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Metastatic Adenocarcinoma of Unknown Primary Site. A Randomized Study of Two Combination Chemotherapy Regimens

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Abstract—*Of 101 patients with symptomatic adenocarcinoma or undifferentiated carcinoma of unknown primary site, 95 were evaluable for the effects of two randomized chemotherapy regimens. Forty-eight patients received combination doxorubicin and mitomycin C (DM) and 47 received combination cisplatin, vinblastine and bleomycin (PB). Response rates were not significantly different between the two treatment groups, 42% for DM and 32% for PVB, with an overall response rate of 37.1%. Survival differences for DM and PVB treated groups were not significantly different, with 18 weeks and 25 weeks median survivals respectively. Toxicities were unequal for the two treatment groups with increased haematological toxicity for DM and greater gastrointestinal toxicity for PVB.*

The authors conclude both therapies were of limited efficacy in the treatment of ACUP patients and emphasize that only symptomatic patients should be considered for such therapies.

INTRODUCTION

METASTATIC adenocarcinoma and undifferentiated carcinoma from an unknown primary site (ACUP) remains a common clinical presentation in oncology practice. The role of chemotherapy in management of these patients has not been defined. We have reported that doxorubicin and mitomycin C (DM) was of some value treating symptomatic patients with metastatic ACUP [1]. Others have reported antitumour activity using different regimens [2, 3].

Cisplatin has a broad spectrum of antitumour activity and in combination with vinblastine and bleomycin, synergistic antitumour activity has been claimed in germ cell malignancy and other tumour types [4, 5]. We, and others [6, 7], have described a subgroup of patients with metastatic ACUP who have an extragonadal germ cell tumour variant which often responds to combined cisplatin, vinblastine and bleomycin (PVB) therapy. Combined cispatin and vindesine has been reported to have significant antitumour activity in advanced non small cell lung cancer (NSCLC) [8], but the addition of bleomycin to this regimen did not improve the results [9]. Finally cisplatin has reported activity against disseminated gastric carcinoma [10]. These sites include many of the more common primary sites identified in ACUP patients [11–13], and therefore a comparison of a combination of a cisplatin, vinblastine and bleomycin containing regimen with a doxorubicin and mitomycin C containing regimen was undertaken in symptomatic ACUP patients.

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PATIENTS AND METHODS

One hundred and one patients (62 males and 33 females) with ACUP were randomized, following their informed consent. Randomization by ballot was performed by a data manager in a separate and central location upon patient entry to the study.

Six patients withdrew their consent for inclusion in the study before receiving therapy but were included in the analysis. Patients' ages ranged from 29 to 74 years (mean 55).

All patients had measurable metastatic disease and a histologic diagnosis of undifferentiated carcinoma or adenocarcinoma from biopsy of a metastatic site. In no patient was a primary site identified prior to commencing chemotherapy. All patients had normal renal function (serum creatinine < 120 μmol/l), hepatic function (serum bilirubin < 30 μmol/l) and bone marrow reserve (white cell

count $> 4 \times 10^9/l$ and platelet count $> 100 \times 10^9/l$). Patients with serious intercurrent disease, an expected survival time of less than 1 month, those who had received extensive radiotherapy in the preceding 4 weeks, or who had received prior chemotherapy, were excluded from the trial.

'Predominant' site of metastatic disease was defined at commencement of randomized treatment as the metastatic lesion of greatest disease bulk.

Investigations

In keeping with our earlier studies, investigations aimed at diagnosis were limited [12]. In patients who had not had prior investigations to identify a primary tumour site, only serum acid phosphatase, serum beta subunit of human chorionic gonadotrophin, serum alpha feto protein, chest radiograph, biochemical and haematologic tests were undertaken. A liver radionuclide scan, grey scale abdominal ultrasound study or computer tomographic scan was performed when there was no other means of monitoring response to treatment.

All patients had lung diffusion capacity for carbon monoxide measured prior to commencing therapy and patients remaining on PVB had this repeated after every two courses.

