9. Casazza AM, Pratesi G, Giuliani F, Di Marco A. Antileukemic activity of 4-demethoxydaunorubicin in mice. *Tumori* 1980, **66**, 549–564.
10. Casazza AM, Bertazzoli C, Pratesi G, *et al.* Antileukemic activity and cardiac toxicity of 4-demethoxydaunorubicin. *Proc Am Ass Cancer Res* 1979, **29**, 16.
11. Carella AM, Santini G, Martinengo M, *et al.* 4-demethoxydaunorubicin (Idarubicin) in refractory or relapsed acute leukemias. A pilot study. *Cancer* 1985, **55**, 1452–1454.
12. Daghestani A, Arlin ZA, Leyland-Jones B, *et al.* Phase I and II clinical pharmacologic study of 4-demethoxydaunorubicin (idarubicin) in adult patients with acute leukemia. *Cancer Res* 1985, **45**, 1408–1412.
13. Bennett JM, Catowsky D, Daniel MT, *et al.* Proposed revised criteria for the classification of acute myeloid leukemia. *Am Intern Med* 1985, **103**, 626–629.
14. Ellison RR, Holland JF, Weil M, *et al.* Arabinosyl-cytosine: an useful agent in the treatment of acute leukemia in adults. *Blood* 1968, **32**, 507–513.
15. Preisler HD. Failure of remission induction in acute myelocytic leukemia. *Med Ped Oncol* 1988, **4**, 275.
16. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
17. Ardia A. Statistical report. Milan, Farmitalia Carlo Erba, 1988.
18. Rees JKH, Gray RG, Swirsky D, Hayhoe FGJ. Principal results of the medical research council 8th acute myeloid leukaemia trial. *Lancet* 1986, **ii**, 1236–1241.
19. Gunz FW. Epidemiology. In: Gunz FW, Henderson ES, eds. *Leukaemia*. New York, Saunders, 1983, 17–48.
20. Brincker H. Estimate of overall treatment results in acute non-lymphocyte leukemia based on age specific rates of incidence and of complete remission. *Cancer Treat Rep* 1985, **69**, 5–11.
21. Foon KA, Zighelboim J, Yale C, Gale RP. Intensive chemotherapy is the treatment of choice for elderly patients with acute myelogenous leukemia. *Blood* 1981, **58**, 467–469.
22. Berman E, Gee TS, Kempin S, *et al.* A comparative trial of idarubicin and cytarabine versus daunorubicin and cytarabine in patients with untreated acute non lymphocytic leukemia. In: Mandelli F, Polli E, Clarkson B, eds. *Idarubicin in the Treatment of Acute Leukemia*. Amsterdam, Excerpta Medica, 1987, 37–41.
23. Tucker J, Thomas E, Gregory WM, *et al.* Acute myeloid leukemia in elderly adults. *Hematol Oncol* 1990, **8**, 13–21.
24. The Toronto Leukemia Study Group. Results of chemotherapy for unselected patients with acute myeloblastic leukemia: effect of exclusions on interpretation of results. *Lancet* 1986, **i**, 786–790.
25. Lambertenghi-Deliliers G, Pogliani E, Maiolo AT, *et al.* Idarubicin in sequential combination with cytosine arabinoside in the treatment of relapsed and refractory patients with acute non-lymphoblastic leukemia. *Eur J Cancer Clin Oncol* 1987, **23**, 1041–1045.
26. Wiernik PH, Case DC Jr, Periman PO, *et al.* A multicenter trial of cytarabine plus idarubicin or daunorubicin as induction therapy for adult nonlymphocytic leukemia. *Semin Oncol* 1989, **16** (Suppl.2) 25–29.
27. Vogler WR, Velez-Garcia E, Omura G, Raney M. A phase three trial comparing daunorubicin or idarubicin combined with cytosine arabinoside in acute myelogenous leukemia. *Semin Oncol* 1989, **16** (Suppl.2), 21–24.

