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A Randomised Clinical Trial Comparing Idarubicin and Cytarabine to Daunorubicin and Cytarabine in the Treatment of Acute Non-lymphoid Leukaemia

A Multicentric Study from the Italian Co-operative Group GIMEMA

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255 patients with acute non-lymphoid leukaemia (ANLL), observed between October 1984 and June 1987, entered a chemotherapy regimen consisting of induction therapy with cytarabine in combination with idarubicin (IDA/ARA) or daunorubicin (DNR/ARA), followed by consolidation with four courses of IDA+ARA plus 6-thioguanine (6-TG) or DNR+ARA+6-TG and a 6 month maintenance therapy with 6-TG and ARA. The median age was 62 years (range 55–78 years) and 33 were aged more than 70 years. The treatment groups were comparable for median age, FAB type, performance status and initial blood counts. 249 patients were randomised, 124 to the IDA/ARA arm and 125 to the DNR/ARA arm. Complete remission was achieved in 50 patients (40%) on the IDA/ARA treatment program and 49 patients (39%) on DNR/ARA. No definite differences were found between patients receiving IDA/ARA and those treated with DNR/ARA as far as complete response (CR), overall survival, failure free and relapse free survival are concerned. 74% of the complete responders in the IDA/ARA arm and 51% in the DNR/ARA arm achieved CR after a single course of treatment. Resistant leukaemia was observed in 13.7% of the patients in the IDA/ARA arm and in 31.2% in the DNR/ARA one, whereas hypoplastic death occurred in 29% and 14.4%, respectively. In conclusion, our data failed to show any advantage of idarubicin over daunorubicin even though there is some evidence that IDA, despite the higher toxicity, is more rapid in eradicating leukaemia as proved by the higher CR rate obtained after one course of induction.
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INTRODUCTION

IN SPITE of the progress made in recent years in the treatment of acute non-lymphoid leukaemia (ANLL), age remains one of the most unfavourable prognostic factors; therefore the therapy of ANLL in patients aged more than 60 years is still controversial [1–5].

So far, to overcome this limitation, scientists involved in the treatment of these patients have either reduced the dosage of the chemotherapeutic combinations utilised in younger people [6] or investigated the use of new drugs with high therapeutic index.

Idarubicin is a new anthracycline [7] which in experimental leukaemias has proved to be 4–5 times more powerful than daunorubicin [8,9], and seems characterised by a more favourable therapeutic index [10]. Moreover, in phase I–II studies it has been shown to be an active antileukaemic agent [11,12]. In order to verify these experimental data, in October 1984, the GIMEMA group undertook a multicentric randomised study comparing idarubicin plus cytarabine (IDA/ARA) vs. daunorubicin plus cytarabine (DNR/ARA) in previously untreated patients with ANLL aged between 55 and 80 years. Aims of the study were (1) to compare the efficacy and toxicity of the combination IDA/ARA vs. DNR/ARA as induction treatment in this particular group of patients; (2) to verify if a combined postremission therapy based on idarubicin or daunorubicin would influence the duration of remission, relapse free survival, failure free survival and overall survival.

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PATIENTS AND METHODS

From October 1984 to June 1987, 255 patients aging from 55 to 80 years with a cytological diagnosis of ANLL according to FAB criteria [13] entered the study. The median age was 62 years, and 33 patients were aged more than 70 years. Patients with previous myelodisplastic disorders were included in the study. Exclusion criteria were: absence of informed consent, age over 80 years, prior therapy for leukaemia, left ventricular ejection fraction less than 50%, presence of clinically important pathology involving liver (SGPT and SGOT > three times normal values and/or bilirubin >3 mg/dl), kidney (creatinine > 3 mg/dl) or respiratory system, CNS involvement and blastic crisis of chronic myelogenous leukaemia.

Eligible patients were centrally randomised to receive either daunorubicin 45 mg/m^2/day for 3 consecutive days or idarubicin 12 mg/m^2/day for 3 consecutive days in combination with cytarabine 100 mg/m^2/day in a continuous intravenous infusion from days 1–7. The anthracycline drugs were administered as intravenous bolus injection over 5 minutes. A bone marrow examination was performed 20 days after the start of treatment and then twice weekly until recovery of bone marrow cellularity was detected.

