Eur J Cancer Clin Oncol, Vol. 24, No. 11, pp. 1721–1725, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00

Intermediate and High Dose Ara-C and m-AMSA for Remission Induction and Consolidation Treatment of Patients with Acute Myeloid Leukemia: an EORTC Leukemia Cooperative Group Phase II Study

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Abstract—*Seventy-nine patients (aged 17–76 years) with acute myelogenous leukemia in first (56) or second (3) relapse, primary refractory leukemia (15) or leukemia occurring as secondary malignancy that developed after a preleukemic phase (3) or after another tumor (2) were given remission induction therapy consisting of cytosine arabinoside (Ara-C, 1 g/m² as a 2-h infusion every 12 h for 6 days) and m-AMSA (120 mg/m², i.v. on days 5, 6, 7). In total 45 patients (57%) achieved complete remission. Younger patients and those with a relatively low initial white blood cell count, a good performance status or in first relapse had a higher response rate.*

Thirty-five patients were given one or two courses of consolidation chemotherapy consisting of Ara-C (3 g/m² as a 2-h infusion every 12 h for 4 days) and m-AMSA (120 mg/m² i.v. on day 5). Three patients received an allogeneic bone marrow graft after the induction courses and four patients received an autologous bone marrow transplantation after consolidation therapy. The median of the disease-free survival curve was 21 weeks. The median duration of survival was 25 weeks. The response rate for this intermediate dose Ara-C regimen is satisfactory and does not differ from that reported for high dose Ara-C. The impact of consolidation chemotherapy in bad risk acute myelogenous leukemia is questionable.

INTRODUCTION

CYTOSINE ARABINOSIDE (Ara-C) and, to a lesser extent, the anthracyclines given as remission induction therapy for acute myeloid leukemia (AML) produce a dose-related response in adults. Thus the remission percentage has increased during the past fifteen years from approx. 25% to 65% of the patients treated [1]. Duration of remission appears to be dependent on the intensity of the consolidation and/or maintenance therapy. Current strategy tends toward short-term repeated intensive cytostatic courses following remission induction. With this approach a median duration of remission of up to 41 months has been reported [2]. Treatment of acute leukemia secondary to another malignancy or leukemia preceded by a preleukemic phase is difficult, although preliminary results suggest that higher doses of cytosine arabinoside might improve the prognosis for these patients. Once relapse occurs only 25% of the patients achieve a second complete remission; moreover the duration of a second remission is usually short, ranging from 2 to 6 months. High dose Ara-C (3 g/m², every 12 h for 6 days) has effectively induced remission in 40–50% of patients who did not respond to standard dose Ara-C [3–7]. Intermediate dose Ara-C (0.5–1 g/m² every 12 h + anthracyclines or m-AMSA) was

Accepted 23 June 1988.
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effective in patients with relapsed leukemia and produced less toxicity than high dose Ara-C [6–9]. High dose Ara-C has also been given as consolidation therapy to AML patients in first remission and a median disease-free survival of more than 2 years has been reported [10–12]. The objectives of the current phase II study performed by the EORTC Leukemia Cooperative Group were to determine the tumor response rate in refractory or relapsed AML produced by intermediate dose Ara-C and m-AMSA as well as the effect of consolidation therapy with high dose Ara-C and m-AMSA and to assess the toxicity of these regimens.

MATERIALS AND METHODS

In 1983 the EORTC Leukemia Cooperative Group started a phase II trial to study the effectiveness of the combination of Ara-C and m-AMSA in patients with relapsed AML, secondary acute leukemia or primary refractory AML.

The remission induction regimens consisted of:

- cytosine arabinoside: 1000 mg/m^2, every 12 h as a 2 h infusion for 6 days,
- m-AMSA: 120 mg/m^2, i.v. on days 5, 6 and 7.

After complete remission was achieved patients received one or two consolidation courses consisting of cytosine arabinoside (3000 mg/m^2, every 12 h as a 2-h infusion for 4 days), and m-AMSA (120 mg/m^2, i.v. on day 5). Each consolidation course was followed by a treatment-free interval of 6–8 weeks. The number of courses was determined by the toxicity of and tolerance for the previous consolidation course.

