our phase II trial yielded an objective response rate of 35%, with a median survival of 12 months for all patients and 17 months for the responders. Response was linked to good symptom control and responders showed marked improvement in their performance status. Moreover the LV–5′DFUR oral regimen was well tolerated; haematological toxicity, primary leukopenia and thromcytopenia were minimal, gastrointestinal toxicity was mild, and neurological toxicity was not a problem.

Presently, it seems that 5′DFUR biochemically modulated with LV and administered orally every 2 days gives an increase in overall response rate compared to conventional 5-FU or 5′DFUR regimens.[14,21]

In a future trial, we plan to prolong the treatment in responders and SD patients, to increase survival time, and obtain clinical benefits in terms of an improved quality of life and reduction or stabilization of pain.

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