科技资料

New Findings on Aclarubicin in the Treatment of Acute Myeloid Leukemia

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Preface

Since the introduction of new anthracycline derivatives and anthrachinone analogues a few years ago, aclacinomycin A (Aclarubicin) has become an established agent for the treatment of hematologic malignancies. A special symposium was therefore held during the congress of the German Society of Hermatology and Oncology in Hannover in October 1989 to provide an up-to-date overview. Leading experts from the United States, Sweden, and Germany reported on the results being obtained with aclacinomycin A, alone or combined with other agents, in patients with acute leukemias and myelodysplastic syndromes. This book is based on their contributions.

As regards single-agent treatment, aclacinomycin A in myelodysplastic syndromes is dealt with, as well as its application in older patients with acute myeloid leukemia. Four contributions are devoted to the use of aclacinomycin A in combination with conventional or intermediate-dose cytosine arabinoside or etoposide in patients with relapsed or refractory acute myeloid leukemia. The results reported indicate that aclacinomycin A has substantial activity in the treatment of hematologic malignancies.

In summary, this book provides a valuable update on the current status of aclacinomycin A as used by experts in the treatment of hematologic malignancies.

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Inhalt

Aclarubicin in Single Agent and Combined Chemotherapy of Adult Acute Myeloid Leukemia

P. S. MITROU[1]

The present contribution summarizes the results of treating acute myeloid leukemia (AML) with aclarubicin (ACM) in three consecutive studies. Some of the results have recently been published elsewhere [1–3].

Single Agent Therapy

In the first study 40 patients with relapsing or resistant acute leukemias were treated with ACM 25 mg/m^2 i.v. daily for 7 days. Twenty-nine patients with AML were evaluable. All patients were pretreated with daunorubicin and/or doxorubicin. The overall response rate was 31% (Table 1), with eight complete remissions (CR 27%). A high CR rate was achieved in patients treated at first relapse without prior reinduction. Three CR of AML at first relapse with previously unsuccessful reinduction or at second or later relapse were achieved. Six patients who had previously failed to respond to anthracycline-containing induction regimes did not respond to ACM (Table 1). The median duration of ACM-induced CR was 5.5 months.

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Table 1. Treatment results with ACM in single-agent therapy of AML

	No. of patients	CR		PR		Failure	
		n	%	*n*	%	*n*	%
All patients	29	8	27	1	4	20	69
First relapse without prior reinduction	12	6	50	0		6	50
First relapse with previously unsuccessful reinduction	11	2	18	0		9	72
Second or later relapse	5	1		0		4	
Primary treatment failure	6	0		1		5	

ACM in Combined Chemotherapy with Cytosine Arabinoside (Ara-C): A Pilot Study

The daily dose and schedule of ACM used in the first study yielded encouraging results. Therefore, a pilot study was undertaken to study the side effects and the therapeutic efficacy of ACM in combination with Ara-C. Ara-C was given as a continuous intravenous infusion (CIVI) (100 mg/m^2) over 7 days. ACM was given as a bolus of 18 mg/m^2 i.v. daily for 7 days in patients less than 50 years of age. The daily dose was lower in patients more than 50 years of age (12 mg/m^2). Eighteen patients were included in the study, 13 with previously un-

Table 2. Pilot study: combination of ACM + Ara-C in the treatment of AML

	No. of patients	CR	Failure	Early death
Alle patients	18	13	4	1
Previously untreated patients	13	10	3	0
1st relapse	5	3	1	1
Patients < 50 years	9	5	3	1
Patients > 50 years	9	8	1	0

treated AML and 5 at first relapse. None of these patients had any history of previous myeloproliferative or myelodysplastic syndromes or antineoplastic treatment for diseases other than AML. A high rate of CR was achieved in this study (Table 2), ten out of 13 CR being induced with the first course of chemotherapy. From the results it appears that the rate of CR was independent of disease status or age of the patients (Table 2).