Complete remission (CR) was defined as the disappearance of all signs and symptoms of leukemia, a normal bone marrow aspirate with normal cellularity and <5% blast cells among all white cells, and a normal blood smear. Partial remission (PR) was obtained when the bone marrow contained no more than 5–25% blast cells, and no blast cells were seen in the peripheral blood. All patients were nursed in single rooms, usually without laminary flow facilities but with mask and handwashing regulations. Sterile food was not given; most patients received corticosteroid eyedrops during the period of Ara-C administration. Erythrocyte and random donor or single donor platelet infusions were given when indicated. Patients were examined every 3 months at which time complete blood and bone marrow studies were carried out.

The patient data register was maintained at the EORTC Data Center in Brussels (Belgium).

Disease-free survival (DFS) was defined as the time from CR to leukemia relapse or death in remission. The duration of survival was calculated from registration to time of death; the time to latest follow up was considered a 'censored' observation.

Survival curves were calculated according to the Kaplan–Meier method [13]. The classical chi-square test (for linear trend) was used to compare the response rates (for variables with ordered categories).

RESULTS

From September 1983 to January 1987, a total of 92 patients in 11 institutions entered the study. Eight patients were subsequently considered ineligible since five of them had a CML blast crisis, two had received prior high dose Ara-C therapy, and no data were available for one patient. Five patients were not evaluable since they received inadequately low dosages of Ara-C. Fifty-six patients were treated for a first relapse, and three for a second relapse. Fifteen patients had failed to respond to previous standard remission induction treatment, three patients had previously exhibited a preleukemic phase and two patients had a secondary leukemia. The median age was 45 years (range 17–76 years); 12 patients were over 50 years of age. The median and mean white blood cell counts were 3.6 × 10^9/l and 12 × 10^9/l, respectively (range 1–151 × 10^9/l). Other patient characteristics are shown in Table 1.

Complete remission was achieved in 45 cases (57%), 43 after the first cycle and two after the second cycle. Nine patients (11%) reached partial remission, six were absolutely resistant, eight had prolonged hypoplasia followed by leukemic regrowth and 11 died in the hypoplastic phase (14%). Seventy-six patients received 100 ± 25% of the required Ara-C dose, one patient received 2/3

Table 1. Patient characteristics

		Patients	Percentage
Age (years)	<45	41	51.9
	45–60	25	31.6
	61–76	13	16.5
WBC (× 10^9/l)	<5	49	62.0
	<25	20	25.3
	>25	10	12.7
Performance status	0	24	30.4
	1	26	32.9
	2	18	22.8
	3	11	13.9
FAB classification	M1	13	17.3
	M2	29	37.2
	M3	4	1.3
	M4	17	21.5
	M5	10	13.4
	M6	2	2.9
Stage of disease	Relapse	59	74.7
	Refractory	15	19.0
	Preleukemic	3	3.8
	Secondary	2	2.5
Total		79	100.0

of the required dose and two patients received twice the required dose. Sixty patients were given 100 ± 20% of the required m-AMSA dose; in 16 cases the schedule was modified such that one patient did not get any m-AMSA, eight patients received m-AMSA only once and seven patients only twice. Three other patients were given 132, 139 and 146% of the required dose, respectively. Prognostic factors for complete remission are shown in Table 2; older patients and those with an initially high white blood cell count, poor performance status or not in first relapse exhibited a lower response rate. The median duration of hospitalization during remission induction was 32 days (range 16–73 days) and the median duration of aplasia (granulocytes $<0.5 \times 10^9$/l, thrombocytes $<10 \times 10^9$/l) was 21 days (range 10–47 days). Toxicity of the induction regimen is shown in Table 3.

Out of 45 patients who achieved complete remission, 35 received one (29 patients) or two (six patients) consolidation courses. Consolidation therapy was not given due to previously experienced major toxic reactions (pneumonitis or paralytic ileus) in five cases, allogeneic bone marrow transplantation in three cases and an early relapse in two cases. Forty-one courses consisted of 100 ± 10% of the required doses of Ara-C and m-AMSA. The duration of hospitalization was shorter during consolidation than durating induction (median = 26 days, range 10–41 days); the same applied for the duration of aplasia (median = 18 days, range 10–46 days). Side-effects of the consolidation phase are shown in Table 3. Three patients received an allogeneic bone marrow transplantation after the induction course. They survived for 20, 22 and 104+ weeks. Four patients underwent an autologous bone marrow transplantation after one or two consolidation courses. They survived for 22, 37, 48 and 121+ weeks. The median overall disease-free survival was 21 weeks (18% of 2 years). In July 1987, 25 patients had suffered a bone marrow relapse, one a skin relapse; eight had died while in complete remission and 11 were alive in complete remission. The median duraion of the survival time (from the start of treatment) was 25 weeks, and at 2 years only 17% of the patients were alive.