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Phase II Trial of Cisplatin for Adenocarcinoma of Unknown Primary Site

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The activity of cisplatin against advanced metastatic adenocarcinoma of unknown primary site (ACUP) was evaluated in 21 patients. Cisplatin (100 mg/m^2) was given as a 4-h continuous infusion every 3 weeks, with appropriate fluids and diuretics. The overall response rate was 19% with 1 complete remission for 12 months and 3 partial remissions lasting from 4 to 7 months. 7 patients achieved stable disease and in 9 patients the disease was progressive. The median duration of response was 6.5 months. The median survival 7.5 months. The median survival of the total patient group was 5 months (range 1–18 months). Toxicity comprised mainly nausea and vomiting, mild creatinine elevation and leukocytopenia. Slight ototoxicity was observed in 6 patients.
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INTRODUCTION

PATIENTS with adenocarcinoma from an unknown primary site (ACUP) are common in most general medical and oncology practices [1, 2]. The need for elaborate and intensive investigation to elucidate the primary site has been recently studied and limited investigation only has been recommended [3–5]. Intensive investigation is rarely successful in locating the primary tumour site. The evaluation should therefore be directed to the identification of any tumour for which effective or at least specific therapy is available and the identification of those sites requiring local therapy to prevent any imminent complication.

The prognosis for these patients has, in general, been poor. The median survival from diagnosis is 2–6 months [2, 3]. Information on the use of chemotherapy is limited. There are only a few publications describing the use of a single drug

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Table 1. Metastatic sites and response to cisplain

Patient	Response status*	Histological grading	Sites of metastases: Skin	Lung	Liver	Bone	Nodes	Other
1	CR	3	—	—	—	—	×	
2	PR	2	—	×	×	—	×	
3	PR	1	—	×	—	—	×	
4	PR	2	×	×	—	×	×	Ascites
5	SD	1	×	×	—	—	—	
6	SD	1	—	×	—	×	—	
7	SD	1	—	—	×	—	—	Skin: PR
8	SD	1	×	—	×	—	×	
9	SD	3	—	—	×	—	—	
10	SD	3	—	×	—	—	—	Node: PR
11	SD	2	—	×	×	×	—	
12	PD	1	—	—	×	—	—	
13	PD	3	—	×	×	×	×	
14	PD	1	—	×	×	—	—	
15	PD	3	—	×	×	—	×	
16	PD	4	—	×	—	×	—	
17	PD	3	—	×	×	—	×	
18	PD	3	—	—	×	×	—	
19	PD	2	—	×	×	—	—	
20	PD	1	—	×	—	—	—	
21	PD	4	—	×	×	—	×	

*CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
1 = Well differentiated, 2 = moderately differentiated, 3 = poorly differentiated and 4 = histologically ungraded adenocarcinoma.

Table 2. Toxicity according WHO criteria [10]

	WHO grade 0	1	2	3
Leucocytes	13	5	3	—
Platelets	20	0	1	—
Haemoglobin	17	3	1	—
Nausea/vomiting	3	2	5	11
Creatinine	11	9	1	—
Neurotoxicity	19	2	—	—

chemotherapy in this situation. 5-fluourouracil has a reported response rate of 4–14% [6, 7] without, however, any impact on survival [5]. In a very small group of patients doxorubicin has given an increase in median survival [5].

Recently, for patients with advanced, poorly differentiated adenocarcinoma new treatment strategies, in the form of cisplatin-based chemotherapy, have been proposed [8, 9]. The present study was undertaken to investigate the efficacy of cisplatin in the treatment of ACUP.

MATERIALS AND METHODS

All consecutively admitted patients with ACUP who fulfilled the eligibility criteria entered the study. No patients with poorly differentiated carcinoma were included. There was proven progression in all treated patients. Further eligibility criteria included adequate renal function (serum creatinine clearance > 60 ml/min) and bone marrow reserve (white cell count $\geq 4 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l) and WHO performance status 0–2. All patients had normal values of serum acid phosphatase, α-fetoprotein and β-chorionic gonadotropin. Patients' characteristics and the results of treatment are given in Table 1.

