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Aclarubicin (Aclacinomycin A) in the Treatment of Relapsing Acute Leukaemias

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Abstract—*Forty patients with relapsing acute leukaemias were treated with aclacinomycin A (aclarubicin, ACM), 25 mg/m² i.v. daily for 7 days. Twenty-nine patients with acute myeloid (AML) and five with acute lymphoblastic (ALL) leukaemia were evaluable. The overall response rate was 29.5%. Eight complete (CR) and one partial (PR) remissions were achieved in AML (31%). A high CR rate was induced in patients treated at first relapse without prior reinduction (6/12 patients). A small proportion of leukaemias resistant to daunorubicin or doxorubicin responded to ACM (3/17 patients). Median remission duration was 5.5 months (range: 2-9 months). The most common toxic effects were nausea, vomiting, stomatitis and diarrhoea. Acute cardiotoxic effects were documented in three patients. Congestive cardiomyopathy was not observed despite prior treatment with anthracyclines. We conclude that the present dose scheduling of ACM is effective in the treatment of relapsing AML and that it should be introduced in combined chemotherapy in phase III trials to compare its activity to that of daunorubicin or doxorubicin.*

INTRODUCTION

ANTHRACYCLINE antibiotics and cytosine arabinoside are the most commonly used cytotoxic agents in the treatment of acute myeloid leukaemia [1]. Since the long-term administration of anthracyclines is limited by their cumulative cardiotoxicity, an effort has been made toward the detection of analogues which do not share the cardiotoxic effect.

Aclacinomycin A (ACM) is an anthracycline antibiotic isolated from *Streptomyces galilaeus* [2] which has shown less cardiotoxicity than daunorubicin (DNR) or doxorubicin (ADM) in animal experiments [2-4]. ACM differs from other anthracycline antibiotics with respect to chemical structure and biological activities [2]. The cellular uptake occurs more rapidly than doxorubicin. ACM accumulates predominantly in the cytoplasm [5] and inhibits RNA synthesis *in vitro* at a much lower concentration than DNA synthesis [2, 6]. It interferes with the late S/G_2 and G_1 phases of the cell cycle [7, 8].

In recent phase I and II studies ACM showed significant antileukaemic activity, particularly in acute non-lymphoblastic leukaemia [9-14]. However, the optimal daily dose and schedule remained undetermined. Since high daily doses of ACM for 2-3 days induced a low remission rate with a rather high frequency of toxic side-effects [12], a phase II study was initiated to evaluate the efficacy of low daily doses of ACM administered for 7 days in relapsing leukaemias.

MATERIALS AND METHODS

Patients

Adult patients with acute myeloid (AML) or lymphoblastic (ALL) leukaemia were eligible for entry in this study after they had relapsed or had failed anthracycline-containing chemotherapy for remission induction. Leukaemias were

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classified according to the cytologic and cytochemical criteria of the FAB-classification [15]. All patients had adequate cardiac, renal and hepatic function. The expected survival was >4 weeks. There were no restrictions on the amount of prior chemotherapy including DNR and ADM. The pretreatment evaluation included a haemogram, bone marrow aspiration, screening biochemical profile, ECG and X-ray examination of the chest. Patients were monitored with blood cell counts daily and biochemical profile twice a week. Thirty-five patients had 3-4 ECGs during the treatment course with ACM. Continuous ECG monitoring or radionuclide cardiac scan were not performed.

The principal characteristics of the patients are summarized in Table 1. All patients had received daunorubicin (DNR) and/or doxorubicin (ADM). The majority of patients were treated at the first relapse with ACM. Six patients had never achieved remission despite at least two courses of intensive induction chemotherapy. Six out of 40 patients were considered unevaluable for the following reasons: early death (one patient), further treatment refused (two patients), protocol violation (two patients) and treatment discontinuation because of persisting ECG changes (one patient). All these patients received only one course or less of chemotherapy and their post-treatment data were insufficient for response evaluation.

Table 1. Characteristics of the patients

Total No. of the patients		40
Sex		
Female		21
Male		19
Age (yr)		
Median		45
Range		18-64
AML		35
ALL		5
Median cumulative doses (mg/m²) of prior chemotherapy, median (range)		
Daunorubicin	290 (60-900)	25
Doxorubicin	220 (85-480)	21
Ara-C	3100 (650-15,060)	38
6-Thioguanine	2940 (494-19,300)	32
Other	— —	24
Duration of first remission (months)		
Median		8
Range		3-21
Relapses		
1st relapse		25
2nd relapse		8
4th relapse		1
Primarily chemotherapy resistant		6
No. of ACM courses		
Median		2
Range		1-4
Evaluable for response to ACM		34
AML		29
ALL		5

Treatment

One cycle of ACM treatment consisted of the daily administration of 25 mg/m² i.v. (bolus) on 7 consecutive days with a cumulative dose per course of 175 mg/m². Bone marrow cytology was repeated 14 days after the initiation of therapy. Patients who did not respond received a second ACM course. Supportive therapy with antibiotics and blood products was administered when required. Complete (CR) and partial (PR) responses were defined by the CALGB criteria [16].

RESULTS

Twenty-nine patients with AML and five patients with ALL were evaluable for response to ACM. The median number of ACM courses was two (Table 1). Eleven patients received one course and died of progressing leukaemia or of infections or bleeding in the aplastic phase after chemotherapy. Twenty-three patients received two or more cycles.

