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Phase II Trial of Methotrexate–FAM (m-FAM) in Adenocarcinoma of Unknown Primary

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Abstract—*Nineteen patients with adenocarcinoma of unknown primary were treated with the m-FAM regimen, consisting of methotrexate* 50 mg/m^2 *days* 0, 28; *5-fluorouracil* 600 mg/m^2 *days* 1, 8, 29, 36; *Adriamycin®* 30 mg/m^2 *days* 1, 29; *and mitomycin-C* 10 mg/m^2 *day* 1. *All drugs were recycled every* 56 *days. No complete responses were seen. Seven patients* (37%) *achieved partial remission for a median duration of* 11 *months. An additional nine patients* (47%) *had stable disease for a median duration of* 6 *months. Median survival for responders was* 16 *months and was* 10 *months for those with stable disease. Toxicity was acceptable. This Phase II study attempted to evaluate the clinical impact of the pharmacological modulation of 5-fluorouracil with methotrexate, the goal being improvement of the results of FAM alone in adenocarcinoma of unknown primary. However, the addition of methotrexate, at least in the schedule employed in this study, did not appear superior to FAM.*

INTRODUCTION

THE PROGNOSIS of patients with adenocarcinoma of unknown primary is poor, with a median survival in the range of 3–4 months. The combination of 5-fluorouracil (5-FU), doxorubicin and mitomycin (FAM), which is widely used in the therapy of advanced gastric adenocarcinoma, has been studied in the setting of adenocarcinoma of unknown primary with a response rate of 30% and a median survival of 10 months in previously untreated patients [1]. By incorporating methotrexate into the FAM regimen, we sought to exploit the reported synergism between 5-FU and methotrexate [2, 3]. A Phase II trial of methotrexate–FAM (m-FAM) was conducted simultaneously by the Institut Gustave Roussy in France and the Lombardi Cancer Center, Georgetown University.

PATIENTS AND METHODS

The m-FAM regimen is shown in Table 1. It differs from the original FAM regimen as described by Macdonald *et al.* [4] only in the addition of methotrexate at a dose of 50 mg/m^2 administered as an i.v. bolus injection 18 h before the 5-FU on days 1 and 29.

The study included 19 patients with pathologically documented adenocarcinoma of unknown primary, as defined by a negative clinical examination except for evidence of metastatic disease. All had measurable disease, and none had received prior chemotherapy. Other requirements included an adequate marrow reserve (WBC >3500/mm^3, platelet count >100,000/mm^3) and a serum creatinine <1.5 mg/dl. Patients with significant ascites or pleural effusions were excluded. All had a Karnofsky performance status of at least 60%, with a mean of 90%. Patient characteristics are summarized in Table 2.

RESULTS

Patients received a mean of 3.5 cycles of chemotherapy (range 1–8 cycles). No complete responses were seen. Seven patients achieved partial remission (greater than 50% reduction) for an overall response rate of 37% with a median duration of response of 11 months. An additional nine patients (47%) had stable disease for a median duration of 6 months (range 2–15 months). Median survival for the entire group was 15 months (range 3–19+ months). For responders median survival was 16 months and those with stable disease had a 10 month median

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Table 1. m-FAM regimen

Drugs	Day 0	1	8	15	22	28	29	36	43	50	56
Methotrexate* 50 mg/m² i.v.	×					×					REPEAT CYCLE
5-Fluorouracil 600 mg/m² i.v.		×	×				×	×			
Adriamycin® 30 mg/m² i.v.		×					×				
Mitomycin-C 10 mg/m² i.v.		×									

*Administered by bolus injection 18 h prior to FAM.

Table 2. Patient characteristics

No. of study patients	19
Sex	
Male	7
Female	12
Age in years	
Mean	49
Range	28–72
Performance status (Karnofsky)	
100%	9
90%	3
80%	5
70%	0
60%	2
Metastatic sites	
Pulmonary alone	5
Pulmonary + pleural	4
Pulmonary + liver	2
Pulmonary + bone	2
Pulmonary + adrenal	1
Three or more sites	5

survival. Responders were comparable to non-responders in terms of performance status.

Among the responders, three had pulmonary metastases alone, two had pulmonary and bone involvement, one had pulmonary and pleural involvement, and one had liver and pleural involvement plus a pelvic mass.

Toxicities included one incident of ECOG grade 4 leukopenia (WBC $<1000/mm^3$) and thrombocytopenia (platelets <25,000), but otherwise were limited to mild to moderate myelosuppression, nausea and vomiting, mucositis and alopecia.

DISCUSSION

The problem of metastatic cancer presenting with an unknown primary site is not uncommon, comprising 3–15% of patients seen in referral centers, and adenocarcinoma represents 40–50% of these cases [5–7]. Treatment of these patients has been generally disappointing [6, 8] and only a few studies have demonstrated a benefit for responders in terms of survival [1, 9, 11].

In a previous study [1] the FAM regimen demonstrated a 30% response rate among 43 patients with adenocarcinoma of unknown primary, with a median survival for all patients greater than 10 months. Those patients with stable or responsive tumors survived a median greater than 14 months, versus only 6 months for those with unresponsive disease ($P < 0.05$).

This present Phase II study of m-FAM attempted to evaluate the clinical impact of the pharmacological modulation of 5-fluorouracil with methotrexate. Similar attempts have been made in the therapy of other cancers, including gastric [12] and breast [13], with some encouraging results. Treatment with methotrexate results in intracellular accumulation of phosphoribosyl pyrophosphate (PRPP), a substrate required for ribosylphosphorylation of 5-fluorouracil. When cells with increased levels of PRPP are treated with 5-fluorouracil, the intracellular conversion of 5-fluorouracil to FdUMP and FUTP is greatly enhanced. FdUMP forms a ternary complex with thymidylate synthetase and methylenetetrahydrofolate, thereby inhibiting DNA synthesis [14, 15]; FUTP inhibits protein synthesis by incorporation into RNA as a false messenger [15, 16]. The result is increased cytotoxicity of 5-fluorouracil with the pre-administration of methotrexate.

The dose of methotrexate and the interval between the delivery of methotrexate and 5-fluorouracil required to fully exploit the pharmacologic modulation of 5-fluorouracil are not known. This study sought to determine if the addition of moderate doses of methotrexate to the FAM regimen would result in improved therapeutic efficacy over

FAM alone without compromising patient tolerance.

While the toxicity of the m-FAM regimen was acceptable, the addition of methotrexate did not seem to enhance the results over FAM alone. Response rates and survival for the two regimens appear comparable. Further studies of this regimen, perhaps with alteration in the dosage of methotrexate and/or the interval between administration of methotrexate and 5-fluorouracil, may yield superior results.

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