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Clinical report

Phase II trial of 5-fluorouracil, folinic acid and recombinant α-2a-interferon in patients with advanced colorectal cancer

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A clinical trial regimen modulating 5-fluorouracil (5-FU) with both folinic acid (FA) and recombinant α-2a-interferon (rα-2a-IFN) was noted to have a response rate of 54% and median survival of 16.3 months (Grem *et al.*, *J Clin Oncol* 1993, 11: 1737–45). Reported herein is a phase II trial performed to further examine this regimen in metastatic colorectal cancer. Fifty-one patients with histologically proven, measurable advanced colorectal cancer with no prior therapy for metastatic disease were enrolled. rα-2a-IFN, 5 MIU/m^2/day was given s.c. on days 1–7. FA, 500 mg/m^2/day, and 5-FU, 370 mg/m^2/day, were given i.v. on days 2–6. Cycles were repeated at 3 week intervals. Three complete and 12 partial responses were observed for an overall response rate of 29% (95% confidence interval: 18–45%). The median time to treatment failure and median survival were 4.6 and 15.5 months, respectively. Dose-limiting toxicities encountered were gastrointestinal, and included diarrhea, stomatitis, nausea and vomiting. These results do not support the concept of using concurrent rα-2a-IFN and FA as biochemical modulators of 5-FU. We observed increased toxicity and similar efficacy compared to using either modulator separately with 5-FU. [© 1999 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, colon cancer, folinic acid, rα-2a-interferon.

Introduction

Fluorouracil (5-FU) remains the most commonly prescribed agent in both adjuvant therapy for colorectal cancer and the treatment of advanced disease.[1,2] Clinical research on 5-FU over the past 15 years has focused on its biochemical modulation using various agents, including folinic acid (FA),[3–5] methotrexate,[6] *N*-(phosphonoacetyl)-L-aspartic acid (PALA),[7,8] interferons[9–11] and trimetrexate.[12]

FA increases the intracellular folate pools, hence stabilizing the tertiary complex formed by fluorodeoxyuridine monophosphate (FdUMP), 5,10-methylenetetrahydrofolate and thymidylate synthase (TS), and prolonging TS inhibition.[13] A meta-analysis of large clinical trials of 5-FU with FA demonstrated an increased response rate compared to 5-FU alone (23 versus 11%).[14] However, this increased response rate did not result in a conclusive improvement in overall survival.[14] The combination of 5-FU with FA has gained widespread acceptance for the treatment of advanced colorectal cancer and as adjuvant therapy in patients who have undergone potentially curative resections.[15]

Following the original report in 1989 by Wadler *et al.*[16] of impressive response rates using the combination of 5-FU and recombinant α-2a-interferon (rα-2a-IFN) in metastatic colorectal cancer, several phase I and II trials have investigated the possible synergy between these agents. Several preclinical studies attempted to elucidate the mechanism underlying this synergy.[17–20] Multiple mechanisms by which interferons may modulate 5-FU activity have been proposed.[21] These include rα-2a-IFN-mediated increased formation of the active metabolite FdUMP with an associated increased inhibition of TS, suppression of the up-regulation of TS, increased DNA single-strand and double-strand breaks, enhancement of natural killer cell-mediated cytotoxicity, and decreased 5-FU clearance resulting in an increased 5-FU area under the

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curve.[17-24] However, large randomized trials have failed to demonstrate the superiority of 5-FU plus rα-2a-IFN regimens compared to less expensive, less toxic 5-FU plus FA regimens.[25,26]

Initial trials of 'double' biomodulation of 5-FU with concurrent FA and rα-2a-IFN showed promising results. Grem *et al.* studied a regimen of 5-FU, FA and rα-2a-IFN, and reported a response rate of 54% in advanced colorectal cancer [95% confidence interval (CI): 39-70%].[27,28] The median time to treatment failure (TTF) and median survival duration were 7.8 and 16.3 months, respectively. There was, however, significant toxicity, primarily grade 3 and 4 mucositis and diarrhea.[27,28] These impressive results led to the introduction of this regimen by the National Surgical Adjuvant Breast and Bowel Project (NSABP) into the adjuvant therapy for surgically resected Dukes B and C colon cancer patients (NSABP C-05). Other investigators, however, have been unable to reproduce these promising results using various schedules of combined 5-FU, FA and rα-2a-IFN[29-35] (Table 1).

