Eur J Cancer Clin Oncol, Vol. 24, No. 4, pp. 765–768, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00

5-Fluorouracil, Doxorubicin and Mitomycin C (FAM) Combination Chemotherapy for Metastatic Adenocarcinoma of Unknown Primary

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Abstract—*The prognosis of patients with adenocarcinoma of unknown primary (ACUP) is dismal. Various chemotherapy regimens have yielded disappointing response rates and survival. Based on a promising report of Goldberg* et al. (J Clin Oncol 1986, **4**, 395–399) *we performed a phase II study with 5-fluorouracil, adriamycin and mitomycin C (FAM). Only three out of 22 evaluable patients achieved a partial response (14%) for a duration of 22, 30 and 74+ weeks. Median survival was 54+ weeks (range 35–74+ weeks) for responding patients and 33+ weeks (range 9–74+ weeks) for all treated patients. One patient (5%) developed mitomycin C induced hemolytic uremic syndrome. FAM cannot be recommended for routine use in patients with ACUP.*

INTRODUCTION

THE PROGNOSIS of patients with metastatic adenocarcinoma of unknown primary (ACUP) is poor. In a retrospective review of 245 patients, Markman reported a median survival of 3.1 months [1]. At autopsy the primary tumor can only rarely be identified, mostly in the pancreas, the stomach or in the lungs [2].

Objective response rates of 0–16% have been reported with 5-fluorouracil as a single agent [3–5]. Combination chemotherapy including adriamycin yields response rates of 0–50% [5–8] usually of short duration. A regimen including 5-fluorouracil (5-FU), adriamycin (ADM) and mitomycin C (MMC) (FAM) has been recommended for these patients because it has shown activity in patients with metastatic gastric cancer [9], adenocarcinoma of the pancreas [10] and adenocarcinoma of the lung [11], while a study of Goldberg *et al.* [12] resulted in a 30% response rate in patients with ACUP. To try to confirm the latter results we performed a phase II study with the same FAM regimen, in patients with ACUP.

MATERIALS AND METHODS

Twenty-three patients with measurable lesions of metastatic adenocarcinoma of unknown primary, 19 histologically proven and four cytologically proven, were treated with combination chemotherapy consisting of 5-FU, ADM and MMC. The FAM regimen was administered in 8 week cycles by i.v. bolus. 5-FU was administered at a dose of 600 mg/m^2 on days 1, 8, 29 and 36; ADM at a dose of 30 mg/m^2 on days 1 and 29; and MMC at a dose of 10 mg/m^2 on day 1 of each course. Treatment was discontinued for either progression or toxicity.

The minimum diagnostic evaluation for all patients included history and physical examination, chest X-ray, blood morphology and biochemistry, mammography in females and determination of serum acid phosphatase in men. Additional investigations are shown in Table 1.

Patients with bone lesions, ascites or pleural effusion as the only metastatic lesions were not considered eligible, as were patients with previous radiotherapy to the sole indicator lesion.

Patients were evaluated for response after each course of chemotherapy. However, patients with rapidly progressive disease after 4 weeks of treatment were documented as progressive disease.

Tumor response was evaluated by standard WHO criteria [13]; complete response was defined as the disappearance of all known disease for at least 4 weeks; partial response as a more than 50% decrease in the sum of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks; stable disease as a less than 50% decrease and a less than 25% increase in measurable or

Accepted 27 November 1987.
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Table 1. Additional investigations

Diagnostic procedure	No. of patients
CT scan abdomen	17
Abdominal ultrasound	12
Bone scan	10
Isotopic liver–spleen scan	9
Intravenous pyelogram	9
Thyroid scan	8
Barium enema	7
Upper GI series	7
Bronchoscopy	6
CT scan chest	4
Cystoscopy	3
Gastroscopy	1
Laparoscopy	1

Table 3. Sites of presentation

	No. of patients
Liver	7
Lymph nodes	7
Bone	6
Lung	5
Pleural/pleural effusions	4
Retroperitoneal	3
Intra-abdominal	2
Skin	2
Mediastinal	2
Other	2

