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Short communication

High-dose ara-C and etoposide in refractory or relapsing acute leukemia

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Summary. A total of 32 patients (15 men and 17 women) presenting with relapsing or refractory acute leukemia were treated with a 3-h infusion of 3 g/m^2 cytosine arabinoside (ara-C) twice daily on days 1–6 and a 1-h infusion of 100 mg/m^2 etoposide on days 1–5. In all, 6 subjects had acute lymphocytic leukemia (ALL); 25 had acute myeloid leukemia (AML) of types M1 (n = 6), M2 (n = 10), M4 (n = 5), and M5 (n = 4); and 1 had mixed-type leukemia. The median age was 35 years (ranges, 16–62 years). Of the patients presenting with AML, 11 were primarily refractory and 3 became refractory after their first relapse. Six subjects had an early first relapse following a complete remission (CR) that lasted <6 months and five, a second relapse. Another patient underwent a primary relapse after >6 months but had been heavily pretreated. In all, 5 subjects with refractory AML achieved a CR [36%; 95% confidence interval (CI), 10%–62%) as did 7 patients exhibiting relapsing AML (58%; CI, 30%–86%). Three patients who had relapsing or resistant ALL achieved a CR. Side effects consisted of severe hematotoxicity associated with granulocytopenia of <500/mm^3 that lasted for a mean of 23.6 days and thrombocytopenia of <20,000/mm^3 whose mean duration was 20.8 days. Marked gastrointestinal toxicity and infections were also prevalent. Cutaneous and ocular toxicity as well as allergic, pulmonary and cerebellar side effects were observed in a few cases. We conclude that the combination of high-dose ara-C and etoposide is a powerful but toxic induction regimen for refractory or relapsed acute leukemia.

Introduction

The prognosis of patients presenting with refractory or relapsing acute myeloid and lymphocytic leukemia (AML, ALL) is poor. The administration of effective therapeutic regimens is neccessary to obtain a remission of sufficient quality to enable further consolidation treatment that is likely to produce a cure, e.g. allogeneic and autologous bone marrow transplantation (BMT).

High-dose cytosine arabinoside (ara-C) has been given for relapsing or refractory acute leukemia as a single agent, in combination with anthracyclines or m-AMSA, or followed by asparaginase [3, 5, 10–12, 22–25]. Combinations with anthracyclines may involve the risk of cumulative cardiotoxicity in heavily pretreated patients. Etoposide has shown considerable activity against AML, especially in monocytic or myelomonocytic leukemia [7, 13]. High-dose etoposide is extremely effective as a conditioning treatment for patients with ALL who are in partial remission [21]. A synergistic action of ara-C and etoposide in L1210 leukemia has been demonstrated [19]. On the basis of these findings, we treated patients presenting with relapsing or refractory acute leukemia with high-dose ara-C and etoposide.

Patients and methods

Between January 1985 and December 1988, 32 patients (15 men and 17 women) were enrolled in a single-centre study. The protocol was approved by the ethics committee of the Hannover Medical School, and informed consent was obtained from all subjects prior to study entry. The patients' median age was 35 years (range, 15–62 years). In all, 26 subjects had AML (types: M1, 6; M2, 10; M4, 5; M5, 4 mixed, 1) and 6 had ALL. The status of refractoriness was defined as follows:

1. Resistant leukemia – (A) primary non-response, with hypercellular marrow and unchanged leukemic infiltration being evident at 8 days after a minimum of one course of conventional therapy; (B) no second CR after one course of conventional reinduction therapy.

2. Relapsing leukemia – (A) early relapse within the first 6 months of the first CR; (B) second or subsequent relapses; (C) late relapse after an initial CR that lasted for >6 months.

The treatment consisted of a 3-h infusion of 3 g/m^2 ara-C two times daily on days 1–6 and a 1-h infusion of 100 mg/m^2 etoposide on days 1–5. Seven patients received an initial course of consolidation therapy on the same dosing schedule. One subject was given high-dose ara-C and mitoxantrone for consolidation due to allergic reactions to etoposide. A second and a third consolidation course comprising 100 mg/m^2

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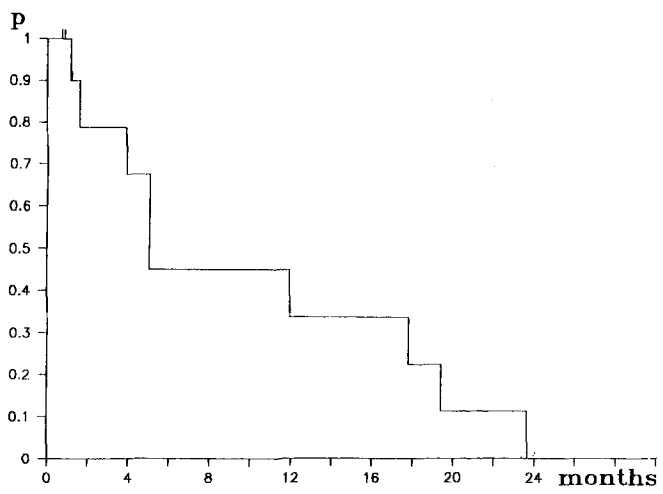