Drug regimen

Cisplatin (100 mg/m^2) was administered in 1000 ml normal saline as a 4-h continuous infusion in between 1 l prehydration and 2 l posthydration. Treatment was given every 3 weeks. 60 mmol KCl and 20 mmol $MgCl_2$ was added to the saline. If urine output fell below 100 ml/h, 20–40 mg of furosemide was administered. The maximum number of cycles was 6. All patients received standard metoclopramide 3 mg/kg in 50 ml saline intravenously in 30 min in combination with 50 mg diphenhydramine. If this was not successful 10 mg dexamethasone given intravenously was added to this combination.

Evaluation

Complete response (CR) was defined as the complete disappearance of all symptoms and signs of disease for a minimum of 4 weeks. Partial remission (PR) was defined as a $\geq 50\%$ reduction of the product of the two largest perpendicular diameters of all measurable lesions for a minimum of 4 weeks. Stable disease (SD) was defined as a $< 50\%$ reduction or a $< 25\%$ increase of measurable lesions. Progressive disease (PD) was defined as the appearance of new lesions or a $\geq 25\%$ increase in any lesions [10].

RESULTS

From August 1986 to October 1989 21 patients—16 men and 5 women, 27–67 years of age (mean 48)—entered the study. All patients had histologically proven adenocarcinoma with measurable metastatic disease. 8 patients had a good differentiated adenocarcinoma, 4 a moderately differentiated and 7 patients a poorly differentiated adenocarcinoma, and 2 patients histologically ungraded adenocarcinoma. Immunohistochemistry was performed in most patients but despite this evaluation it was not possible to identify the site of the primary tumour. Routine chest X-ray, abdominal CT scanning, screening for occult blood in the faeces and haematuria (> 5 erythrocytes) revealed no primary site.

The overall response rate (1 CR + 3 PR) was 19% with a confidence interval of 6–43% (Table 1). 7 patients achieved SD and in 9 patients the disease was progressive. Moreover, 2 patients had a PR in 1 site (1 patient in the skin, 1 in a lymph node) and SD in the other localisations. These responses were considered as SD. The patient with a CR had a remission of supraclavicular lymph-nodes for 12 months. She died of brain metastases after 18 months. The duration of the PRs was 7, 6 and 4 months. The median duration of response was 6.5 months. 2 patients had PD after one cycle. The median survival of the responding patients was 7.5 months. The median survival of the total patient group was 5 months (range 1–18 months).

Toxicity was as could be expected for cisplatin treatment (Table 2) and comprised mainly nausea and vomiting, mild creatinine elevation and leucocytopenia. Slight ototoxicity was observed in 6 patients. In 2 patients the diagnosis of a primary

adenocarcinoma of the lung was apparent during follow-up. All patients have died. Autopsy was performed in only 4 of them. In 3 the primary site could be determined (lung, pancreas, liver).

A remarkable finding was that 5 patients died with brain metastases.

DISCUSSION

This phase II study indicates the activity of cisplatin against ACUP. The overall response rate was 19%. There are only a few reports of other single drugs tested in this disease. The most commonly employed agent was 5-fluorouracil. If one excludes studies with less than 10 patients then activity was further reported only for doxorubicin and cyclophosphamide [5]. Because of the poor prognosis and the heterogeneous possible site of origin of the tumour one is apt to strive for a broad range of drugs in combination chemotherapy schedules. Various regimens have been reported [7, 11–14]. The response rates vary from 14 to 50%. The number of patients studied is, however, very limited, leading to broad confidence interval limits. Moreover, there are probably subsets of patients with ACUP that have very responsive tumours and subsets who have very resistant tumours. The fact that these patients are all placed in one category makes evaluation quite difficult.

Woods *et al.* [12] described a randomised treatment using 2 combination chemotherapy regimens. One regimen combined doxorubicin and mitomycin, the other consisted of a cyclophosphamide, methotrexate and 5-fluorouracil. Although both regimens demonstrated a wide range of antitumour activity, the regimen containing doxorubicin and mitomycin was found to be superior. However, these results have been questioned [15].