Table 2. Patient characteristics

Evaluable	22
Median age (years)	55.6 (range: 31–75)
Sex	
male	14 (64%)
female	8 (36%)
Performance status (WHO)	
0	10 (45%)
1	9 (41%)
2	3 (14%)
Interval diagnosis/treatment	
overall (median)	12 weeks
no previous treatment (14)	4 weeks
previous radiotherapy (8)	24 weeks
Number of sites of metastases	
1	6
2	14
> 2	2

evaluable lesions; and progression as an increase greater than 25% in the size of one or more measurable or evaluable lesions or the appearance of new lesions. Duration of partial response and survival were calculated from the time of start of chemotherapy. No patient was previously treated with chemotherapy. Clinical characteristics of the 22 evaluable patients are shown in Tables 2 and 3.

RESULTS

Of the 23 patients treated, one patient was inevaluable because of an ischemic cerebral event 6 days after the start of treatment, which precluded further therapy. No complete responses were achieved. A partial response was observed in three patients (14%). In two patients the durations of response were 22 weeks and 30 weeks. The survival in these two patients was 35 and 52 weeks respectively. In the third patient duration of response and survival is 74+ weeks.

Stable disease was achieved in 10 patients (45%). Two of them are still alive after a follow-up of 44 weeks and 61 weeks. The duration of stable disease ranged from 10 weeks to 52+ weeks with a median of 23+ weeks. The survival of the patients with stable disease ranged from 11 weeks to 81 weeks with a median of 41+ weeks.

Of the 22 evaluable patients nine (41%) had progressive disease after one course of chemotherapy. The median survival of these patients was 17 weeks.

Grades 3 and 4 hematologic toxicity were observed in four patients (18%), two with leukopenia and two with thrombocytopenia. Septicemia was not observed. Alopecia occurred in all patients who received more than one cycle of chemotherapy. One patient with a partial response developed the hemolytic uremic syndrome (HUS) after the fifth course of FAM after a total dose of MMC of 50 mg/m^2. Chemotherapy was discontinued and only symptomatic treatment was given, avoiding red blood cell transfusions. No renal biopsy was perfor-

med. The patient is still alive 17 months after starting treatment, 8 months after the first signs of HUS. Renal function is still deteriorating with a serum creatinine level of 411 μmol/l (normal < 120). In the remaining patients the FAM regimen was well tolerated and could usually be given on an outpatient basis.

DISCUSSION

An extensive search for a primary lesion in the absence of signs, symptoms or laboratory abnormalities has not been found useful in patients with ACUP [14]. Newer techniques, however, may be helpful in diagnosis and treatment. Reviewing biopsies with special stains, immunofluorescence studies, surface marker analysis, hormone receptor assays and electron microscopy may all be needed to identify treatable or curable tumors [15]. Especially in patients with lymph nodes as the only site of disease immunopathology often offers the possibility to distinguish certain anaplastic carcinomas from high grade lymphoma [16]. Greco *et al.* [17] reported an objective response rate of 56% in patients with undifferentiated (adeno) carcinomas, predominantly in the midline, with cisplatin combination chemotherapy. A proportion of these patients are believed to have an extragonadal germ cell tumor. Apart perhaps from the above mentioned subset of patients prognosis of disseminated ACUP is poor and no effective chemotherapy is available.

Goldberg *et al.* [12] reported an overall response rate of 30% with the use of the same FAM regimens as used in the present study. In 22 evaluable patients we observed a response rate of only 14%, with a duration of 42+ weeks.

Although the FAM regimen is well tolerated concerning subjective and hematologic toxicity the risk of the MMC induced hemolytic uraemic syndrome (HUS) increases with the cumulative dose of MMC [18]. Indeed one of our patients developed HUS. This patient had a relative long survival after the first signs of HUS, but continued to have deteriorating renal function, despite cessation of chemotherapy and avoidance of red blood cell transfusions.

We believe that combination chemotherapy in ACUP should be reserved only for selected patients with a good performance status and in an experimental setting. For the remaining patients those measures should be offered that provide the best palliation to increase meaningful survival.

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