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Fluorouracil, Doxorubicin, Cisplatin and Altretamine in the Treatment of Metastatic Carcinoma of Unknown Primary

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Abstract—*Eighty-five patients, median age 55 years, with evolutive metastatic carcinoma of unknown primary (CUP) were included in this study. The treatment combination consisted of fluorouracil (5-FU) (600 mg/m² in a 30 min infusion) days 1 and 8, doxorubicin (DXR) (30 mg/m² by i.v. bolus injection) day 1 and cisplatin (CDDP) (80 mg/m² in a 4-h infusion) day 1. Altretamine (HMM) (150 mg/m²) was administered orally days 2–8, therapy being resumed every 29 days. An objective response was noted in 18/85 patients (21%) with a median duration of response of 7 months. Thirty-three/77 patients (43%) who had tumor-related symptoms were relieved of their troubles. The overall median survival of patients was 7 months; the median survival of responders was 12.5 months. Toxicity occurred in one-third of patients (mainly digestive and hematologic), leading twice to a halt in treatment and to drug dose reduction in 26/77 (33%) evaluable patients. Such a regimen is of limited efficacy, has a non-negligible toxicity and appears of little interest in such a palliative situation.*

INTRODUCTION

PATIENTS with a metastatic carcinoma with no obvious primary site represent a quite common situation [1, 2] which has been recently characterized [3]. The treatment of these CUP is purely palliative: poor status patients need only a symptomatic attitude; a few patients may benefit from a locoregional treatment (surgery and/or radiotherapy) if there is an apparently single metastatic site [2]; other patients who are evolutive or symptomatic may be controlled by chemotherapy. Many trials have already been published so far, sometimes reporting high response rates, but these responses are often short with poor survival duration.

As non small-cell lung [4, 5] and digestive (mainly pancreatic) [1, 6, 7] cancers are the most commonly found primaries responsible for CUP, we ran a phase II study which was according to De Vita's criteria [8] and combining active drugs against these cancers, i.e. 5-FU [9], DXR [9, 10], CDDP [11] and HMM [9].

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MATERIALS AND METHODS

Patients

Between January 1981 and February 1987, 85 patients having metastatic carcinoma with no primary site identified before the start of chemotherapy were entered in the study. The patients were so defined according to Neumann and Nystrom's criteria [1], i.e. (1) when we had histologic proof of malignant disease and (2) when neither interrogation nor physical examination or usual biological tests guided us towards a primary site. Moreover, the CT scans of abdomen and pelvis which were performed were normal or revealed only metastatic extent. It is to be noted that every time a histologic diagnosis of 'undifferentiated carcinoma' was made, we required immunohistologic confirmation that it did not correspond to lymphoma, squamous-cell, germ-cell or neuro-endocrine tumors, which were excluded from this study. Eligibility criteria were a biopsy-proven carcinoma, a Karnofsky performance status index ≥50%, measurable or evaluable lesions, evolutive disease at initiation of treatment and normal haematologic, renal, cardiac and hepatic functions (apart from abnormalities due to cancer extent). Patient characteristics are summarized in Table 1. Moreover, 77/85 patients had tumor-related symptoms.

Table 1. Patient characteristics

Characteristics	Number of patients
Sex	
Male	45
Female	40
Median age and range (years)	55 (21–74)
Karnofsky performance status	
≥70%	74
<70%	11
Carcinomas	
Adenocarcinomas	59
well-differentiated	1
moderately well-differentiated	13
poorly differentiated	17
mucinous	8
simplex	20
Undifferentiated carcinoma	26
Site(s) of evaluable metastasis	
Nodes	48
Lung	42
Liver	30
Abdomen	12
Bone	11
Skin	9
Various	3

Treatment

Chemotherapy consisted of the association of 5-FU, 600 mg/m^2 by a 30 min infusion days 1 and 8, DXR, 30 mg/m^2 i.v. bolus injection day 1 and CDDP, 80 mg/m^2 day 1. *Cis*-platinum was administered as a 4-h infusion, diluted in 1000 ml of a 0.9% sodium chloride solution and following hyperhydration for a minimum period of 4 h. HMM, 150 mg/m^2, was given orally, days 2–8. Therapy was resumed at day 29 and was discontinued when patients presented tumor progression, intolerable toxicity, a 550 mg/m^2 DXR maximum dose or death. All our patients had antiemetic medications to prevent CDDP-induced emesis, consisting in high doses of metoclopramide [12] and since 1985 a combination of methylprednisolone and metoclopramide as previously reported [13]. A total of 386 courses of therapy were administered, with a mean number of 4.5 per patient (range 1–18).

