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Preliminary Results of Consolidation Therapy with High-Dose Cytosine Arabinoside for Patients with Bad-Risk or Relapsed Acute Leukemia or Lymphoblastic Non-Hodgkin's Lymphoma

WIM G. PETERS, ROEL WILLEMZE and LOUISA P. COLLY

Department of Hematology, Building 1 C_2-R, Leiden University Medical Center, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands

Abstract—*High-dose Ara-C consolidation therapy for patients with primary refractory or relapsed acute leukemia (AML and ALL) or relapsed lymphoblastic non-Hodgkin's lymphoma (LNHL) was investigated. Between January* 1983 *and January* 1986, 47 *adult patients with primary refractory or relapsed AML, ALL or lymphoblastic NHL received a remission induction regimen that included intermediate-dose Ara-C* (1g/m^2/2hr q 12hr × 12). *Of the twenty-nine* (61.7%) *patients who achieved complete remission sixteen (AML* 9, *ALL* 5, *LNHL* 2) *received* 1-3 *consolidation courses that included high-dose Ara-C* (3g/m^2/2hr q 12hr × 8). *Three patients died as a result of major infections during the pancytopenic phase that followed the first consolidation course and 6 relapsed at 4, 4, 6, 8, 9 and 16 months; at the moment of this report the remaining 7 patients have been in continued remission for 8 to 28 months (6 have been in continued complete remission for ⩾ 11 months). The predicted median disease-free interval for patients who survived consolidation therapy is 16 months. Of the 13 patients who did not undergo consolidation chemotherapy 2 subsequently underwent allogeneic bone marrow transplantation and 3 died as a result of major infectious complications while in complete remission. Eight patients received no further treatment because they refused or had previously experienced severe toxicity. The median disease-free interval for this group was only 3 months. Our preliminary data on brief intensive consolidation therapy for patients with relapsed or primary refractory leukemia or non-Hodgkin's lymphoma suggest that this kind of treatment prolongs disease-free interval.*

INTRODUCTION

FOR PATIENTS with refractory or relapsed acute myelogenous leukemia (AML) standard remission induction therapy yields complete remission rates of approx. 25%. This second remission is, as a rule, brief and median survival after the initial relapse is generally less than 6 months [1]. The same applies for relapsed acute lymphoblastic leukemia (ALL) or lymphoblastic non-Hodgkin's lymphoma (LNHL), although a second complete remission can be achieved in 30–50% of these patients especially if relapse occurs after completion of maintenance chemotherapy. On the other hand, the duration of remission in such cases is usually disappointing [2].

Upon administration of higher doses of cytosine arabinoside (Ara-C) the complete remission rates for patients with refractory or relapsed acute leukemia increased to 50–70% [3–8]. In addition, intermediate (ID) and high-dose cytosine arabinoside (HDAra-C) have been shown to be effective in relapsed high-grade malignant non-Hodgkin's lymphoma [8–11]. Without consolidation therapy the median duration of complete remission is reported to be 3–6 months.

Prolongation of complete remission has been achieved in patients with acute myelogenous leukemia in first remission with the use of brief intensive consolidation treatment with high-dose cytosine arabinoside [14–17]. We investigated the effect of short-term intensive consolidation therapy (high-dose cytosine arabinoside) in patients with bad-risk or relapsed acute leukemia or lymphoblastic non-Hodgkin's lymphoma after complete remission was achieved with a protocol including intermediate-dose cytosine arabinoside.

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Address correspondence to: W.G. Peters.

PATIENTS AND METHODS

Between January 1983 and January 1986, 47 patients with acute myelogenous leukemia (AML 26), acute lymphoblastic leukemia (ALL 10) and lymphoblastic non-Hodgkin's lymphoma (LNHL 11) were placed on a remission induction regimen consisting of Ara-C (1 g/m^2/2hr q 12hr × 12), m-AMSA (115 mg/m^2 for 1, 2 or 3 days) ± VP16.213 (120 mg/m^2 for 2 days) and prednisone (60 mg/m^2 for 7 days). The group consisted of 25 males and 22 females with a median age of 36 years (range 15–58 years). The patients were treated for a first relapse of their disease (AML 14, ALL 2, LNHL 2), a second relapse (AML 2, ALL 1, LNHL 4), a third relapse (ALL 3) or failure of standard induction therapy (AML 5, ALL 4, LNHL 5). Moreover, 5 previously untreated patients with AML were included because their disease developed after a preleukemic phase. According to the FAB classification the AML patient group was composed of 13 M1, 2 M2, 1 M3, 8 M4 and 2 $M5_b$ patients.

The immunologic ALL subtypes were common-ALL (2), T-cell ALL (2), B-cell ALL (1), pre-B-cell ALL (1), non-B- non-T-cell ALL (4). Of the 11 patients with lymphoblastic non-Hodgkin's lymphoma 8 had the T-cell and 3 the Burkitt type; according to the Ann-Arbor staging system all had stage IV disease.