Patients not achieving complete response (CR) after the first course received a second course of either idarubicin (12 mg/m^2/day intravenously for 2 days) or daunorubicin (45 mg/m^2/day intravenously for 2 days) plus cytarabine (100 mg/m^2 as a continuous infusion for 5 days). Patients not in CR after the second course were considered as resistant. Complete remission was defined according to the Cancer and Leukaemia Group B (CALGB) criteria [14].

Non-responders were classified according to Preisler *et al.* [15] whereas toxicity was assessed according to WHO criteria [16].

All patients who achieved CR received consolidation therapy as soon as their neutrophil count reached 1.0×10^9/l. Consolidation therapy consisted of idarubicin (12 mg/m^2) or daunorubicin (45 mg/m^2) on day 1 associated to cytarabine, 50 mg/m^2 subcutaneously plus 6-thioguanine (6-TG) 50 mg/m^2 orally, every 8 h from days 1–5 for a total of four courses repeated every 4–6 weeks. Thereafter a maintenance treatment consisting of 18 courses with 6-TG, 100 mg/m^2 from days 1–4 and cytarabine 100 mg/m^2 on day 5, interspersed with a 5–7 days interval, was given. The prophylaxis of leukaemic meningosis was not contemplated in this study.

All patients received prophylactic oral nystatin or amphotericin B and chemoprophylaxis with adsorbable (trimethoprim-sulphametoxazole or norfloxacin) antibiotics. Febrile episodes were treated with a combination of broad spectrum antibiotics (a betalactamic plus an aminoglycoside). Patients not responding to the antibiotic therapy after 4–6 days of treatment received systemic amphotericin B.

Platelet transfusions were employed in patients with overt haemorrhagic manifestations or when platelet count dropped below 20.0×10^9/l. A complete clinical and laboratory evaluation including electrocardiogram (ECG) and bidimensional echocardiography was performed in all patients at diagnosis and at the end of induction phase. Moreover, blood cell count and liver and renal blood tests were performed daily and twice weekly, respectively, during the entire period of induction.

Statistical analysis

The efficacy variables which were compared in the two treatment groups were frequency and duration of CR, number of courses to remission, time to CR and survival curves (relapse free survival, failure free survival and overall survival). Tests on proportions (efficacy, toxicity) were done using the χ^2 test. Remission and survival duration were estimated using the Kaplan–Meier method. Comparisons between the two treatment groups were made using the log rank test and the generalised Wilcoxon test. The sample size has been calculated in order to detect a difference of within 15% assuming a failure free survival rate of standard treatment at 12 months of 0.20; using a two-tailed log rank test at a significant level of $\alpha = 0.05$, with a power of 0.80, 123 patients per arm were needed. All randomised patients were evaluated for the efficacy of the treatment on the basis of an "intention to treat" while analysis of toxicity was performed on treated patients [17].

Table 1. Distribution of patients in the participating centres

Participating centres	Total patients	IDA/ ARA	DNR/ ARA
Cattedra di Ematologia, Universita "La Sapienza", Roma	37	20	17
Clinica Medica, Bari	32	14	18
Ematologia "Molinette Hospital", Torino	25	16	9
Ematologia "San Camillo Hospital", Roma	17	6	11
Ematologia "Cervello Hospital", Palermo	14	8	6
Ematologia "San Giovanni Rotondo Hospital", Foggia	14	8	6
Cattedra Ematologia, Catania	12	8	4
Clinica Medica 1, Perugia	12	5	7
Ematologia, Pescara	10	3	7
Ematologia, Ila Facolta Medicina, Napoli	10	6	4
Ematologia, Reggio Calabria	10	3	7
Ematologia, Latina	9	4	5
Ematologia "Cardarelli Hospital", Napoli	9	3	6
Ematologia, Ancona	7	4	3
Ematologia, "Università Cattolica", Roma	7	4	3
Ematologia "Businco Hospital", Cagliari	6	2	4
Ematologia "Pugliese Hospital", Catanzaro	6	3	3
Ematologia, Avellino	5	3	2
Patologia Medica 1, Palermo	3	2	1
Cattedra Ematologia, Torino	3	0	3
Cattedra Ematologia, Sassari	2	1	1
Ematologia, Messina	1	1	0
Clinica Medica, Policlinico II, Napoli	1	0	1
Ematologia, "Ospedale Civile", Nuoro	1	1	0
Ematologia "Nuovo Pellegrini Hospital", Napoli	1	1	0
Ematologia "San Carlo Hospital", Potenza	1	1	0
Total	255	127	128