To determine the efficacy of 'double modulation' of 5-FU by FA and rα-2a-IFN we conducted a multi-institutional phase II study in patients with metastatic colorectal cancer using the regimen initially described by Grem *et al.*

Patients and methods

Eligibility criteria

All patients were required to have histologically confirmed colorectal cancer, bidimensionally measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of $\leqslant 2$ and a life expectancy of at least 12 weeks. They had not received any chemotherapy for metastatic colorectal cancer and any adjuvant chemotherapy had to have been completed at least 12 months prior to their enrollment in the study. All patients had an absolute granulocyte count $> 1.5 \times 10^9$/l, a platelet count $\geqslant 100 \times 10^9$/l, a total bilirubin level $\geqslant 2.0$ mg/dl, an alanine transaminase level $\leqslant 4$ times the upper limit of normal and a serum creatinine level $\leqslant 2.0$ mg/dl. All patients were older than 16 years of age and had no severe intercurrent illnesses. Women of child-bearing age were tested for pregnancy prior to the initiation of therapy and were instructed to use contraceptives during therapy. Patients with cerebral metastases were not eligible for the study. All patients were informed of the investigational nature of the study, and provided written informed consent in accordance with institutional and federal guidelines, with the right to withdraw at any time.

Table 1. Selected phase I/II trials of 5-FU, FA and rα-2a-IFN for the treatment of metastatic colorectal cancer

Trial	Patient no.	CR no.	PR no.	% OR
Cascinu[29]	45	6	17	51
Grem[27]	44	3	21	54
Kreuser[30]	45	1	13	31
Labianca[31]	56	2	13	24
Loffler[31]	54	4	23	50
Punt[33]	10	0	3	30
Schmoll[34]	32	0	3	9
Yalavarthi[35]	31	0	7	23
Total	317	16	100	35

Treatment plan

This was a single-arm, non-randomized trial using the regimen described by Grem *et al.*[27] rα-2a-IFN, 5 MIU/m^2/day, was administered s.c. on days 1-7. Leucovorin, 500 mg/m^2/day, was given i.v. over 30 min on days 2-6. One hour after each dose of FA was infused, 5-FU, 370 mg/m^2/day, was administered i.v. over 15 min. To reduce the severity of mucositis, patients were instructed to use ice chips by mouth beginning 5 min before 5-FU infusion was started and continuing for 30 min after its completion. Courses of treatment were repeated every 21 days as long as all toxicities had resolved.

Toxicities were graded according to the criteria of the National Cancer Institute and dose modifications were performed based on the toxicities encountered, as specified in the original trial using this regimen.[27] For hematologic toxicity of grade 0-1, the 5-FU dose was increased by 15% in the next course. No change was made with grade 2 or 3 hematologic toxicity, but the 5-FU dose was decreased by 15% for grade 4 hematologic toxicity, and for grade 3 and 4 stomatitis, diarrhea or other non-hematologic toxicities. In addition, the rα-2a-IFN dose was reduced by 25% for grade 3 or 4 constitutional symptoms or if the performance status declined by one level from the baseline. All chemotherapy courses were held until the absolute granulocyte count was $\geqslant 1.5 \times 10^9$/l and the platelet count was $\geqslant 80 \times 10^9$/l.

Treatment was continued for at least two courses if there was no disease progression. Patients achieving a complete remission (CR) were to continue therapy for 12 months, while patients with partial responses (PR) were to continue the regimen until there was evidence of disease progression. Those patients with stable

disease or with minor responses were allowed to continue therapy at the discretion of the study chairman.