After one remission induction course 29/47 (61.7%) patients (AML 17/26, ALL 7/10, LNHL 5/11) achieved complete remission (defined as the disappearance of all signs and symptoms of leukemia or lymphoma, a normal bone marrow aspirate with normal cellularity and fewer than 5% blast cells of all white cells and a normal blood smear).

After complete remission 2 patients underwent allogeneic bone marrow transplantation. Sixteen patients did not have a compatible family donor and therefore received 1–3 consolidation courses of high-dose cytosine arabinoside, as shown in Fig. 1. Each course was initiated 1–2 weeks after complete normalization of the peripheral blood count (leucocytes $> 1.5 \times 10^9$/l, platelets $> 100 \times 10^9$/l). Eleven patients did not undergo consolidation therapy.

In this study we compared the disease-free interval for patients who received consolidation treatment with that found for patients who did not undergo consolidation. Disease-free interval was calculated from the moment complete remission was achieved.

RESULTS

The characteristics of the 16 patients who received 1–3 consolidation courses (regimen A or B; see Fig. 1) are listed in Table 1. The reasons for limiting consolidation therapy to only one course are summarized in Table 2. During the pancytopenic phase that followed the first consolidation course, two patients died of pseudomonas septicemia and one of disseminated candidiasis. Of the remaining 13 patients, 6 relapsed at 4, 4, 6, 8, 9, and 16 months and at the time of this report 7 are in continued complete remission for 8–28 months. The characteristics of the 11 patients who did not undergo consolidation therapy are given in Table 3. Three patients died in an early phase of complete remission due to major infectious complications. Three patients did not receive consolidation therapy, because interstitial pneumonitis (attributed to Ara-C) developed during induction treatment and 5 patients refused further courses. In Fig. 2 the disease-free intervals of patients who did undergo and survived consolidation therapy (n = 13) and those who did not (n = 8) are compared. The predicted median disease-free interval for patients who survived consolidation therapy is 16 months and 3 months for those who did not undergo consolidation therapy. Although the difference between both curves is significant (p = 0.0012) according to the log-rank test definite conclusions are not allowed because of the heterogeneity of both groups.

REGIMEN	DAY				
	1	2	3	4	5
A. Ara-C (3 g/m^2/2 hr q 12h)	x	x	x	x	
m-AMSA (115 mg/m^2)					x
B. Ara-C (3 g/m^2/2 hr q 12h)	x	x	x	x	
m-AMSA (115 mg/m^2)	x				x
VP.16.213 (120 mg/m^2)	x				x
Prednisone (60 mg/m^2)	x	x	x	x	x

Fig. 1. High-dose cytosine arabinoside consolidation regimens.

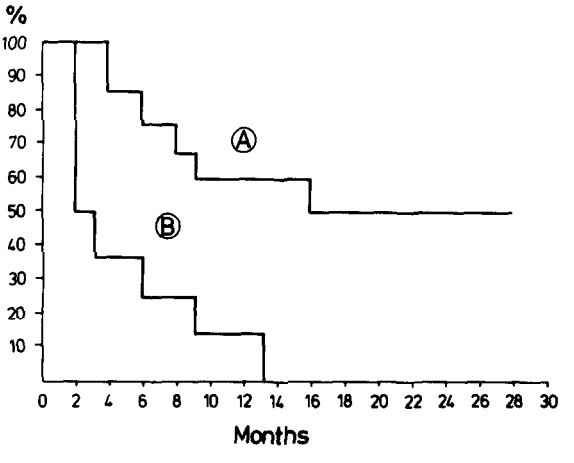

Fig. 2. Effect of high-dose cytosine arabinoside consolidation therapy on disease-free interval in patients with bad-risk acute leukemia and lymphoblastic non-Hodgkin's lymphoma.

Table 1. Characteristics of 16 patients who underwent consolidation therapy

Pat. No.	Age	Sex	Diagnosis	Diagnostic subtypes/ stage	Stage of disease	Previous remission duration (months)	Cytogenetics	No. of consolidation courses (A or B)	Outcome*	Duration of CCR (months)
1	28	M	AML	M4	2nd relapse	23	46,xy	2 A	Relapse	16
2	57	F	AML	M4	Induction failed†	—	46,xx	1 A	CCR	15+
3	57	F	AML	M5b	1st relapse	17	46,xx	3 A	Relapse	9
4	34	F	AML	M4	After preleukemia	—	46,xx	3 A	CCR	11+
5	23	M	AML	M1	1st relapse	41	46,xy/ 46,xy,t(3;5)	1 A	Relapse	8
6	39	M	AML	M4	Induction failed	—	46,xy/ 47,xy,+22	2 A	CCR	8+
7	33	M	AML	M1	1st relapse	12	45,x,t(8,21) (q24-2;q22)-y	1 A	Early death	1
8	51	F	AML	M4	1st relapse	23	46,xx/ 48,xx,+4,+10	1 A	Early death	1
9	58	M	AML	M2	1st relapse	19	46,xy	1 A	Early death	1
10	20	F	ALL	Non-B, non-T	Induction failed	—	n.p.‡	1 A	CCR	28+
11	21	M	ALL	Common	Induction failed	—	46xy	2 B	CCR	19+
12	26	M	ALL	Non-B, non-T	3rd relapse	34	n.p.	1 A	Relapse	4
13	23	F	ALL	Common	1st relapse	39	n.p.	2 B	Relapse	4
14	40	F	ALL	Pre-B	Induction failed	—	n.p.	1 B	Relapse	6
15	29	F	LNHL	T-cell, stage IV	Induction failed	—	n.p.	2 B	CCR	19+
16	28	M	LNHL	T-cell, stage IV	2nd relapse	8	n.p.	2 A	CCR	21+