RESULTS

From October 1984 to June 1987, 255 patients from 26 Italian centres were referred for the study. The list of participating centres and the distribution of patients in the two groups for each centre are shown in Table 1. 124 patients were randomised to the IDA/ARA treatment arm and 125 to DNR/ARA treatment; 6 patients were not eligible, 1 because of misdiagnosis and 5 because of major protocol violation. The characteristics of all 249 patients evaluable for treatment in both induction arms are shown in Table 2. The most important prognostic factors [age, FAB classification, white blood cells (WBC) and platelet count] were similarly distributed between the two groups;

Table 2. Patients' characteristics

	IDA/ARA	DNR/ARA
No. of patients	124	125
Sex		
Male	65	75
Female	59	53
Age		
<60	41	49
61–65	35	38
>65	48	38
Median	63	62
Range	55–78	55–76
FAB		
M1	29	27
M2	33	38
M3	5	2
M4	32	35
M5	20	15
M6	5	6
No data	–	2
Performance status (Zubroc)		
0	6	3
1	27	30
2	62	60
3	26	23
4	2	6
No data	1	3
WBC × 10^9/l		
Median	11	13.5
Range	0.6–267	0.8–315
Platelets (× 10^9/l)		
Median	54	62.5
Range	3–387	2–382

however, a slight but not significant prevalence of patients over 65 years was present in the IDA/ARA arm.

Induction remission

The results of induction therapy for the evaluable patients are shown in Table 3. The IDA/ARA and DNR/ARA treatment arms resulted in 40% (50/124) and 39% (49/125) of CR respectively. In the IDA/ARA program, 74% (37/50) of the complete responders achieved CR after one course, while in the DNR/ARA program only 51% (25/49) of the responders achieved CR after one course ($P=0.02$).

Resistant leukaemia as cause of failure was observed in 13.7% (17/124) of the patients belonging to the IDA/ARA arm and in 31.2% (39/125) of the patients belonging to the DNR/ARA arm. Moreover 5/124 patients in the IDA/ARA arm and 6/125 in the DNR/ARA arm were not treated after randomisation, while in 9 (5 in the IDA/ARA arm and 4 in the DNR/ARA arm) there was a regeneration failure (Preisler III). These 20 patients were also considered treatment failures.

Early deaths, defined as death before the treatment evaluation, was observed in 8% of the patients in the IDA/ARA arm and in 7.2% of the patients in DNR/ARA arm, respectively. Hypoplastic deaths were 14.4% in the DNR/ARA regimen and 29% in the IDA/ARA regimen.

A statistically significant difference, between the two induction treatments, as far as the pattern of failures is concerned (deaths vs. other failures), was present ($P=0.001$).

Table 3. Response to treatment

	IDA/ARA (%)	DNR/ARA (%)
No. of randomised patients	124	125
Complete remission	50(40.3)	49(39.2)
Courses to remission		
1	37(74)	25(51)
2	13(26)	24(49)
Death	47(37.9)	27(21.6)
Early death	10(8.0)	9(7.2)
Hypoplastic death	36(29.0)	18(14.4)
Death during regeneration	1(0.8)	0
Other failures	27(21.7)	49(39.2)
Resistant	17(13.7)	39(31.2)
Others*	10(8.0)	10(8.0)

IDA/ARA: 5 patients not treated; 5 regeneration failure (Preisler III)
DNR/ARA: 6 patients not treated; 4 regeneration failure (Preisler III).
Homogeneity test of response to treatment between the two groups: $\chi^2 = 11.8$ (df = 2, $P = 0.003$); CR vs. failures: $\chi^2 = 0.033$ (df = 1, $P = 0.86$); death vs. other failures: $\chi^2 = 11.75$ (df = 1, $P = 0.001$); comparison of the number of courses to remission: $\chi^2 = 5.58$ (df = 1, $P = 0.02$).