Fig. 1. Disease-free survival in patients with AML

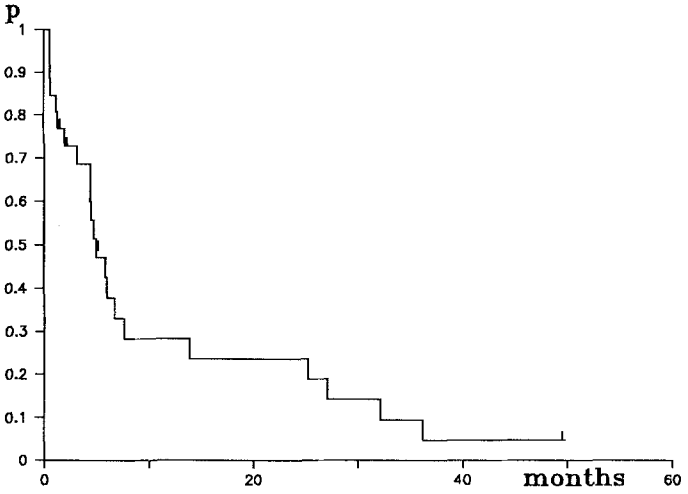

Fig. 2. Total survival in patients with AML

m-AMSA and 100 mg/m^2 i. v. etoposide on days 1–5 was given in three and two cases, respectively. There was no maintenance therapy. While in CR, two patients underwent allogeneic BMT and one, autologous BMT; another subject underwent unrelated allogeneic BMT while in relapse.

Toxicity was quantified according to WHO criteria and response was classified according to the criteria of the cancer and leukemia Group B (CALGB) [16]. The follow-up period for survival and disease-free survival is currently complete for all but one patient who is alive in relapse after spending 50 months. Subjects who underwent BMT were censored at the time of the transplantation.

Results

Response to therapy

A total of 32 courses of high-dose ara-C and etoposide were given as induction treatment and 7 cycles were given as initial consolidation therapy. The overall treatment results are summarized in Table 1. The CR rate in resistant AML was 36% (CI, 10%–92%), and that in relapsing AML was 58% (CI, 30%–86%). All CRs were achieved after one treatment course. In AML, the median duration of remission and median survival amounted to 5 months (see Figs. 1, 2). Two patients with AML underwent allogeneic BMT while in CR; one relapsed and died after 8 months, and the other remains alive and well after 60+ months. Three of six subjects with ALL achieved a CR (CI, 9%–91%); the three remissions lasted for 2, 2.6+, and 10.6 months, and the survival of the six patients was 0.3, 3.0+, 3.2, 4.1, 5.6, and 17.2 months. One patient underwent autologous BMT within 2.6 months of achieving a CR and remains alive and well after 28+ months.

Toxicity

The toxic side effects encountered in the present study are summarized in Table 2. Significant hematotoxicity was prevalent, with granulocytopenia of <500/μl lasting for a mean of 23.6±7.3 days and thrombocytopenia of <20,000/μl lasting for a mean of 20.8±6.6 days. Some patients experienced severe infections. Four deaths occurred during induction therapy. Gastrointestinal side effects comprising nausea, diarrhea, and mucositis were noted in a considerable number of patients. One subject died of a gut perforation following consolidation chemo-

Table 1. Results and status of relapse or refractoriness of patients with acute leukemia

Group[a]	AML				ALL			
	n	CR (%CR)	NR	ED	*n*	CR (%CR)	NR	ED
Resistant:								
A	11	3 (27%)	7	1	–	–	–	–
B	3	2 (67%)	1	–	2	1 (50%)	–	1
All	14	5 (36%)						
Relapsing:								
A	6	3 (50%)	1	2	2	1 (50%)	1	–
B	5	3 (60%)	1	1	2	1 (50%)	1	–
C	1	1 (100%)	–	–				
All	12	7 (58%)						
Entire study	26	12 (46%)	10	4	6	3 (50%)	2	1

[a] For definitions, see Patients and methods
NR, Non-response; ED, early death

Table 2. Toxicity of high-dose ara-C and etoposide during 32 induction cycles in relapsing or refractory acute leukemia