CR or PR was achieved in ten patients with AML or ALL (Table 2). Nine patients with AML responded to ACM (31%). The median age (49.5 yr) of the responding patients was similar to that of the entire group. Responses were induced in acute myeloid or myelomonocytic and monocytic leukaemia. Twenty-four patients were treated with ACM at their first relapse. A high reponse rate was induced in patients without prior chemotherapy for relapse (Table 2). Eleven patients were treated for first relapse with anthracycline-containing regimens and did not respond. Two of them subsequently entered complete remission to ACM treatment. A partial remission was achieved in 1/6 patients who failed to respond to daunorubicin and/or doxorubicin combination chemotherapy for remission induction. One complete remission was observed in patients with a second relapse (Table 2). This patient relapsed 5 months after reinduction for first relapse with ACM and entered a second remission to ACM treatment. Remission was observed in every case after the first cycle of ACM

Table 2. Treatment results

	No. of patients	CR (%)	PR (%)	Failure
Evaluable patients	34	9 (26.5)	1 (3)	24 (70)
AML (M1-M5)	29	8 (27.5)	1 (3.5)	20 (69)
AML (M1, M2)	23	7 (30.5)	1 (4.5)	15 (65)
AML (M4, M5)	6	1	0	5
ALL	5	1	0	4
First relapse without prior reinduction	12	6 (50)	0	6 (50)
First relapse with prior unsuccessful reinduction	11	2 (18)	0	9 (82)
Second relapse	5	1	0	4
Primary treatment failure	6	0	1	5

treatment. The median remission duration was 5.5 months (range 2-9 months).

Bone marrow aplasia was documented in four patients, who finally did not enter remission. Two of them died of infection in the aplastic phase.

Toxicity

Mild gastrointestinal toxicity (nausea, vomiting, anorexia) was the most common side-effect (Table 3). Stomatitis or diarrhoea were observed in 15% of the patients. Transient elevation of liver enzymes (>2 pretreatment value) with or without hyperbilirubinemia occurred in seven patients. In 3/35 cases ECG changes (T-wave inversion, ST-depression) were seen. One of these patients had previously received 900 mg/m^2 daunorubicin.

DISCUSSION

Aclacinomycin as single-agent therapy was found to be an effective agent in relapsed AML, with an overall remission rate of 31%. This is a high response rate in a heavily pretreated patient population comparable to those reported with Ara-C, DNR or *m*-AMSA [17-19]. Treatment results with ACM depended on the pretreatment characteristics of the patients. ACM treatment induced a high response rate (6/12 patients) in patients at first relapse without prior reinduction. The CR rate in this patient group is very similar to those reported by other investigators with DNR in previously untreated patients with ANLL [20] or with combination chemotherapy at the time of first relapse [21]. In contrast, the response rate in patients with primarily chemotherapy-resistant AML or with an unsuccessfully pretreated first relapse were much lower. However, three of these patients (two CR and one PR) responded to ACM despite resistance to prior treatment with DNR or ADM. It is therefore conceivable that ACM is not cross-resistant to DNR and ADM. Lack of cross-resistance between ACM and DNR or ADM was strongly suggested by Machover *et al.* [13].

Table 3. Side-effects of ACM

Side-effect	No. of patients (%)
Nausea, vomiting	18/40 (45)
Anorexia	16/40 (40)
Stomatitis	6/40 (15)
Diarrhoea	6/40 (15)
ECG changes	3/35 (6)
Elevation of liver enzymes	7/40 (17)

Although ACM has been found to be active in AML in the studies published so far [9-14], the results have been rather heterogeneous; CR rates varied from 13 [12] to 44% [13] in previously treated AML patients. The different response rates may be a reflection of inter-institutional differences in patient referral patterns. Additionally, from the results of the studies it would appear that dose and schedule of ACM influenced the treatment results. Daily administration of low ACM doses for 7-10 days induced higher CR rates [13, present study] than high doses for three days [12, 14]. Low daily doses of ACM for prolonged periods induced complete remissions at much lower cumulative doses per cycle (150-175 mg/m^2) [13, present study] than high doses for 3 days (240-360 mg/m^2) [12, 14]. This difference seems to be important, since the total dose per cycle correlated to severity and frequency of toxic effects [13].

The results of earlier phase I/II studies [22, 23] suggested that the response rate in acute

leukaemias may correlate to the total dose of ACM administered. However, the later work of this group [13] demonstrated that small daily doses with a rather low cumulative dose per cycle (150 mg/m²) are more effective than high doses. Complete responses can be attained with a single course of ACM [13]. The present study confirmed these data. All remissions were induced after a 7-day course of ACM with a cumulative dose of 175 mg/m². Therefore daily doses of 15 or 25 mg/m² on 10 or 7 consecutive days are a very effective schedule of ACM in the treatment of acute leukaemias.

The number of patients with ALL included in this study is too small for evaluation of the activity of ACM in this type of leukaemia. In the series published so far [9-11, 22] 44 patients with relapsing or refractory ALL were treated with ACM. Five (11%) CR and 4 PR (9%) were achieved with an overall response rate of 20%.

Severe side-effects were not observed. Gastrointestinal toxicity was the most common side-effect described in earlier studies [9-14]. Acute cardiotoxic effects were detected in three cases. However, the patients were not closely monitored for cardiac toxicity. Continuous ECG monitoring revealed a higher frequency of ECG abnormalities and arrhythmia [12]. It is unclear whether the higher incidence is related only to closer monitoring or to the differences in dose scheduling and total dose per cycle noted above. Congestive cardiomyopathy was not observed in our or earlier studies [9-14, 22].

In conclusion, the daily dose and schedule of ACM used in the present study yielded encouraging results. Therefore a randomized trial is now underway to compare ACM + Ara-C to DNR + Ara-C in the treatment of AML at the time of first relapse.

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