Toxicity

In responding patients the median duration of WBC $<1.0\times10^9$/l and platelets $<100.0\times10^9$/l was 12.5 days (range 1–29) and 26 days (range 14–141), respectively, in the IDA/ARA regimen, while in the DNR/ARA regimen was 11 days (range 5–35) and 25 days (range 11–71), respectively. These differences were not statistically significant. However, the median nadir of WBC, but not that of platelets was significantly different between the two treatments since IDA/ARA produced a deeper WBC median nadir than DNR/ARA (Table 4). The incidence of clinical complications during the induction treatment was similar in both the induction regimens, except for infections which were more frequent in the IDA/ARA group even though the difference was not statistically significant ($P=0.06$).

No statistically significant differences were found for transaminases values between the two treatment groups, while a higher incidence of elevated serum bilirubin levels was observed in the IDA/ARA treatment group. Moreover, the incidence of elevated blood urea and nitrogen (BUN) and serum creatinine levels was higher in the IDA/ARA treatment group as compared to the

Table 4. Haematological toxicity according to drugs actually administered

	IDA/ARA ($n = 49$)	DAR/ARA ($n = 50$)*	P†
Median WBC nadir (range) (× 10^9/l)	0.40(0.1–1.4)	0.55(0–3.5)	0.01
Median platelet nadir (range) (× 10^9/l)	12(0–50)	10.5(0–48)	0.6

*1 patient randomised to IDA/ARA actually received DNR/ARA.
†Wilcoxon test.

Table 5. Induction toxicities: statistical analysis of selected laboratory tests

Toxicity	Grade	IDA/ARA (n = 120)	DNR/ARA (n = 121)	χ^2	P	d.f.
Hepatic	0					
Bilirubin	1+2					
	3+4			9.4	0.009	2
	0 vs.					
	(1+2+3+4)	54	78			
	(1+2) vs.	42	26	9.3	0.002	1
	(3+4)	8	4	0.1	0.75	1
SGOT	0	69	74			
	1+2	30	30			
	3+4	8	6	0.42	0.8	2
SGPT	0	64	66			
	1+2	40	38			
	3+4	5	7	0.4	0.82	2
Alkaline	0	67	63			
phosphatase	1+2+3+4	26	30	0.41	0.52	
Renal						
BUN	0					
	1+2					
	3+4					
	0 vs.			6.7	0.034	2
	(1+2+3+4)	65	83			
	(1+2) vs.	37	27	5.54	0.02	1
	(3+4)	9	3	1.25	0.26	1
Creatinine	0	80	103			
	1+2+3+4	31	10	13.6	<0.001	

DNR/ARA (P<0.001) (Table 5). 1 patient in each arm died because of liver toxicity.

Severe cardiac toxicity consisting of arhythmias, myocardial infarction, cardiogenic shock and congestive heart failure (CHF) have been reported in both the induction treatment arms. As shown in Table 6, 2 fatal events, namely a ventricular fibrillation and a cardiogenic shock, occurred in the IDA/ARA arm, while in the DNR/ARA arm 1 fatal myocardial infarction occurred. The cardiac postmortem histological examination performed in 2 of these patients did not reveal the specific findings associated with an anthracycline-induced cardiomyopathy. It is interesting to note that the CHFs occurring in both arms were all reversible and most of them consisted of lower limb oedema resolved with diuretics and digitalis. Moreover, 2 patients with CHF on the IDA/ARA arm already had pre-existing cardiopathy.

For the myocardial function parameters, no change was observed at the end of induction treatment compared to the baseline values.

Table 6. Cardiac toxicity

	IDA/ARA	DNR/ARA
Ventricular fibrillation	1 (Fatal)	0
Myocardial infarction	0	1 (Fatal)
Cardiogenic shock	1 (Fatal)	1
Congestive heart failure	3	1

No. of patients.

