

Fluorouracil, Imidazole Carboxamide Dimethyl Triazeno, Vincristine, and bis-Chloroethyl Nitrosourea (FIVB) in Colon Cancer

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Summary. *One hundred and sixty patients with advanced metastatic colon cancer were treated with the drug combination of 5-fluorouracil (FU), imidazole carboxamide dimethyl triazeno (ICDT, DTIC), vincristine (VCR), and bis-chloroethyl nitrosourea (BCNU). All the agents were given in each cycle of treatment. The patients also received continuous ethylestranol. Special care was taken to ensure that the ICDT was not at any time exposed to light. Toxic effects included fall in hemoglobin, leukopenia, thrombocytopenia, alopecia, stomatitis, nausea and vomiting, and occasional diarrhea. Among 112 patients who had had no prior exposure to cytostatic agents, complete remission (CR) was recorded in 12, and partial remission (PR) in 31. The median duration of remission in these patients was 5.2 months. The median survival for the whole group was 8.4 months: for responders the median survival was 10 months, and for non-responders, 5.4 months. PR was also documented in 10 of 48 patients who had received prior treatment with FU or FU plus methyl-1,3-cis(2-chloroethyl-1-nitrosourea) (MeCCNU).*

Introduction

In 1974, in a randomized clinical trial, we found the four-drug combination of 5-fluorouracil (FU), imidazole carboxamide dimethyl triazeno (ICDT, DTIC), vincristine (VCR), and bis-chloroethyl nitrosourea (BCNU) (FIVB) superior to FU as a single agent in the treatment of patients with advanced colon cancer [6]. The value for the difference in the numbers of responders in the FU and FIVB groups indicated a one-in-four possibility that this had occurred by chance. Douwes has published results similar to ours with FIVB in advanced colon cancer [3].

Various drug combinations have been investigated in patients with metastatic colon cancer, and the failure of the combinations of FU plus cyclophosphamide (CTX) plus methotrexate (MTX) or FU plus CTX plus 1-2(chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) [15] to improve upon the results reported with FU alone have led to conclusions that no drug combinations have been found that are superior to FU alone. When a drug known to be of no value in the treatment of colon cancer, such as CTX [11] is added to the FU regimen, the failure to improve FU results [2] is not surprising. Prospective randomized clinical trials of FU plus methyl-1,3-cis(2-chloroethyl)-1-nitrosourea (MeCCNU) plus VCR versus FU showed advantage for the three-drug combination [5, 10]. In studies in which MeCCNU was only given during alternate courses improved response rates were not confirmed for this combination [7]. The alternate-course scheduling of MeCCNU was used by the Eastern Cooperative Oncology Group (ECOG) and showed no statistical advantage over FU [4]. In ECOG randomized trials, slight but not statistically significant improvement resulted when DTIC was added [9]. In patients previously treated with FU, the response rate to MeCCNU plus ICDT was superior to MeCCNU plus VCR or MeCCNU plus B-2TGDR. Some therapeutic effect for DTIC is therefore confirmed. The light sensitivity of DTIC was demonstrated in 1962, and subsequent reconfirmation of the importance of this finding continues to be published [1, 8, 12]. None of the United States studies of DTIC in the treatment of colon cancer have ensured that precautions were taken to protect the drug from light.

Prognostic factors such as performance status (PS) ($P < 0.001$), weight loss in the 6 months prior to study entry ($P < 0.001$), and prior chemotherapy are of finite prognostic significance and have been shown to have a cumulatively greater influence upon

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survival than the treatment program in the ECOG studies [9].

The present paper deals with patients with metastatic colon cancer treated with the FIVB regimen, with a view to examining these results with reference to patient discriminants, drug scheduling, and administration, as well as ancillary treatment. Patients with rectum cancer are not included, as the pilot study of the FIVB combinations had shown this to be less active in rectum cancer [13, 14].

