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Dacarbazine and Fotemustine in Advanced Colorectal Cancer

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BIOCHEMICAL MODULATION of 5-fluorouracil by leucovorin, methotrexate, *N*-phosphonacetyl-L-aspartate (PALA) or interferon [1], is a current area of interest in clinical research in advanced colorectal cancer. However, randomised studies have shown little, if any, survival advantage over 5-fluorouracil given alone in most instances [2]. New drugs are clearly needed. Fotemustine (FOTE) is a new nitrosourea that has demonstrated some activity in phase 2 studies against colorectal cancer [3], melanoma, renal cell carcinoma and brain tumours [4, 5].

Preclinical experiments demonstrate that the main mechanism of resistance to this class of alkylating agents is the efficient DNA repair mechanism mediated by the enzyme O^6-alkylguanine-DNA alkyltransferase (ATase) [6]. In experimental tumour systems resistance to nitrosoureas may be temporarily reversed by inactivating ATase. This can be accomplished by the administration of a methylating agent such as dacarbazine (DTIC) [7]. We have transferred this concept to the clinic and tested the sequential combination of DTIC (500 mg/m^2 intravenous bolus) followed 2 h later by FOTE (100 mg/m^2 in 150 cc of 5% isotonic glucose solution) in patients with advanced measurable colorectal cancer. The cycle was repeated after 4 weeks if toxicity allowed and if no progression was observed.

The study was designed according to Simon's two-stage optimal design [8]. P_0 and P_1 were set at 20% and 40%, respectively. Setting alpha error at 0.05 and beta error at 0.20, the combination had to be rejected for untreated patients if three or fewer responses were observed among the first 13 patients or if 12 or fewer responses were observed in 43 patients. Standard WHO criteria were used to assess response and toxicity.

The patients' characteristics are shown in Table 1. A total of 30 cycles were administered (median 2). Thrombocytopenia was the most prominent toxicity, with 26% of patients suffering from WHO grade 3–4, while 1 patient only had leukopenia grade 3. Other toxicities were very mild, including nausea and vomiting that was well controlled by ondansetron. Interestingly, the only patient who did not receive the serotonin antagonist suffered from grade 3 vomiting.

No partial or complete responses were observed in the first 13 previously untreated patients and the study was terminated. 6 stable disease and 7 failures were observed among these patients. No response was also obtained in an additional 6 patients who failed prior chemotherapy with 5-fluorouracil (3 stable disease and 3 failures). These data indicate the lack of activity of this combination in advanced colorectal cancer. A longer interval between the two agents might have allowed significant depletion of ATase activity [6]. The importance of the interval between the agents may be as critical as it is for the sequential methotrexate-5-fluorouracil combination where no synergy occurs clinically for short (<4 h) intervals [9], as compared with longer intervals [10].

Table 1. Patients' characteristics

Patients entered	19
No previous treatment	13
Prior treatment with 5-FU	6
Males	14
Females	5
Median age	64
Median ECOG performance status	1
Site of primary: colon	9
Site of primary: rectum	10
Sites of metastatic disease	
Liver only	7
Liver + abdominal wall	1
Liver + lung	3
Liver + lung + pelvis	1
Lung only	2
Lung + pelvis	2
Lung + lymph-nodes	1
Peritoneum	2

1. Allegra CJ. Biochemical modulation: a modality that has come of therapeutic age. *J Clin Oncol* 1991, **9**, 1723–1726.
2. Hansen RM. Systemic therapy in metastatic colorectal cancer. *Arch Intern Med* 1990, **150**, 2265–2269.
3. Bleiberg H, Becquart D, Michel J, Cavalli F, Gerard B. Phase II trial of fotemustine in advanced colorectal cancer. *Eur J Cancer* 1990, **26**, 1260–1261.
4. Jacquillat CI, Khayat D, Banzet P, *et al.* Multicentric study of the nitrosourea fotemustine (S 10036) in advanced malignant melanoma (AMM) including patients with cerebral metastases. *2nd International Congress on Neo-Adjuvant Chemotherapy*, Paris 1988, Abstract E3, 2.
5. Pignon T, Vialette J-P, Ruggieri S, *et al.* Radiation therapy (RT) plus concomitant fotemustine for brain metastasis from non small cell lung cancer (NSCLC). *Proc ASCO* 1992, **11**, Abstract 1059.
6. Brent TP, Houghton PJ, Houghton JA. O^6-Alkylguanine-DNA alkyltransferase activity correlates with the therapeutic response of human rhabdomyosarcoma xenografts to 1-(2-chlorethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea. *Proc Natl Acad Sci USA* 1985, **82**, 2985–2989.
7. Siow Ming Lee, Thatcher N, Margison GP. O^6-Alkylguanine-DNA alkyltransferase depletion and regeneration in human peripheral lymphocytes following dacarbazine and fotemustine. *Cancer Res* 1991, **51**, 619–623.
8. Simon R. Optimal two stage designs for phase II clinical trials. *Controlled Clin Trials* 1989, **10**, 1–10.
9. Herrmann R, Spehn J, Beyer JH *et al.* Sequential methotrexate and 5-fluorouracil: improved response rate in metastatic colorectal cancer. *J Clin Oncol* 1984, **2**, 591–594.
10. Marsh JC, Bertino JR, Katz KH, *et al.* The influence of drug interval on the effect of methotrexate and fluorouracil in the treatment of advanced colorectal cancer. *J Clin Oncol* 1991, **9**, 371–380.

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