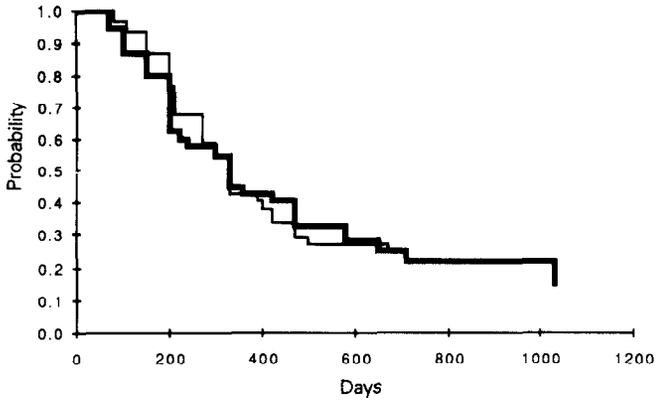

Fig. 1. Kaplan–Meier plots of probability of relapse free survival for patients receiving idarubicin (— or daunorubicin (——).

Duration of response and survival

The median CR duration was 274 days for the IDA/ARA group and 239 days for the DNR/ARA group. Median relapse free survival duration was 299 and 284 days in idarubicin and daunorubicin treated patients, respectively (Fig. 1). The overall failure free survival duration is shown in Fig. 2. No significant differences between the two treatments were found as far as CR duration, relapse free and failure free survival duration are concerned.

The median survival duration for the IDA/ARA group was 87 days; 97 patients died (78.2%) and 27 patients were censored. The DNR/ARA group had a median survival duration of 169 days, with 86 patients dying (68.8%) and 39 patients censored. These differences in survival duration between the two arms of induction treatment were not statistically significant, either by the log rank test (P=0.23) or by the Wilcoxon test (P=0.09).

DISCUSSION

The opinions of clinical investigators about to treat ANLL in the elderly are controversial. Evidence supporting either intensive combination therapy or conservative treatments is present in the literature. At first glance the very high induction death rate in our group of patients treated with idarubicin containing regimen would support the choice of a conservative treatment. This is indeed the strategy followed by most institutions, as clearly shown by the Medical Research Council (MRC)'s 8th acute myeloid leukaemia trial in which only 305

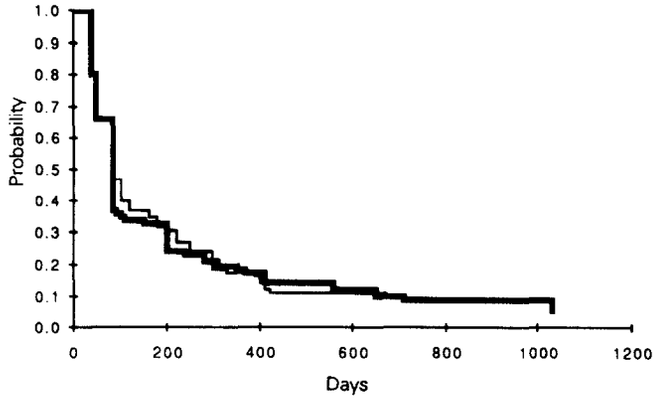

Fig. 2. Kaplan–Meier plots of failure free survival for patients receiving idarubicin (—) or daunorubicin (——).

(27%) of the 1127 patients included in the analysis were older than 60 years [18]. However, it is well recognised that over half of all cases of ANLL are aged above 60 years [19–20]; therefore, the majority of clinical studies dealing with the treatments of ANLL in the elderly are biased by some selection criteria. As a consequence of this policy the observed remission rates and induction death rates in such studies with a selected populations are not representative of the real outcome of ANLL in elderly patients.

In contrast, the 255 patients referred to the present study represent 53% of all patients aged from 15 to 80 years treated by the GIMEMA group from April 1984 to June 1987.

In the present study, idarubicin in combination with cytarabine has produced a CR rate of 40% (50/124) while the combination DNR/ARA has produced a CR rate of 39% (49/125). The remission rates are in agreement with those described in the literature ranging from 15% [20] to 76% [21] depending upon the clinical setting where patients were treated (general hospital or high specialised centre treating only selected patients).

No statistically significant differences in duration of remission, relapse free, failure free and overall survival were observed between the two arms.