Patient evaluation

All patients had a pre-treatment history, physical examination, chest X-ray and laboratory studies, including a complete blood count, urinalysis, carcinoembryonic antigen (CEA) measurement and serum chemistries. Computed tomography of the involved sites was performed to define the extent of disease. Complete blood counts were performed weekly during the first course and then prior to the start of each course. History and physical examination were performed prior to each course, and a CEA measurement and chemistry profile were obtained at least once per course. Radiologic evaluation was performed after every two courses. The longest diameter and its perpendicular were measured for each tumor, and tumor size was reported as the product of the two measurements. The criteria for response used in the original report of this regimen were used in the evaluation of our patients.[27]

Statistical methods

The method proposed by Simon for conducting phase II trials was used.[36] After 45 patients were accrued the regimen would be declared worthy of further investigation if at least 20 responses (44%) had been documented. Early termination would be deemed appropriate if no more than nine responses (36%) were observed in the first 25 patients. This design would therefore have at least a 0.92 power to detect a minimum response of 55%. If the true response rate was no greater than 35%, the regimen would be rejected with a probability of at least 0.63. Survival curves were calculated using the Kaplan–Meier method.

Results

The characteristics of the 51 patients enrolled in the study are listed in Table 2. All the patients had colorectal tumors histologically confirmed to be adenocarcinoma. Major sites of metastatic disease were liver, lung, lymph nodes and soft tissues. Most patients had excellent performance status (0–1); only two of the 51 patients had a performance status of 2 at the study entry. The median age was 58 years (range 28–76 years). Eighty percent of patients enrolled in the study had not received any prior adjuvant chemotherapy. Prior adjuvant chemotherapy in the other 20% consisted of: 5-FU only (one patient), 5-FU plus FA (six patients), 5-FU plus levamisole (one patient), 5-FU plus rα-2a-IFN (one patient) and 5-FU plus FA plus rα-2a-IFN (one patient). Forty-seven patients were evaluable for response to therapy and all 51 patients were evaluable for toxicities. Four patients received only one course of the treatment and refused further participation secondary to toxic side effects. These included grade 3 diarrhea and grade 2 stomatitis in one patient, grade 3 nausea and anorexia in one patient, grade 4 diarrhea in one patient, and rα-2a-IFN-related fever in one patient.

Table 2. Patient characteristics

Characteristic	Patient no.
Total patients	51
Age [median (range)]	58 years (28–76 years)
Sex	
female	21
male	30
Performance status (ECOG)	
0	20
1	29
2	2
Sites of metastases	
liver	35
lung	7
lymph nodes	9
soft tissue/omentum	3
ovaries	1
Prior therapy	
none	5
chemotherapy (adjuvant)	10
immunotherapy	3
radiation	4
surgery	44

A summary of the toxicities encountered is presented in Table 3. Dose escalation was permitted if minimal toxicities were encountered with the initial course. Only one patient received dose escalation to 425 mg/m^2/day dose level. This patient subsequently developed grade 4 granulocytopenia. At the 5-FU dose of 370 mg/m^2/day, the most common dose-limiting toxicities were gastrointestinal. Grade 3 or 4 diarrhea occurred in 19 patients (37%), resulting in subsequent 5-FU dose reductions. Grade 3 or 4 stomatitis developed in 14 patients (28%). Nausea and vomiting were common toxicities, occurring in 21 (41%) and 19 (37%) patients, respectively. However, only one patient developed grade 4 nausea and/or vomiting. Malaise was noted in only three patients (6%); none

Table 3. Toxicity by NCI criteria (n=51)

Toxicity	No. of patients by grade of toxicity			
	1	2	3	4
Fatigue	6	9	7	0
Nausea	8	10	3	0
Stomatitis	8	11	12	2
Alopecia	3	2	0	0
Skin reaction	7	2	2	1
Vomiting	3	9	6	1
Diarrhea	9	14	13	6
Granulocytopenia	3	4	4	3
Drug-induced fever	6	8	0	0
Anemia	2	5	0	0
Thrombocytopenia	2	1	2	0
Malaise	1	2	0	0

had greater than grade 2 malaise. Fatigue occurred in 22 patients (43%), with grade 3 fatigue in seven (14%).