In patients with advanced poorly differentiated carcinoma of unknown primary site, two studies established activity of cisplatin-based chemotherapy. In these studies patients with poorly differentiated adenocarcinoma were also included. It was found by Van der Gaast *et al.* [9] that the response rate in poorly differentiated carcinoma was higher than that of poorly differentiated adenocarcinoma (79% versus 35%) and all the complete responses occurred in this subgroup. Greco and Hainsworth [16] obtained similar significant results. However, when analysed in a multivariate analysis the histology was not shown to have independent predictive value [16]. In their group of patients only tumour localisation in the mediastinum, retroperitoneum or lymph-nodes predicted a superior treatment outcome. In our study, only 1 out of 7 patients with a poorly differentiated adenocarcinoma responded. This patient had a localisation in the lymph-nodes. The 3 patients with a partial response had a good (1 patient) or a moderately differentiated (2 patients) adenocarcinoma. We conclude that cisplatin adds to the limited number of chemotherapeutic agents which have modest activity in ACUP. It is worthwhile to investigate cisplatin in combination treatment for ACUP.

1. Nystrom JS, Weiner JM, Mesknik Wolf R, *et al.* Identifying the primary site in metastatic cancer of unknown origin. *JAMA* 1979, **241**, 381–383.
2. Altman E, Cadman E. An analysis of 1539 patients with cancer of unknown primary site. *Cancer* 1986, **57**, 120–124.
3. Stewart JF, Tattersall MHN, Woods RL, Fox RM. Unknown primary adenocarcinoma: incidence of overinvestigation and natural history. *Br Med J* 1979, **1**, 1530–1533.
4. Nissenblatt MJ. The CUP syndrome (carcinoma unknown primary). *Cancer Treat Rev* 1981, **8**, 211–214.
5. Markman M. Metastatic adenocarcinoma of unknown primary site: analysis of 245 patients seen at the Johns Hopkins Hospital from 1965–1979. *Med Pediatr Oncol* 1982, **10**, 569–574.
6. Johnson RO, Castro R, Ansfield FJ. Response of primary unknown cancers for treatment with 5-fluorouracil (NSC-19893). *Cancer Chemother Rep* 1964, **38**, 63–64.
7. Moertel CG, Reitemeier RJ, Schutt AJ, Hahn RG. Treatment of the patient with adenocarcinoma of unknown origin. *Cancer* 1972, **30**, 1469–1472.
8. Greco FA, Vaughn WK, Hainsworth JD. Advanced poorly differentiated carcinoma of unknown primary site: recognition of a treatable syndrome. *Ann Intern Med* 1986, **104**, 547–553.
9. Gaast A van der, Verweij J, Henzen-Logmans SC, Rodenburg CJ, Stoter G. Carcinoma of unknown primary: identification of a treatable subset? *Ann Oncol* 1990, **1**, 119–122.
10. WHO. *Handbook for Reporting Results of Cancer Treatment.* WHO Offset Publication No. 48, Geneva, WHO, 1979.
11. Valentine J, Rosenthal S, Arsenan JC. Combination chemotherapy for adenocarcinoma of unknown origin. *Proc Am Assoc Cancer Res* 1979, **20**, 349.
12. Woods RL, Fox RM, Tattersall MHN, Levi JA, Brodie GN. Metastatic adenocarcinomas of unknown primary site. *N Engl J Med* 1980, **2**, 87–89.
13. Anderson H, Thatcher N, Rankin E, *et al.* VAC (vincristine, Adriamycin, cyclophosphamide) chemotherapy for metastatic carcinoma from an unknown primary site. *Eur J Cancer Clin Oncol* 1983, **19**, 49–52.
14. Walach N, Horn Y. Combination chemotherapy in the treatment of adenocarcinoma of unknown primary origin. *Cancer Treat Rep* 1987, **71**, 605–607.
15. Bitran JD, Desser RK, Kozloff MF, Billings AA, Shapiro CM. Chemotherapy of metastatic adenocarcinoma of unknown origin. *N Engl J Med* 1980, **2**, 1478.
16. Greco FA, Hainsworth JD. Carcinoma of unknown primary site. *Ann Oncol* 1990, **1**, 98–99.

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