Drug regimens

Patients were randomized to DM (doxorubicin 50 mg/m^2 i.v. on day 1 and then every 21 days, and mitomycin C 20 mg/m^2 i.v. on day 1 and then every 42 days) or PVB (cisplatin 60 mg/m^2 i.v. on day 1 and then every 2 days, vinblastine 4 mg/m^2 i.v. on day 1 and day 2, then every 21 and 22 days, and bleomycin 15 mg as a single dose intramuscularly on day 1, 8 and 15 continuing weekly).

Duration of therapy

Tumour response was assessed at 6-weekly intervals. Patients responding or with stable disease on DM continued to a maximum of four injections of mitomycin C and eight of doxorubicin (maximum cumulative dose 400 mg/m^2). Patients responding or with stable disease on PVB continued to a maximum of two courses after achieving maximal response or until receiving 300 mg bleomycin, whichever occurred first. Patients with progressive disease on DM crossed over to receive PVB and those with progressive disease on PVB were crossed over to DM.

Standard World Health Organization criteria of response wewe employed [14]. Durations of response and survival were measured from the times of randomization.

RESULTS

Fifty-one patients were randomized to receive DM and 50 to receive PVB. The patient groups were well matched for age, performance status and male to female ratio, however there were 18 patients with 'predominant' hepatic metastases in the PVB group compared to eight in the DM group (Table 1).

Overall tumour regression (PR or CR) was documented in 35 patients (35%).

Twenty of 51 patients (39%) receiving DM responded (all partial responses) compared to 15 of 50 patients (30%) on PVB therapy (one complete response and 14 partial responses) (not significant by chi-square test). There was no difference in response rate according to sex or to interval between diagnosis and commencement of chemotherapy.

Overall the median duration of tumour response was 17 weeks (range 7–66 weeks), compared to 23 weeks (range 9–66 weeks) for the PVB treatment group and 14.5 weeks (range 7–45 weeks) for the DM group. Thirty-three patients crossed over to receive the alternative chemotherapy regimen after having no response (15 patients) or a relapse (16 patients) to the initial regimen. Five patients (15%) responded to the alternative regimen, three patients to DM and two patients to PVB. Only two of these five patients had responded to their initial regimen (one each to DM and PVB).

Differences in survival between PVB and DM treated patients were not significant (Fig. 1). The median survival time from the start of chemotherapy was 18 weeks in the DM group and 25 weeks in the PVB group ($P > 0.05$ by log-rank test).

Patients with predominant hepatic metastases at presentation had a shorter survival time ($P < 0.01$ by log-rank test, Fig. 2), but the probability of tumour regression on chemotherapy in these patients was not significantly different from that of other patients. In patients without predominant hepatic metastases at presentation those treated with PVB survived longer than those receiving DM (mean survivals 30 weeks and 26 weeks, respectively). There were no differences in response rate or duration of survival between PVB or DM treated groups within patient cohorts defined by predominant metastatic site.

Toxicity was different for the two chemotherapy regimens. Significant nausea and vomiting occurred in 40 patients receiving PVB and 27 patients receiving DM ($P = 0.002$ by Fisher's exact test). Severe myelotoxicity (WCC $< 1.0 \times 10^9/l$) occurred in 20 patients receiving DM and nine patients receiving PVB ($P = 0.015$ by Fisher's exact test).

Significant thrombocytopenia (platelet count $< 50 \times 10^9/l$) developed in nine patients on DM and in one patient on PVB ($P = 0.008$ by Fisher's exact test). Non-life threatening haemorrhage

Table 1. *Patient characteristics according to treatment group*

	Doxorubicin and mitomycin C	Cisplatin, vinblastine and bleomycin
	Number of patients	
Sex		
Male	31	35
Female	20	15
Age range (year)	29–74 (54)*	31–71 (55)*

*Mean age shown in parentheses.