Materials and Methods

One hundred and sixty patients with measurable metastatic colon cancer were studied. Measurable and/or evaluable disease sites for all patients entered on study were liver metastases in 91, lung in 34, peritoneal mass in 58, and bone in four patients. A full blood count was performed and serum electrophoretic pattern, alkaline phosphatase, bilirubin, serum glutamic oxaloacetic transaminase, α GT, urea uric acid, and creatinines were done at the start of treatment and at regular intervals thereafter. Patients with a performance status (PS) of 4 were excluded from the study, as were patients with abnormal kidney functions or hemogram determination below normal. ECOG PS was used¹ in 112 previously untreated patients. Patients with rectum cancer were not included in this series. At the start of treatment, the ratings were PS 0, 17; PS 1, 42; PS 2, 38; PS 3, 15. Loss of body mass of ≥ 10 kg within the preceding 6 months was recorded in 46 and a loss of less than 10 kg in 66 patients prior to entry on study.

Each treatment cycle consisted of (1) FU 450 mg/m² IV per day for 4–5 days, adjusted to the nearest 100-mg dose; (2) ICDT 260 mg/m² IV per day on days 1 and 2 of each cycle, adjusted to the nearest 100-mg dose; (3) VCR 1.0 mg/m² IV on day 1; (4) BCNU 50 mg/m² on day 1, adjusted to the nearest 100-mg dose; and (5) ethylestranol 2 mg twice daily throughout the treatment time, started if possible at least 3 days before the start of cycle 1. (Ethylestranol was added because of its hematopoietic supportive effect and also because of its general anabolic effect.) Subsequent treatment cycles were started on day 35 and at 5-weekly intervals thereafter. When cumulative hematopoietic toxicity occurred, treatment cycles were postponed and when a longer-term response was obtained, treatment cycles were restarted every 6th and later every 8th week. Particular attention was paid to the technique of drug administration. On day 1, an IV infusion of glucose in normal saline was started. Metoclopramide 1–2 mg was then injected into the tubing. When this had washed through, the FU was injected into the tubing and after 1 or 2 min the VCR was similarly injected into the tubing. The BCNU was freshly prepared and injected rapidly through the tubing, the speed of injection being dictated by the degree of venous spasm experienced by the patients. When the BCNU had been washed through, the ICDT was drawn up in such a way as to prevent all light exposure. An opaque syringe with opaque tubing between the point of entry of the needle and the patient's arm was used, to prevent exposure of the ICDT to light. If marked pain was experienced during ICDT administration, it was usually an indication that this agent had been exposed to light. In patients where the ICDT was accidentally exposed to light in the

syringe or administration set, nausea and vomiting were usually more severe.

Three groups of patients were included: 112 patients with no prior treatment, 29 patients who had had prior treatment with FU, and 19 patients who had received prior FU plus MeCCNU.

Results

Toxic Effects

ECOG toxicity criteria were used, and the toxicity scores are set out fully in Table 1. The major side-effects encountered were hematopoietic suppression, nausea and vomiting, diarrhea, and alopecia. Nausea and vomiting and diarrhea were never more than moderate, and always controllable. While hematopoietic suppression of grade 1 or 2 occurred in a large number of patients, severe or life-threatening hematopoietic toxicity was seen only in a few patients (see Table 1).

Therapeutic Effects

The therapeutic results were graded as follows: complete remission (CR), partial remission (PR) (shrinkage of all measurable lesions by at least 50%) improvement (IMP), no change (NC), and progressive disease (PD). If hepatomegaly was the primary indicator, there had to be a reduction of the sum of liver measurement below each costal margin at the midclavicular line and xiphoid process by at least 30%, with no worsening of pretreatment abnormalities of liver function. Subjective improvement and/or increase in body mass were not considered measurable criteria, but all patients who were graded as CR or PR and had good tumor shrinkage showed improved PS, and in many cases also gained weight.