At the initial dose of 370 mg/m^2/day of 5-FU, three patients (6%) developed grade 4 granulocytopenia and required 5-FU dose reduction in subsequent courses. The median granulocyte nadir at this dose level occurred on day 15 and was 2.6×10^9/l (range 0.0–7.5×10^9/l); the median duration of granulocytopenia was 5 days (range 2–18 days). No patients required hospitalization for febrile neutropenia. Thrombocytopenia was seen infrequently, with only two patients (4%) developing grade 3 thrombocytopenia.

Three patients achieved a CR and 12 achieved PR, giving an overall response rate of 29% (95% CI: 18–45%). In addition, 20 patients (39%) had either a minor response or stable disease. All 51 patients died of colon cancer, with a median time to treatment failure of 4.6 months. The median length of the overall survival was 15.5 months.

Discussion

During the past decade, clinical research in advanced colorectal cancer has focused on biochemical modulation of 5-FU, using a variety of agents, to increase its therapeutic efficacy. One such agent, FA, has been established as the modulatory agent of choice in the therapy of colorectal cancer.[15] Other agents investigated include PALA, methotrexate and trimetrexate.[6–12] Interferons were also found to be promising agents able to act synergistically with 5-FU to increase its cytotoxicity.[17–20] The initial clinical trials combining 5-FU with rα-2a-IFN produced impressive response rates, stimulating interest in this method of 5-FU biomodulation.[16]

Grem *et al.* reported a regimen combining 5-FU, rα-2a-IFN and FA in metastatic colorectal cancer.[28] A response rate of 54% (95% CI: 39–70%), including three CRs and 21 PRs was seen among 44 evaluable patients. The median TTF and overall survival were 7.8 and 16.3 months, respectively. 5-FU doses were escalated in 10 patients from 370 to 425 mg/m^2/day. Grade 3 and 4 toxicities included mucositis in 37% of patients, diarrhea in 40%, rash in 7%, fatigue in 14% and granulocytopenia in 13%.

Using the same regimen, inclusion criteria and dose modification criteria, we treated 51 patients with metastatic colorectal cancer with no prior chemotherapy for metastatic disease. Patients had an excellent performance status (0–1), with only two patients having a performance status of 2. Three patients (6%) achieved a CR and 12 patients (24%) achieved a PR, providing an overall intent-to-treat response rate of 29% (95% CI: 18–45%). The median time to disease progression and median overall survival duration were 4.6 and 15.5 months, respectively. These results do not support the concept of using rα-2a-IFN plus FA together to biochemically modulate 5-FU. The efficacy observed was similar to that which could be achieved using 5-FU plus rα-2a-IFN or 5-FU plus FA.[5,9,16]

The grade 3 and 4 toxicities encountered using this three-drug regimen included diarrhea (37%), stomatitis (27%), granulocytopenia (14%), thrombocytopenia (4%), rash (6%), fatigue (14%), nausea and/or vomiting (20%) and rise in bilirubin (2%) (Table 3). These are similar in pattern and frequency to the toxicities reported in the original report of this regimen.[28]

The initial results of this regimen in advanced diseased led to the introduction of this regimen into the adjuvant therapy of colon cancer. However, the NSABP C-05 trial has failed to show a disease-free survival or overall survival advantage for the dually modulated 5-FU regimen with an associated increased toxicity when compared to 5-FU plus FA alone.[37]

Conclusion

Despite the initial enthusiasm for combining modulators of 5-FU, the approach of using both FA and r-2a-IFN with 5-FU has not demonstrated any enhanced therapeutic activity and is associated with increased toxic side effects, including stomatitis, diarrhea and granulocytopenia. Similarly, introduction of this regimen into the adjuvant treatment of surgically resected stage II and III colon cancer (NSABP C-05 trial) has failed to produce an increase in progression-free survival or overall survival compared to a 5-FU plus FA regimen.[37] Future research on the treatment of

colorectal cancer in both the adjuvant and metastatic disease settings should therefore focus on the identification of novel agents.[38,39]

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