	Predominant site of metastatic disease	
Hepatic	8	18
Pulmonary	13	11
Node	11	12
Bone	12	6
Peritoneum	2	2
Other	5	1
Total	51	50

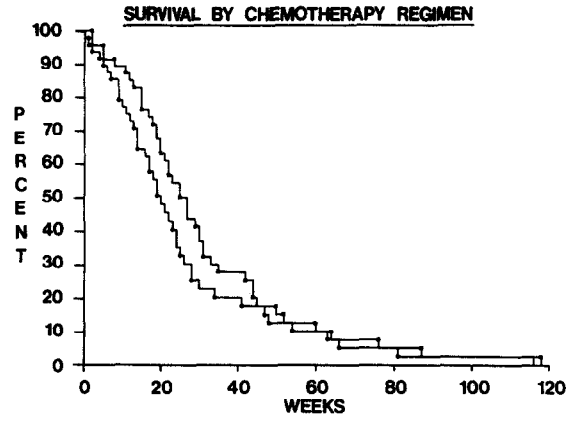

Fig. 1. *Survival by chemotherapy regimen. Life table analysis comparing DM (squares) and PVB (circles) treatment groups.*

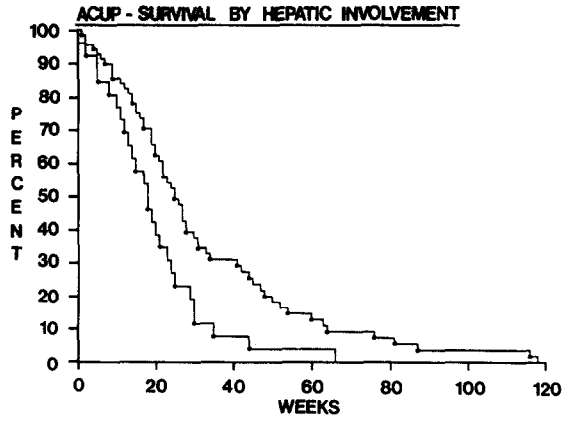

Fig. 2. *ACUP—survival by hepatic involvement. Life table analysis comparing all patients with hepatic metastases (circles) and all other patients (squares).*

occurred in four patients on DM (three patients with spontaneous bruising associated with thrombocytopenia and in one patient with normal platelet count following tissue biopsy). No patient on PVB had a haemorrhagic complication.

None of the patients receiving mitomycin C developed the hemolytic-uraemic syndrome [15]. Mucositis with mouth ulceration occurred in six patients on DM and five patients on PVB.

Three patients on PVB and one patient on DM had an asymptomatic and sustained serum creatinine rise greater than 20 μmol/l. There was no apparent hepatic or pulmonary toxicity for either group. Alopecia occurred in the majority of patients in both groups.

DISCUSSION

Although patients with ACUP constitute a common clinical presentation to oncology units, their management is little discussed in the literature.

The appropriate investigations to determine a primary site in these patients has been discussed, and all studies agree that this is found in only a minority of ACUP patients and rarely influences treatment [11, 12, 16]. Empirical chemotherapy to relieve symptoms not treatable by radiotherapy has been advocated and response rates between 12 and 36% are reported [1, 17].

In this trial only symptomatic patients were treated and no significant difference in survival between groups receiving DM or PVB was demonstrated. Response rates to DM were similar to our earlier report [1]. The poorer prognosis associated with predominant liver involvement at presentation was again seen [18], and in this setting PVB and DM had similar efficacy. In AUP patients without metastatic liver disease, PVB may have a greater anti-tumour effect compared to DM, since a survival

advantage for PVB appeared in this subset analysis. However, data derived from subset analyses should be viewed with caution. The greater subjective gastrointestinal toxicity of PVB is a substantial disadvantage in patients with limited survival expectation and although no serious infection or haemorrhage occurred in patients receiving DM its haematological toxicity is also of concern.

We conclude that both regimens are of limited efficacy in patients with metastatic ACUP, and rcommend that only symptomatic patients be considered for cytotoxic therapy.

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