Monitoring

All patients had physical examination, blood cell counts, liver function tests and chest radiography before chemotherapy was started. Abdominal ultrasonography and/or CT scan were performed only when we had no other way of evaluating treatment response [14]. According to Stewart *et al.* [15] and Neumann and Nystrom [1] no other investigations were performed. Clinical and biological evaluation was made before each treatment course, and radiologic evaluation was performed every two cycles. Standard WHO criteria were used [16] to evaluate the objective response: complete response (CR) was defined as the disappearance of all perceptible tumors; partial response (PR) was defined as a reduction of at least 50% of total tumor mass without any evidence of progressive disease elsewhere after two cycles of chemotherapy. No change (NC) was defined when neither a 50% tumoral decrease nor a 25% increase in measurable lesion size could be established. Progressive disease (PD) was a 25% or more increase in the size of one or more evaluable lesions, or the appearance of new lesions. We also evaluated the subjective response to tumor-related symptoms (mainly abdominal or liver pain, dyspnea and/or cough). Standard WHO criteria were also used to evaluate toxicity.

Statistical methods

Survival times were calculated from the start of chemotherapy. Duration of response was evaluated from the onset of response to the data of PD or death when noted. Plots were made by the Kaplan–Meier method and comparisons were made with the Mantel–Haenszel test.

RESULTS

Of 85 patients who entered the study eight patients died from their disease within 1 month of starting chemotherapy. They were not evaluable for toxicity but were nevertheless included in efficacy (as PD) and in survival analysis.

Toxicity

Toxicity could be evaluated in 77 patients and is listed in Table 2. No iatrogenic death occurred; chemotherapy had to be stopped twice due to hematologic toxicity for one patient and to cardiac toxicity for another. For this patient, DXR appears only to be partially responsible for cardiac dysfunc-

Table 2. Toxicity of combination treatment in metastatic CUP

WHO grading	Number of patients with toxic effects 0	1	2	3	4
Nausea vomiting	38	17	14	8	0
Diarrhea	61	10	5	1	0
Oral mucositis	71	0	4	0	0
Infection	0	0	2	0	0
Hemorrhage	0	0	2	0	0
Leukocytes	50	14	8	5	0
Platelets	70	2	4	1	0
Hemoglobin	60	7	10	0	0
Creatinine	68	9	0	0	0
Cardiac function	76	0	0	1	0
Peripheral neurotoxicity	73	3	1	0	0

tion since only 300 mg of the drug was delivered (for a maximum dose of 1100 mg). Nevertheless the patient also had diabetes mellitus and hypertension, and was treated for bilateral lung metastases. Cardiac decompensation was probably the result of all these factors. Drug dose reduction was also necessary in 26/77 (35%) mainly due to hematologic, gastrointestinal and renal toxicity. No other side-effects were observed. It is to be noted that the eight patients who had WHO grade 3 nausea and vomiting spontaneously stopped taking HMM tablets.

Efficacy

Efficacy could be evaluated in 85 patients; 15 PR and three CR were observed. The overall response rate was 21% (95% confidence interval, 0.12–0.29). The median duration of response was 7 months (range 4–16 months) with a maximum response noted at an average of three courses (range 1–5). Neither the pathology (adenocarcinoma vs. undifferentiated carcinoma) nor the bulk of disease appeared to have prognostic influence on response (respectively $P = 0.09$ and 0.93). It is to be noted that the bulk of disease was evaluated either by the number of metastatic tissues or by the size of metastatic lesions allowing us to distinguish two groups, i.e. important tumor burden (more than three involved tissues or metastases larger than 5 cm) and small tumor burden (less than three tissues or metastases smaller than 5 cm). Data for metastatic tumor sites are listed in Table 3. The results show a better efficacy of the chemotherapy on liver metastases (9/30), lung metastases (11/42) and nodes (15/48) than on abdominal lesions (4/12), bone metastases (1/11) or cutaneous nodes (1/9). Furthermore, 33/77 patients (43%) who initially had tumor-related symptoms were completely (12 patients) or partially (21 patients) relieved after the first or second course of treatment.

Table 3. Responses to combination therapy in metastatic CUP

	PD	NC	PR	CR
All patients				
(85 patients)	29	38	15	3
Metastatic disease				
(85 patients)				
liver (30 cases)	8	13	8	1
lung (42 cases)	13	18	7	4
abdomen (12 cases)	4	4	2	2
nodes (48 cases)	13	20	10	5
bone (11 cases)	5	5	0	1
skin (9 cases)	4	2	0	1
Tumor-related symptoms				
(77 patients)	9	35	21	12

Survival

Median survival is 7 months (range 0.5–35 months) with 50% and 25% of patients alive at 6 months and 1 year respectively (Fig. 1). Median survival for the 18 patients with an objective response is 12.5 months (range 4–26 months) while the median survival of patients who encountered no change or progressive disease is 4.5 months (range 0.5–35 months). Median survival is not correlated with pretreatment performance status ($P = 0.75$). Likewise, neither tumor burden ($P = 0.97$) nor any metastatic tumor site (P values were respectively: liver = 0.66; abdomen = 0.37; lung = 0.55; nodes = 0.57; bone = 0.13) appeared to influence overall survival.

