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Sequential Methotrexate and 5-Fluorouracil in the Treatment of Non-small Cell Carcinoma of the Lung

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Abstract—*The sequential administration of methotrexate (MTX) and 5-fluorouracil (5-FU) has been claimed to be synergistic. To investigate the potential synergism in non-small cell carcinoma of the lung (NSCCL), 16 patients were treated with a 2-hr infusion of MTX* 200 mg/m² *followed after* 2 hr *by 5-FU* 1 g/m². *All patients had an Eastern Cooperative Oncology Group performance status of* >2 *and had received no previous chemotherapy. No responses were seen. This study demonstrates that sequential MTX and 5-FU in this dosage and schedule is ineffective in NSCCL.*

INTRODUCTION

METHOTREXATE (MTX) and 5-fluorouracil (5-FU) are used in combination in many clinical protocols. Several workers have claimed that optimal scheduling can increase the therapeutic effect [1-3].

It has been proposed that pretreatment with MTX significantly enhances the antitumour activity of the MTX/5-FU combination when compared with simultaneous treatment or treatment with 5-FU preceding MTX [2-6]. A number of clinical trials in breast, colon, and head and neck cancer [4, 7-13] have been conducted employing this sequential administration and the majority of these claim increased efficacy, and synergistic action of the combination.

Both MTX and 5-FU have some activity in non-small cell carcinoma of the lung (NSCCL), the response rate to MTX being 16-25% [14-16] and to 5-FU 14-18% [14]. In an attempt to exploit the possible synergism a phase II trial of sequential MTX and 5-FU in the treatment of patients with NSCCL has been conducted.

MATERIALS AND METHODS

Patients

Sixteen patients with measurable, inoperable, histologically or cytologically confirmed NSCCL, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, aged 70 yr or less, with normal renal and hepatic function and adequate bone marrow function, were studied and all patients gave informed consent.

Eight patients had squamous cell carcinoma and eight had adenocarcinoma. Patients with a histological diagnosis of adenocarcinoma had a series of further investigations, including barium studies and IVP, to exclude adenocarcinoma arising from primary sites other than lung.

Five patients had locally inoperable disease and 11 had extensive disease.

No patients had received prior chemotherapy, three patients had received prior radiotherapy: cranial irradiation in one patient and chest irradiation in the other two patients, but not to the sites of assessable disease.

Chemotherapy

Patients received MTX 200 mg/m² as a 2 hr infusion, followed 2 hr after completion of the infusion by an i.v. bolus of 1 g/m² of 5-FU. After 24 hr folinic acid rescue was given 15 mg p.o. six-hourly for 72 hr.

Treatment was given on day 1 and repeated every 28 days, provided that the full blood count was satisfactory and toxicity acceptable. A minimum of two treatment cycles were given unless interrupted by treatment toxicity or tumour progression.

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Response

Response was defined according to WHO criteria [17].

RESULTS

All patients were evaluable for response. No patient achieved a complete or partial response.

Thirteen out of sixteen (81%) demonstrated evidence of progression, and 3/16 (19%) had stable disease after two cycles of treatment. A total of 32 cycles of treatment were given.

Treatment was generally well-tolerated; conjunctivitis occurred in 10%, mucositis in 5% and vomiting in 5%. No bone marrow toxicity requiring treatment delay occurred.

One patient died at home, following a gastrointestinal haemorrhage 13 days after the fourth cycle. A post mortem was not held. However, pretreatment and nadir full blood counts had been satisfactory on each of his preceding three treatment cycles.

DISCUSSION

The lack of any response in this study of previously untreated, relatively fit patients is disappointing. The probability, given no responses out of 16 patients, that the true response rate is greater than 20% is less than 0.05 [18].

The response rates in reported clinical studies [4, 9–13] of sequential 5-FU and MTX range from 23 to 53% for breast carcinoma and from 5 to 50% for colorectal carcinoma. However, Moertel has previously pointed out that the response rate of colorectal carcinoma to 5-FU alone has varied widely, from 8 to 85% [19]. Recent randomised clinical studies conducted by Coates *et al.* [13] in head and neck cancer and colorectal adenocarcinoma compared MTX preceding 5-FU with 5-FU preceding MTX, and demonstrated no difference in response rates to support sequence-dependent effects. A randomised trial by Browman *et al.* [20], also in head and neck cancer, compared 1-hr sequential vs simultaneous MTX and 5-FU, and demonstrated no difference in response rates.

It seems likely, as suggested by the preclinical studies of Benz and Cadman [3, 8], that optimal scheduling and dosage may be required for each tumour; this is clearly impractical in man. The data presented here show that this dose and schedule of MTX/5-FU is inactive in NSCCL.

It remains possible that other schedules and doses may have activity, but in view of the many permutations possible, it will require detailed evidence, perhaps from xenograft studies, to define those regimens, if any, worthy of further study in patients with this tumour.

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