*CCR, continued complete remission.
†Induction failed means failure of initial remission induction therapy.
‡n.p. = not performed.

Table 2. Reasons for giving only one consolidation course

Patient No.	Reason
2	Prohibitive lung toxicity
5	Prolonged pancytopenia
7	Prohibitive infectious problems
10	Refused further courses
12	Refused further courses
14	Extensive aspergillosis of the lungs

Table 3. Characteristics of 11 patients who did not undergo consolidation therapy

Pat. No.	Age	Sex	Diagnosis	Diagnostic subtypes/stage	Stage of disease	Previous remission duration (months)	Cytogenetics	Reason for not receiving	Duration of CR (months)
1	48	M	AML	M1	2nd relapse	12	46xy	Refusal	2
2	25	F	AML	M2	1st relapse	6	n.p.*	Refusal	6
3	26	F	AML	M1	After pre-leukemia	2	n.p.*	Refusal	2
4	43	M	AML	M1	After pre-leukemia	11	46xy,5q-	Lung toxicity	13
5	49	M	AML	M1	1st relapse	16	46xy	Lung toxicity	9
6	19	M	ALL	B-cell	Induction failed	—	n.p.	Death early in CR	1
7	26	M	ALL	T-cell	2nd relapse	7	n.p.	Refusal	2
8	32	F	LNHL	T-cell, stage IV	Induction failed	—	n.p.	Death early in CR	1
9	22	F	LNHL	Burkitt, stage IV	Induction failed	—	n.p.	Death early in CR	1
10	28	M	LNHL	T-cell, stage IV	2nd relapse	7	n.p.	Refusal	3
11	24	M	LNHL	Burkitt, stage IV	Induction failed	—	n.p.	Lung toxicity	3

*n.p. = not performed.

Table 4. Side-effects encountered during 26 consolidation courses with high-dose cytosine arabinoside

Side-effect	Percentage of courses
Nausea, vomiting	100
Drug fever	19.2
Skin rash	23.1
Diarrhea ± paralytic ileus	7.7
Conjunctivitis	7.7
Myalgia	15.4
Cerebellar signs	3.8
Unexplained interstitial lung disease, probably attributable to Ara-C	7.7

SIDE-EFFECTS

The side-effects observed during high-dose cytosine arabinoside consolidation therapy were more or less comparable to those reported in earlier studies [3–7, 12, 13].

The major hematological side-effect was a pancytopenia (granulocytes $\leq 0.5 \times 10^9/l$, platelets $\leq 10 \times 10^9/l$) that lasted 14–21 days (median 19 days) after the consolidation courses. The non-hematological side-effects observed during 26 courses of consolidation therapy are listed in Table 4.

DISCUSSION

For patients with relapsed or refractory acute leukemia or non-Hodgkin's lymphoma the inclusion of intermediate and high-dose Ara-C in remission induction protocols increased subsequent complete remission rates, as has been reported by several centers in the U.S.A. and Europe [3–11]. Most authors did not introduce consolidation therapy after a complete remission had been achieved, so that remission duration was usually no more than 3–6 months. Intensive consolidation courses might prolong the duration of the first complete remission, as has been suggested in several reports [14–17]. Wolff *et al.* [17] reported on 36 patients with AML in first remission who received 1–2 courses of high-dose Ara-C. The actuarial disease-free survival was 42% at 62 months. Hines *et al.* [15] reported that high-dose Ara-C consolidation therapy led to a projected median survival of more than 22 months for a small group of first remission patients.

Our results with brief intensive consolidation chemotherapy with high-dose cytosine arabinoside for patients with relapsed or bad-risk acute leukemia or lymphoblastic non-Hodgkin's lymphoma support the reviewed data. At present, 6 out of 16 patients who received 1–3 courses of high-dose Ara-C consolidation therapy have relapsed and 7 have been disease-free for 8–28 months, whereas all patients who refused consolidation treatment relapsed after a median remission duration of only 3 months.

However, in our study, as well as others on intensive consolidation therapy [14–17], there is no comparison with patients on other intensive chemotherapeutical regimens or those receiving bone marrow transplantation. Moreover, randomization can overcome the problems of patient selection; in our study, for example, only 16 out of 29 (55.2%) patients in remission received at least one consolidation course. Therefore the efficacy of intensive consolidation chemotherapy has not yet been demonstrated convincingly.

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