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5-fluorouracil plus Tauromustine in Advanced Colorectal Cancer: Unexpected Negative Results

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THE INCIDENCE of colorectal cancer is high and despite the intensive search for single agents against this disease, 5-fluorouracil (5FU) remains the best documented and most consistent drug since it produces response rates averaging 20%. A new nitrosourea, tauromustine showed preclinical antitumour activity *in vivo* and *in vitro* and some clinical responses in colon cancer [1]. A phase II trial reported 7 responses out of 54 patients (overall reponse rate 13%) but with 1 complete remission [2]. To improve the response rate further, tauromustine was combined with a 5-day continuous infusion of 5FU, since this intensive 5FU scheme yielded the best results [3].

Only patients with histologically proven symptomatic metastatic colorectal carcinoma and no previous chemotherapy entered the study. Eligibility criteria also included: measurable lesions, WHO performance status 2 or less, age under 75, white cells 4.0 × 10^9/l or more, platelets count 100 × 10^9/l or more, creatinine clearance over 60 ml/min, and serum bilirubin under 25 μmol/l. 5FU was given in a dose of 1000 mg per 24 h by continuous intravenous infusion on days 1–5 and days 22–26, and tauromustine 130 mg/m^2 was given orally on day 1. This cycle was repeated every 6 weeks. Dose modifications and/or delay depended on haematological and gastro-intestinal toxicity scored at the time scheduled for next treatment and according to nadir blood counts. Responses and toxicity grades were defined with WHO criteria.

Between June 1987, and December 1988, 38 patients were entered. 2 patients were not eligible due to renal dysfunction. 5 patients withdrew before a second course, but did not show progression or severe toxicity. Thus 36 patients were evaluable for toxicity and 31 patients were evaluable for response. Pretreatment characteristics of the patients (Table 1) showed the predominance of liver and lung metastases.

Among the 31 evaluable patients there were no complete remissions, 3 partial remissions, 13 cases of no change, and 15 patients with progressive disease. Thus the overall response was 3/31 (10%) (95% confidence interval 2–26%).

Toxicity was generally moderate, mainly myelosuppression and nausea and vomiting. WHO grades 3 and 4 leucopenia was found in only 7 out of 93 cycles; thrombocytopenia (grades 3 and 4) was a little more frequent, but still only seen in 16 out of 93 cycles. Platelet transfusion was needed five times in 2 patients. Life-threatening haemorrhage and/or septicaemia were not seen, perhaps due to dose reduction in 37 cycles (16 cases) and/or delay in 23 cycles (15 cases). Nausea and vomiting were only related to tauromustine: WHO grade 3 in 30 out of 93 cycles (33%). Diarrhoea and stomatitis were infrequent and of low severity. Alopecia did not occur.

Table 1. Patients' characteristics

Eligible	36 (19M/17F)
Evaluable for response	31
Median age (yr; range)	56 (36–72)
Median performance status (range)	1 (0–2)
Primary excised	30
Local recurrence	2
Sites of metastatic disease	
Liver	26
Lung, pleural	10
Cutaneous	6
Lymph nodes	4
Peritoneal seeding	3
Bone	2
No. of tumour sites	
1	20
2	11
3	5

Whereas the response of 5FU and tauromustine as single agents is in the range of 13–20%, the anti tumour effect of the combination was disappointing with an overall response of only 10%. The dosages used were not low. The 5FU dose was chosen to be in-between the intermediate and high dose regimens of Shah *et al.* who had reported a response rate of 16–30% [3]. The choice of the dose of tauromustine was that recommended from phase I trials [4] for previously untreated patients with a minor increase of the cycle duration (6 weeks instead of 5) to fit in with the scheme for 5FU. The side-effects were moderate, but frequently required a delay and/or dose reduction, indicating that dose escalation would not be appropriate. Tauromustine was expected to be more effective since the activity of the older nitrosourea methyl-lomustine was confirmed by a complete remission in the ECTG trial [2]. In reported data the combination of 5FU with methyl-lomustine seemed to be slightly better than either drug alone [5]. In line with a range of chemotherapy the present combination showed no clear effectiveness.

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