Toxicity	WHO grade				
	0	1	2	3	4
Bleeding	18	5	4	4	1
Bilirubin	23	4	3	2	–
Alkaline phosphatase	26	6	–	–	–
SGOT/SGPT	13	10	7	2	–
Nausea	2	–	11	19	–
Diarrhea	3	3	10	16	–
Mucositis	7	9	6	5	5
Creatinine	29	1	1	1	–
Pulmonary	30	–	1	1	–
Allergic	30	–	–	2	–
Cutaneous	14	7	9	2	–
Local infection	28	–	1	3	–
Sepsis	20	–	3	5	4
FUO	16	–	11	4	1
Somnolence	30	–	2	–	–
Neuropathy	30	2	–	–	–
Pain	31	1	–	–	–
Ocular	18	7	5	2	–
Cerebellar	30	1	–	1	–

FUO, Fever of undetermined origin

therapy. Two patients experienced allergic side effects, probably due to etoposide. Conjunctivitis was usually mild. Pulmonary and cerebellar toxicity were infrequent.

Discussion

The rationale of the present study was to improve the efficacy of treatment in a group of patients whose prognosis was extremely poor. Although high-doses of ara-C given as a single agent can overcome resistance, the 31% rate of remission in patients presenting with relapsed or resistant AML is unsatisfactory. In a randomized study of high-dose ara-C vs m-AMSA, the treatment results were comparable [23]. In 62 patients with resistant AML who showed no response after completing a minimum of one course of conventional treatment, the remission rate was only 14.5% [4, 23].

There have been numerous reports on the administration of high-dose ara-C combined with other agents. Anthracycline-containing combinations were given to 204 patients [1, 3, 10, 11, 20, 22, 24, 25] and yielded a 50% CR rate. High-dose ara-C and m-AMSA was similarly effective in 202 patients, resulting in a 52.5% CR rate [6, 12, 17, 26, 27]. In addition, four studies using high-dose ara-C and etoposide [5, 8, 9, 15] have reported achieving a CR rate of 53.5% in 86 patients. A favourable trend was found for this combination vs ara-C alone in a randomized study [15].

The present overall remission rates were comparable with those previously achieved using other combinations. However, this comparison was hampered in that many authors do not report their results separately for refractory and relapsing patients. Furthermore, some studies give no clear-cut definition of refractoriness and do not state the duration of prior remissions. Combinations of anthracyclines and high-dose ara-C have induced CRs in 17.6% of patients presenting with resistant AML [1, 10, 20, 22] and in 73.7% of subjects exhibiting relapsing AML [1, 10, 11, 20, 22]. The administration of high-dose ara-C and etoposide seemed to produce a CR rate that was superior to the above-mentioned result in resistant AML, whereas the remission rate achieved in relapsing patients was lower than that previously reported.

The favourable effect of high-dose ara-C and etoposide in refractory AML may indicate the absence of cross-resistance with anthracycline-containing regimens, which all patients had previously received. To obtain a synergistic action between these two drugs, it may be important that a dose of 500 mg/m^2 etoposide be given on a dosing schedule parallel with that of ara-C. Nevertheless, in the present study the duration of remission was short in AML patients (median, 5 months); similar values of between 3 and 8 months have previously been reported [6, 8, 10, 22, 26, 27].

In resistant or relapsing ALL, CRs have been achieved in 21% of subjects using high-dose ara-C alone. High-dose ara-C and m-AMSA has induced CRs in 64% of 76 patients [2, 17, 18, 27]; however, in the largest of these studies, Ph^1+ subjects were excluded. Two studies using high-dose ara-C and mitoxantrone have reported a CR rate of 40.5% [11, 14]. A 55% CR has been achieved in 18 patients presenting with resistant or relapsing ALL using etoposide and high-dose ara-C [8]. The present results obtained in ALL patients are fully consistent with those previously reported.

The toxicity of high-dose ara-C and etoposide was pronounced but tolerable. For etoposide hematotoxicity is not dose-limiting. The combination of this drug with high-dose ara-C did not increase its myelotoxicity to an intolerable extent. Etoposide given at high doses may cause gastrointestinal toxicity associated with mucositis, involving a risk for the occurrence of bacteremia and invasive fungal infections during myelosuppression. In spite of this factor, the incidence of early death during induction (12.5%) or consolidaton (14%) therapy in our patients seemed to be lower than that reported in previous studies [4, 8, 10, 15, 24, 25, 27].

We conclude that high-dose ara-C and etoposide represents powerful induction therapy in relapsing or refractory acute leukemia. This combination produces considerable acute toxicity but may have the advantage of being less cardiotoxic. Therefore, it warrants further evaluation.

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