Combined Chemotherapy with ACM and Ara-C for Patients Older than 50 Years

Between May 1985 and November 1987 patients with de novo acute nonlymphocytic leukemia were treated in a prospective cooperative study with an age-adapted protocol. ACM and Ara-C were combined for the treatment of patients over 50 years of age with previously untreated de novo AML. Other characteristics of the patients entered are outlined in Table 3. Ineligibility criteria were preceding myelodysplastic syndromes, a subacute course of the AML, or antineoplastic treatment for diseases other than AML. Induction chemotherapy included ACM 12 mg/m^2 daily for 7 days and Ara-C 100 mg/m^2 as continuous intravenous infusion (CIVI) for 7 days. The daily ACM dose was increased during the study to 18 mg/m^2 for the last 31 patients. The study design allowed a second cycle of ACM and Ara-C if the bone marrow showed unequivocal residual leukemia. Patients entering CR

Table 3. Characteristics of the patients

No. of patients	61
female	39
male	22
Age (years), median (range)	62 (52–78)
AML classification	
M1, M2	36
M3	4
M4	12
M5	8
M6	1

Table 4. Chemotherapy

Induction (1 – 2 courses)
ACM 12 or 18 mg/m² i.v. daily for 7 days
Ara-C 100 mg/m² CIVI daily for 7 days
Early consolidation
One cycle of ACM and Ara-C
Late consolidation
1. Amsacrine 50 mg/m² i.v. daily for 5 days Etoposide 75 mg/m² i.v. daily for 5 days Ara-C 75 mg/m² i.v. daily for 5 days
2. Ara-C 600 mg/m², 2-h infusion every 12 h, days 1 – 4

received a consolidation course with ACM and Ara-C and two late consolidation courses (Table 4) but no further maintenance treatment. Fifty-eight out of 61 patients received one or two courses of induction chemotherapy. In three cases treatment was interrupted during the first course of treatment. Responses are outlined in Table 5. Twenty-nine of the patients responded, 25 with a CR. The median overall survival was 7 months (Fig. 1) and the median relapse-free survival 7.5 months (Fig. 2). Patients receiving late consolidation courses had a median survival of 16.5 months and a median relapse-free survival of 12.5 months. The proportion of long-term survivors cannot yet be determined. Forty-six patients died. The time of death is outlined in Table 6.

Table 5. Results of induction chemotherapy

	No.	%
Less than 1 cycle	3	5
Complete remission	25	41
Partial remission	4	6,5
Treatment failure	15	24,5
Early death	14	23

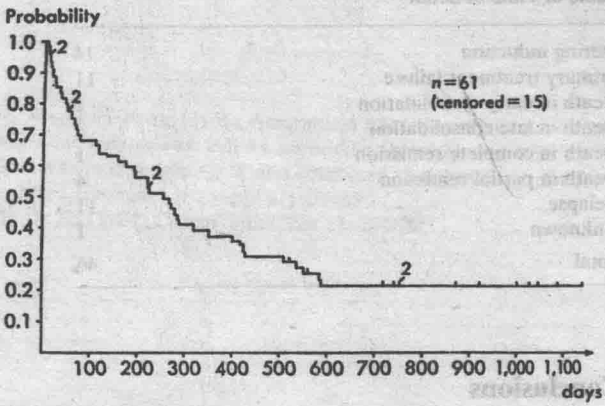

Fig. 1. Overall survival of the patients >50 years. *2*, Patients received autologous bone marrow transplantation

Toxicity

The main nonhematologic side effects are summarized in Table 7. In general, toxicity was rather mild. Cardiac complications were observed in older patients. The median duration of severe leukopenia with less than 250 granulocytes/μl was 16 days for all patients and of severe thrombocytopenia (< 25 000 platelets/μl) 13 days. Severe infections and septicemia were observed in three and seven patients, respectively.

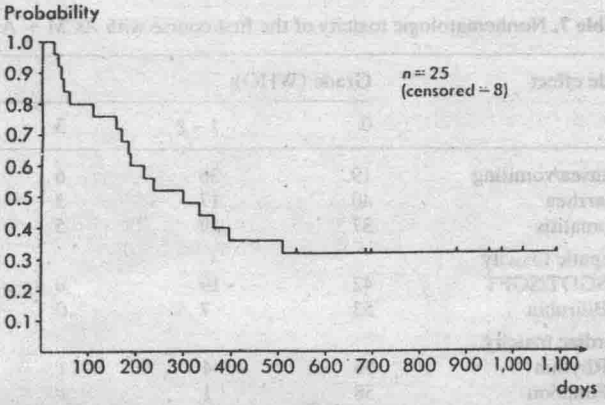

Fig. 2. Relapse-free survival of patients with complete remission

Table 6. Time of death

During induction	14
Primary treatment failure	11
Death in early consolidation	1
Death in late consolidation	3
Death in complete remission	1
Death in partial remission	4
Relapse	11
Unknown	1
Total	46

Conclusions

ACM demonstrated considerable antileukemic activity as a single agent and in combined chemotherapy of AML. The very encouraging results obtained in the pilot sudy were not confirmed in the following phase II study with a higher number of AML patients. However, the results obtained in patients older than 50 years are in the range of those obtained with other anthracycline-containing combinations. It is as yet unclear whether the CR rate in this study is related to the patient selection or to the rather low dose of ACM. The results obtained suggest that further studies are needed to define the optimal dose of ACM in the treatment of AML.