DISCUSSION

Patients with CUP are a quite common problem for oncologists and the management of their disease still represents a therapeutic challenge. Systemic treatment, i.e. chemotherapy, is generally used to relieve symptomatic patients or when there is an important tumor burden in a vital organ, but response rates and patients' survival remain very poor [6, 17]. In our study the toxicity encountered with this chemotherapy regimen appears great, as two treatments had to be stopped and a drug dose reduction was necessary in 26/77 evaluable patients. Limiting toxicities were mainly digestive (nausea and vomiting) and hematologic (leukopenia and thrombopenia). It is to be noted that nearly 10% of patients (8/77) did not take their HMM tablets owing to severe nausea due to the drug. Comparison of the toxicities encountered with those of other chemotherapy regimens appears difficult because of a low number of evaluated patients [11, 18] or because of imprecisely evaluated toxicities [6, 19, 20]. An objective response rate of 21% was achieved in 18/85 patients. Two studies using regimens similar to ours, but without HMM [11, 21] respectively report 2/11 [11] and 5/22 [21] partial responses; these results are not different from ours. Other chemotherapy regimens have reported similar response rates. Kambhu *et al.* [19] reported a 26% objective response in 55 patients treated with mitomycin C, vindesine and doxorubicin. Jadeja *et al.* [22] and Pastertz *et al.* [23] respectively reported a 23 and 28% response using cyclophosphamide, fluorouracil, doxorubicin and cisplatin in 31 and 47 patients. Yet other chemotherapy regimens appear to give better results: Goldberg *et al.* [24] using the FAM protocol report a 30% response in 43 patients; the combination of doxorubicin and mitomycin C used by Woods *et al.* in 1980 [25] and 1987 [17] resulted in 36 and 42% of response in 25 and 48 patients; Anderson *et al.* [26] reported a 50% response in 20 patients using vincristine, doxorubicin and cyclophosphamide. Unlike these

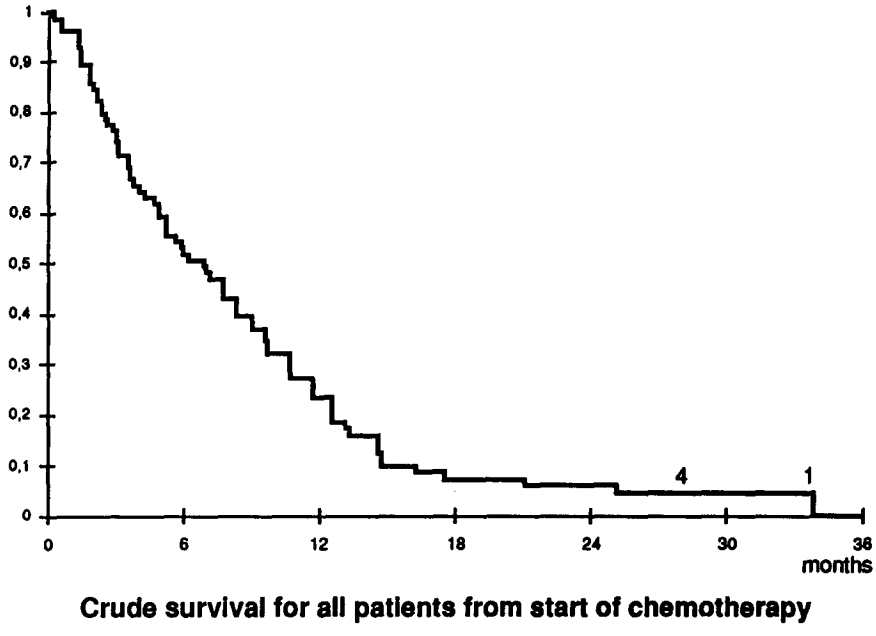

Fig. 1. Crude survival for all patients from start of chemotherapy.

trials, numerous studies report poor results: 16% response with doxorubicin and vindesine for Fiore *et al.* [27] (38 patients), 2/14 responses with fluorouracil, doxorubicin and cyclophosphamide for Valentine *et al.* [20] or 1/22 response with CMF protocol for Woods *et al.* [25]. Thus, no chemotherapy regimen appears to be really better than another. The median duration of response of 7 months in our study compares well with other studies in which durations are reported from 4 to 9 months [17, 25, 26]. From the start of chemotherapy, the overall median survival of 7 months is similar to the survival reported by Pasterz *et al.* [23], Goldberg *et al.* [24] or Anderson *et al.* [26] and Miliken *et al.* [17]. The median survival of patients who achieved a response is 12.5 months, but the chemotherapy selection criteria probably selected only these two groups of patients [28]. In our study, we were unable to find any prognostic factor affecting response or survival. Unlike Pasterz *et al.* [23], we did not find a statistically significant correlation between index performance status before treatment and objective response ($P = 0.41$ by chi-square test) or overall survival ($P = 0.75$). Likewise, no correlation appeared between histologic differentiation or importance of tumor burden and objective response to treatment or overall survival from start of chemotherapy—our results are similar to Pasterz *et al.* [23] and Kambhu *et al.* [19] for these two prognostic factors. Hepatic (30%) or superficial nodes (30%) appeared to respond better to chemotherapy than skin or bone metastases, but survival was similar. Finally, we may conclude that this chemotherapy regimen is of limited efficacy (21%) in patients with CUP, with a noticeable toxicity in one third of patients (moreover, Altretamine tablets were not taken by nearly 10% of patients). In our Institute we have abandoned this combination for such palliative care in patients with limited survival.

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