Table 2. Prognostic factors for response

		CR(%)	*P*-value
Age (years)	<45	73.2	
	45–60	44.0	0.002
	61–76	30.8	
WBC ($\times 10^9$/l)	<5	65.3	
	<25	50.0	0.03
	>25	30.0	
Performance status	0	79.2	
	1	46.2	0.04
	2	50.0	
	3	45.5	
Stage of disease	Relapse	64.4	0.048
	Other	35.5	
Total		57.0	

CR = complete remission.

DISCUSSION

This phase II study shows that in a large cooperative study remission induction with intermediate dose Ara-C and m-AMSA results in complete remission in almost 2/3 of the patients with leukemia in relapse. Those who failed to respond to previous standard induction chemotherapy were more resistant to this regimen, since only 1/3 of these patients achieved remission. Due to differences in the definition of primary refractory disease, it is difficult to compare our data with those reported in the literature. However, our results for relapsed patients who received Ara-C in a dosage of only 1 g/m^2 every 12 h for 6 days are not significantly different from those obtained with other dosages of Ara-C (0.5, 1, 2 or 3 g/m^2 every 12 h for 5–7 days) (Table 4). Although the results for relapsed patients derive from many different centers in the world, the similarity in outcome of the treatment appears to be independent of the dosage of Ara-C used. In several small and uncontrolled studies [19, 20] high dose Ara-C consolidation therapy reportedly increased disease-free survival in AML patients in first remission.

Our study of relapsed and refractory patients in remission shows that, in spite of very intensive consolidation therapy, the median disease-free survival time remained in the range of 5 months. These

Table 3. Side-effects of intermediate and high dose Ara-C/AMSA

	Induction 79 cases		Consolidation 35 cases	
	severe* (%)	total (%)	severe* (%)	total (%)
Hemorrhage	10	56	3	40
Liver	9	49	6	20
Oral	12	54	3	43
Nausea/vomiting	24	85	23	77
Diarrhea (inc. paralytic ileus)	26	69	6	51
Renal	1	26	0	20
Pulmonary	17	32	14	29
Fever due to Ara-C	4	35	6	31
Cutaneous	6	55	6	23
Infection	51	81	31	74
Cardiac arrhythmia	0	10	0	6
Conjunctivitis	0	33	0	34
Cerebellar dysfunction	0	6	0	13

*WHO grade III and IV.

Table 4. Results of high dose Ara-C therapy for resistant and relapsed AML

Author	Schedule	CR(%)	Median duration of CR (months)
Herzig *et al.* [5]	3–4.5 g/m² × 4–16	68	4
Willemze *et al.* [7]	3 g/m² × 12 + DOXO	50	6
Capizzi *et al.* [14]	3 g/m² × 4 + L-ASP	63	5
Hines *et al.* [15]	3 g/m² × 12 + m-AMSA	72	6
Van Prooyen *et al.* [16]	0.5 g/m² × 12 + DOXO	83	5
Herzig *et al.* [5]	3 g/m³ × 12	63	5
	3 g/m² × 12 + DOXO	65	5
Peters *et al.* [17]	1 g/m² × 12 + m-AMSA	54	5
Zittoun *et al.* [18]	3 g/m² × 4 + m-AMSA	36	7

Doxo = doxorubicin; L-Asp = L-asparaginase; CR = complete remission.

results are in accordance with those found for similar patients in several single center studies in the U.S.A. and Europe (Table 4). Although most of the patients in other studies who achieved complete remission did not receive consolidation therapy, the median duration of remission was usually also in the range of 3–6 months. Therefore the results are about the same despite the fact that the majority of our patients received at least one consolidation course of high dose Ara-C. The toxic reactions observed in our trial were quite severe but comparable to those encountered in single institutions. The lack of severe cerebellar toxicity in our series is remarkable. This might be due to the only modest increase in the dosage of Ara-C and the relatively small number of older patients. Since toxicity increases with dosage, it is necessary to choose the lowest active dosage for further studies. On the basis of clinical and intracellular pharmacokinetic data [18], it appears likely that the optimal dose of Ara-C for these leukemic states lies between 0.5 and 1 g/m² given twice a day for approx. 5–7 days. Although the complete remission rate obtained with this intensive protocol is acceptable, the duration of remission is so short that other consolidation procedures must be found in order to make it worthwhile to attempt to increase the survival time for patients with bad risk disease.

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