The results of our study are comparable to those obtained in patients over 60 years of age by the most important randomised trials carried out in ANLL by the CALGB [1, 3]. Moreover, an ongoing trial of idarubicin vs. daunorubicin in association with cytarabine shows similar results in patients over 60 years of age [22].

However, even though the results of our study for CR and survival duration are similar to other studies some aspects are peculiar and deserve further discussion. Firstly, in contrast to usual clinical studies comparing different treatment regimens, analysis here has been carried out on the basis of the "intention to treat" and not of the treatment administered. Due to their very poor condition, 15 patients (8 in the IDA/ARA arm and 7 in DNR/ARA arm) died before treatment was started, soon after having been randomised. These patients were considered early deaths and included in the analysis.

Secondly, in this study there were few exclusion criteria, and many poor-risk patients with infections, low performance status or pre-existing myelodisplasia were included. Consequently, the observed CR rates are noteworthy, considering a recent experience by Tucker *et al.* [23] in which there was a 28% remission rate in a group of 88 patients aged over 60 years. In fact, the importance of the presence of selection criteria for the patients in the evaluation of the results of therapy of ANLL has been well stressed by the Toronto leukaemia group [24].

Thirdly, a significant difference between the two treatment programs in regard to the number of courses required to achieve remission was detected. In particular, on the IDA/ARA arm, 37 of the 50 patients who achieved remission (74%) required one course whereas on the DNR/ARA arm only 25 patients (51%) achieved CR after one course ($P=0.02$). These data are in accordance with the results of Berman *et al.* [22], who reported, using a similar schedule, 85% of complete responders after one course of therapy in the idarubicin treated group and 69% in the daunorubicin arm.

Fourthly, a significant difference was also found between the two treatments as far as the pattern of failures was concerned ($P=0.001$). Resistant leukaemia was the reason for treatment failure in 13.7% of the patients on the IDA/ARA arm and in 31.2% of the patients on the DNR/ARA arm. Induction death rate was 37.9% on the IDA/ARA arm and only 21.6% on the DNR/ARA arm. Moreover, time to reach CR was shorter with idarubicin (median time 27 days) than with the daunorubicin (median time 35 days) combination, but the difference was not statistically significant ($P=0.07$).

Finally, taking into account that all the patients who entered the trial were evaluated, the overall response rate in our multicentric study is fairly good considering that in the study small hospitals as well as major university centres were involved.

Myelosuppression was the main toxicity observed in both arms. However, the IDA/ARA combination produced a deeper WBC median nadir and a higher incidence of infections ($P=0.06$). Cardiotoxicity was not a major problem in either group of patients. Only 8 patients in this series (5 in the idarubicin and 3 in the daunorubicin arm) developed clinical and/or laboratory evidence of cardiac toxicity; however, some of these occurred in the setting of severe infections and/or electrolyte imbalance and/or fluid overload. Therefore a causal relationship between drug therapy and cardiac effects is difficult to establish. These data support the results of several recent studies both in treated [11, 25] and previously untreated [22, 26, 27] patients. However, even though the short-term cardiac evaluation demonstrated that the acute cardiac toxicity has been quite acceptable, no conclusion about chronic cardiotoxicity can be drawn.

Higher serum bilirubin, BUN and serum creatinine levels were observed in the IDA/ARA group. However, the severity (grade 3 and 4) of these abnormal values was not statistically different between the two arms and did not influence the mortality rate of the patients. Moreover, in the majority of patients these abnormalities were observed in the setting of severe infections. It is difficult to establish if in the IDA/ARA arm the higher values of creatinine are related to a larger use of antibiotics or to idarubicin direct toxicity.

In conclusion, these data failed to show any advantage of idarubicin over daunorubicin when the former was given at the dose of 12 mg/m^2 and the latter at that of 45 mg/m^2. However, there is some evidence that idarubicin is more rapid in eradicating leukaemia as provided by the higher CR rate obtained after one course of induction. The better results obtained by Yates *et al.* [3] in elderly patients when reduced doses of daunorubicin were given suggest that reduced doses of idarubicin should be also used in elderly patients in order to decrease the high number of aplastic deaths due to the myelotoxicity.

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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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