Complete or partial remission was observed in 38% of patients with metastatic colon cancer treated with FIVB who had had no prior chemotherapy exposure. CR or PR was achieved in 26 (44%) of 59 previously untreated patients with a PS of 0–1, and in 17 (32%) of 53 patients with a PS of 2–3. A response was achieved by 31 (46%) of 66 patients in whom a weight loss of < 10 kg had been recorded at the start of treatment, and by 12 (26%) of 46 amongst whom a weight loss of ≥ 10 kg was recorded at the start of treatment. Among patients with prior exposure to chemotherapy, the response rate was 20%. Of the patients with no prior chemotherapy, 56% can be considered to have benefited from the treatment, while 37% of patients who had received prior FU or

1 0, fully active; 1, ambulatory, capable of light work; 2, in bed $< 50\%$ of time, capable of self-care but not work activities; 3, in bed $> 50\%$ of time, capable of only limited self-care; 4, ineligible for study

Table 1. Results obtained with FIVB in colon cancer

A. Side-effects		ECOG toxicity grade			
		1	2	3	4
Anemia		40	10	5	2
Leukopenia		34	18	9	4
Thrombocytopenia		52	40	4	2
Alopecia		32	79	—	—
Nausea and vomiting		60	76	0	—
Diarrhea		35	3	0	—

		ECOG toxicity grade			
		1	2	3	4
Anemia	Hgb g/100 ml	9.5–10.9	< 9.5	Transfusions needed	
	Clinical		Sx of anemia		
Leukopenia	WBC × 10 ³	3.0–< 4.5	2.0–< 3.0	1.0–< 2.0	< 1.0
Thrombocytopenia	Plt × 10 ³	90–< 130	50–< 90	25–< 50	< 25
Alopecia		Mild	Severe	Vomiting, intractable	
Nausea and vomiting		Nausea	N + V, controllable		
Diarrhea		No dehydration	Dehydration	Grossly bloody	

B. Response	No. of patients	CR	PR	IMP	NC	PD
Prior treatment						
None (1)	28	4	8	4	2	10
None	84	8	23	16	13	24
	112	12	31	20	15	34
FU	29	1	6	4	5	13
FU + MeCCNU	19	0	3	4	2	10

FU plus MeCCNU benefited from treatment. The response is shown in Table 1. The median duration of remission for the 43 patients without prior chemotherapy exposure who responded to FIVB was 5.2 months. The median survival time for all 112 patients was 8.4 months. Median survival for responders was 10 months, and that for non-responders, 5.4 months. This difference (according to median test for the difference in medians for two samples) was statistically significant at $P < 0.001$.

Discussion

In a randomized study undertaken to compare FU with FIVB, we concluded that the combination regimen gave better therapeutic results than the single agent in treating patients with metastatic colon cancer. The number of evaluable patients with

metastatic colon cancer treated by us with FIVB has now been extended to 160. A response rate of nearly 40% was documented. Side-effects encountered included hematopoietic suppression, nausea and vomiting, diarrhea, and alopecia. However, the majority of patients experienced only grade 1 or 2 toxicity. The median survival of patients who responded was 10 months, while the non-responders had a median survival of 5.4 months ($P < 0.001$). Better response rates were seen in previously untreated patients, in those patients with a better performance status, and in patients with < 10 kg weight loss. We therefore conclude that although the FIVB combination gives a higher response rate than single-agent treatment, real benefit in terms of prolonged survival or improved quality of life cannot be expected with this regimen for many patients with advanced colon cancer. It is of the utmost importance that patient discriminants should be borne in mind

when treatment options are considered. Furthermore, when this combination is used, attention to the technique of drug administration, and careful individual monitoring to determine the optimal drug dose that will cross the therapeutic threshold without causing undue toxicity, appear to be of particular importance. At present, while the literature reflects general pessimism in the approach to the patient with metastatic colon cancer, it is appropriate to look for even relatively minor advances in the treatment of this disease.

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