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Short communication

Sequential moderate-dose methotrexate and 5-fluorouracil in advanced gastric adenocarcinoma

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Summary. A total of 23 patients with advanced gastric adenocarcinoma were treated with a combination of moderate-dose methotrexate (MDMTX), 250 mg/m^2 i.v., with folinic acid rescue and 5-fluorouracil (5-FU) 600 mg/m^2 i.v. Therapy was given every 7 days for 4 courses and then at 14-day intervals. All patients were evaluable for response. No complete responses occurred, but five patients (22%) had partial remissions (95% confidence limit, 5%–39%). The median duration of remission was 6 months, with a median survival of 11 months amongst responding patients. In all, six patients (26%) had stable disease for a median period of 5 months. The overall median survival was 6 months. Therapy was generally well tolerated, with principal toxicities consisting of neutropenia, nausea and vomiting, mucositis and diarrhoea. In terms of activity or survival in advanced gastric carcinoma, the combination of moderate-dose MTX and 5-FU does not appear to offer an advantage over single-agent therapy.

Introduction

Advanced gastric adenocarcinoma is responsive to a number of chemotherapeutic agents. Active single agents such as 5-fluorouracil (5-FU) and doxorubicin produce response rates in the range of 15%–25%, with only a slight prolongation of survival over that achieved with no therapy [11]. The use of combination chemotherapy has gained widespread acceptance on the basis of trials showing higher objective response rates and improved survival among patients responding to therapy, using combinations such as 5-FU, doxorubicin and mitomycin C (FAM) [1]. However, most responses are partial and of short duration, and survival remains on the order of 8–9 months; few patients are long-term survivors. Many trials contain small patient numbers and fail to specify the number of patients with measurable disease, factors which may affect the reliability of response and survival data. Prospectively randomised trials have failed to show a survival advantage for combination chemotherapy over single-agent 5-FU, and when such an advantage for combination therapy has been demonstrated, the single agent has been either a nitrosourea or doxorubicin [8].

The folate antagonist methotrexate (MTX) has limited activity against gastric carcinoma at conventional doses [2]. Higher doses of this drug have been reported to be effective both as a single agent [6] and in combination with 5-FU, and doxorubicin [5, 12] has shown activity in the range of 45%–60%. In view of the apparent dose-response effect of MTX in advanced gastric cancer and the synergism reported for the sequential administration of MTX and 5-FU [3] we decided to undertake a pilot study of this combination in advanced gastric cancer.

Materials and methods

A total of 23 patients with a histologically confirmed diagnosis of advanced gastric adenocarcinoma were entered on trial (Table 1). All patients received 250 mg/m^2 MTX i.v. infused over 30 min, followed 60 min later by 600 mg/m^2 5-FU given as an i.v. bolus. The oral administration of 15 mg folinic acid q 6 h for 8 doses was begun 24 h post-MTX. Treatment was given on days 1, 8, 15 and 22 and then every 14 days. Staging procedures consisted of a complete physical examination, blood count and serum biochemistries, chest X-ray and abdominal computerised

Table 1. Patient characteristics

Patients:	23
Median Age:	61 (range, 34–82)
Sex:	M 16 F 7
Performance status:	
0–1	18 patients
2–4	5 patients
Tumour differentiation:	
Poorly differentiated	13
Moderately well differentiated	2
Well differentiated	2
Unspecified	3
Unknown	3
Prior therapy:	
Chemotherapy	
FAB[a]	7
Doxorubicin	1
DXRT	1
No prior therapy	14
Median number of courses:	8 (range, 1–22)

[a] 5-Fluorouracil/doxorubicin/BCNU

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Table 2. Response and survival data

Response data: Overall	Prior therapy	No prior therapy
23 patients	9 patients	14 patients
PR 5 (22%)	1 (11%)	4 (29%)
SD 6 (26%)	2 (22%)	4 (29%)
PD 12 (52%)	6 (67%)	6 (43%)
Survival data:	**Range (weeks)**	**Median (weeks)**
Overall	1–133	24
PR	40–133	44
SD	18– 56	33
PD	1– 25	13

Table 3. Toxicity data

Toxicity	WHO grade			
	1	2	3	4
Neutropenia	1	5	3	1
Thrombocytopenia	–	2	–	1
Infection	–	–	–	2
Nausea and vomiting	10	5	–	–
Mucositis	8	2	1	–
Diarrhoea	6	–	–	4

axial tomographic (CAT) scanning. The response to therapy was assessed by appropriate radiological procedures and graded according to standard WHO criteria [9]. Patients were reviewed on a regular basis and blood counts were assessed at least weekly. Toxicity was reported according to WHO criteria [9].

Results

All patients were evaluable for response (Table 2). No complete responses occurred. However, of the five patients (22%) who achieved partial remissions (95% confidence limit, 5%–39%), only one had received prior therapy. The median duration of response was 6 months, with a median survival of 11 months. A total of six patients (26%) had stable disease for a median period of 5 months; the median survival for this group was 8 months. The overall median survival for the group of treated patients was 6 months. Toxicity data is presented in Table 3. The principal toxicities were neutropenia, nausea and vomiting, mucositis and diarrhoea. One death occurred due to septicaemia. Severe diarrhoea complicated by dehydration was observed in two patients. Toxicity did not appear to be worse in patients who had received prior therapy.

Discussion

The response rate of 22% achieved in this trial is similar to that achieved with the single agent 5-FU in large studies [4]. Several combinations with higher objective response rates have been reported [1, 7, 10]; however, small patient numbers, wide confidence limits, and variations in patient selection criteria make a comparison of these response rates difficult. More important is the question of survival benefit. The median survival of 24 weeks amongst treated patients and the survival advantage for responding patients are no better than those previously reported for several single and combination therapies [11]. Patients in this trial who had received prior therapy (usually in the form of FAB) showed only an 11% response rate, indicating the probability of appreciable cross-resistance. Treatment was generally well tolerated, with acceptable toxicity.

We conclude that the combination of sequential moderate-dose MTX and 5-FU offers no advantage over single-agent therapy in advanced gastric cancer. Results reported for several combinations containing higher doses of MTX [5, 12] do not suggest a potential impact of further escalation of MTX doses on the survival of these patients.

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