Table 7. Nonhematologic toxicity of the first course with ACM + Ara-C

Side effect	Grade (WHO)			
	0	1 – 2	3	4
Nausea/vomiting	19	36	6	0
Diarrhea	40	17	3	1
Stomatitis	37	19	5	0
Hepatic toxicity				
SGOT/SGPT	42	19	0	0
Bilirubin	53	7	0	1
Cardiac toxicity				
Rhythm	56	4	1	0
Function	58	1	1	1

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Low-Dose Aclacinomycin and Intermediate-Dose Cytosine Arabinoside in Relapsed and Refractory Acute Myelogenous Leukemia

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Abstract

Nineteen patients with relapsed or refractory acute myelogenous leukemia were treated with escalating doses of aclacinomycin (ACLA 20–30 mg/m^2 daily for 5 days) and intermediate-dose cytosine arabinoside (Ara-C 1 g/m^2 twice daily for 4 days). Most patients had received previous therapy with high- or intermediate-dose Ara-C plus mitoxantrone (HAM, IAM) and TAD (6-thioguanine, standard-dose cytosine arabinoside, and daunorubicin). Four patients had had repeated relapses and another three were treated for primary treatment failure following induction with HAM or IAM.

Twelve patients (63%) responded: nine (47%) entered complete remission (CR) and three (16%) had a partial remission. None of the patients refractory to HAM or IAM went into CR. Side effects from this treatment were generally mild. However, urinary tract toxicity with hematuria and dysuria turned out to be dose limiting, since all patients receiving ACLA 30 mg/m^2 experienced grade 2–3 toxicity (WHO). These side effects were mild when ACLA was used at 20 mg/m^2 (grade 1–2 toxicity only, in 21% of patients). Consequently, the study was continued with a fixed ACLA dose of 20 mg/m^2 that was found to be safe and well tolerated. The overall CR rate of 47% compares well with other salvage protocols and ACLA combinations, arguing for further evaluation of this therapeutic approach.

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Introduction

Combination chemotherapy today may induce a complete remission (CR) rate of 60–80% in de novo acute myelogenous leukemia (AML) [1–3]. However, the majority of patients who achieve remission relapse, and as many as 20% fail to achieve an initial remission [4]. The therapeutic options for these poor-prognosis patients are still limited and unsatisfactory. High-dose cytosine arabinoside (HD-Ara-C) in combination with an anthracycline so far represents the most promising approach, inducing remission rates of 30%–70% [5, 6].

Aclacinomycin (ACLA), a second-generation anthracycline antibiotic, has been shown to be effective in the therapy of AML as a single agent and in combination with other drugs [7]. It has been reported to be less cardiotoxic than doxo- and daunorubicin, and there appears to be no cross-resistance with these substances [8, 9]. Thus, ACLA might be suitable for reinduction treatment of conventionally pretreated patients. In order to extend previous experience of this approach [8, 10, 11], the efficacy and toxicity of combination therapy with intermediate-dose Ara-C (2×1 g/m^2 per day; ID-Ara-C) was evaluated in the present study. ID-Ara-C was chosen to obviate the severe toxicity of HD-Ara-C, especially in elderly patients whilst, hopefully, preserving the antileukemic potential of the high-dose regimen [12, 13].

Patients and Methods

Patients treated in this study were those with documented AML in whom primary induction therapy had failed or who had suffered a relapse after one or more prior remissions. All patients were >15 and <65 years of age and had bone marrow aspiration results that confirmed the diagnosis of acute leukemia. Treatment required normal renal and hepatic function as shown by serum creatinine and bilirubin levels of <2 mg/dl. Patients with poor performance status and high white blood cell counts were not excluded. Written informed consent was obtained from each patient before entry to the study.