Low-Dose Cytosine Arabinoside Treatment for Acute Nonlymphocytic Leukemia in Elderly Patients

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Thirty patients older than 65 years of age with acute nonlymphocytic leukemia were treated with low-dose cytosine arabinoside (10 mg/m^2 subcutaneously every 12 hours for 15 to 21 days). Fifteen achieved complete remission and five had partial remission. Treatment was more effective when initial bone marrow cellularity was low (P = 0.007). Four of six patients with secondary leukemia entered complete or partial remission. Therapy was well tolerated with reduced myelosuppression and few number of early deaths. Sixteen patients followed the whole treatment as outpatients. Six of 12 patients who achieved complete remission showed no evidence of post-therapeutic bone marrow aplasia. These data are consistent with the view that low-dose cytosine arabinoside acts on leukemic cells as a differentiating agent.

Cancer 55:1633–1636, 1985.

THERE IS a high incidence of acute nonlymphocytic leukemia (ANLL) in the elderly[1] and the prognosis for these patients is generally considered as poor.[2,3] Hypothetic resistance to chemotherapy and high mortality rates during the post-therapeutic phase of myelosuppression are the two major problems encountered with intensive treatment of elderly patients[4,5] and incitate to find new therapeutic approaches.

In vitro experiments[6,7] have demonstrated the ability of some agents, including low concentrations of cytosine arabinoside (Ara-C), to induce differentiation of leukemic cells. Previous reports[8–10] have shown that complete remission can be obtained with low-dose Ara-C (LD Ara-C) treatment in patients with ANLL and raise the hypothesis of a role in the differentiation of malignant cells.

Therefore, in this study, we used LD Ara-C as an alternative treatment to intensive chemotherapy in 30 patients with ANLL, aged 65 years and older, in order to evaluate its efficiency and toxicity.

Patients and Methods

Thirty previously untreated patients older than 65 years of age (age range, 65–85 years; median 73) were treated for ANLL between March 1982 and April 1983. Diagnosis and classification of the leukemia were done according to the French–American–British (FAB) criteria:[11,12] over 30% of bone marrow (BM) blasts was sufficient for the diagnosis of ANLL. Patients with transformation of myeloproliferative disease, refractory anemia with excess of blasts (RAEB, 5%–20% BM blasts) or RAEB in transformation (20%–30% BM blasts) did not enter the study. Six patients with an history of prior malignancy treated with chemotherapy or radiotherapy (secondary leukemia) were included. BM cellularity was judged as low, normal or high at the sight of the aspirates cell density. No BM biopsy was performed.

All patients were treated with subcutaneous injections of Ara-C, 10 mg/m^2 of body surface area, every 12 hours, for 15 to 21 days. If complete remission was not obtained, additional courses of the same treatment were given at 8- to 15-day intervals. Patients with evidence of progressive disease under treatment or with no improvement in hematologic condition after three courses were considered as a failure.

Whenever possible, patients were treated as outpatients. Clinical examination, blood count, renal and hepatic functional tests were performed every week. Patients were hospitalised in cases of persistent fever or hemorrhage. Transfusions of erythrocytes or platelets were given when necessary. No prophylactic regimen of platelet or granulocyte transfusion was used in this study.

BM specimens were obtained whenever possible every week during the treatment and always two weeks after each course of Ara-C to evaluate response to therapy.

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The authors thank Joseph Morhaim and Sylvie Vernin for preparation of the manuscript.

Accepted for publication March 26, 1984.

Patent Owner Exhibit 2118
IPR2025-01582

TABLE 1. Characteristics of Patients With Complete Remission

Patient no.	Age	Type of ANLL*	Initial bone marrow cellularity	Cytogenetic findings†	Number of courses	Induced cytopenia‡	Induced bone marrow aplasia	Care	Duration of remission (mo)
1	73	M1	Low	ND	2	Yes	No	Outpatient	>6
2	71	NC	Low	ND	1	Yes	Yes	Outpatient	>3
3	76	M4	Low	AA	2	No	No	Outpatient	>8
4	74	M4	Normal	ND	1	Yes	Yes	Outpatient	1
5	70	M1	Low	AN	3	No	No	Outpatient	8
6	65	M2	Normal	NM	1	Yes	Yes	Outpatient	>5
7	70	NC	Normal	AA	2	Yes	Yes	Outpatient	6
8	79	M2	Low	ND	2	No	Unknown	Outpatient	>2
9	85	M2	Low	ND	2	No	Unknown	Outpatient	>6
10	73	M4	High	AA	2	Yes	No	Admission during treatment	3
11	68	M1	Normal	NN	1	Yes	Yes	Admission during treatment	>5
12	73	M2	High	NN	3	Yes	No	Hospital stay throughout treatment	>7
13	70	M1	Normal	NN	2	Yes	Unknown	Hospital stay throughout treatment	>6
14	77	NC	Low	AA	1	No	No	Hospital stay throughout treatment	3
15	80	M1	Low	ND	1	Yes	Yes	Hospital stay throughout treatment	8

* French-American-British classification: M1 denotes acute myelocytic leukemia, M2 acute myelocytic leukemia with differentiation, M4 acute myelomonocytic leukemia, NC denotes not classified ANLL.

† NN: denotes normal metaphases; NA: normal and abnormal metaphases; AA: only abnormal metaphases; NM: no metaphases detected; ND: cytogenetic study not done.

‡ Platelets < 20 × 109/l and/or granulocytes < 0.5 × 10^9/l.

Complete remission (CR) and partial remission (PR) were defined according to the criteria of the Cancer and Leukemia Group B.[13]

Patients who achieved CR or PR received the same chemotherapy, at the same dose, 8 to 15 days every month as maintenance therapy until the relapse occurred.

Statistical comparisons were performed using the Fisher's exact test.

Results

Fifteen of the 30 patients entered complete remission, their characteristics are summarized in Table 1. Five patients had PR, seven failed, and three died during the first 3 months. Response rates did not correlate with age, sex, initial blood counts, or cytogenetic findings. CR rate was the same in M1 and M2 FAB categories, but the three patients with myelomonocytic (M4) leukemia achieved CR. Nine patients had a low bone marrow cellularity at presentation, 8 of them entered CR *versus* 7 of 21 with normal or high cellularity ($P = 0.007$). Among the 6 patients with secondary leukemia, 2 had CR (Patients 3 and 11) and 2 had PR for 6 and 7 months.

Serial examination of bone marrow aspirates during and after treatment was performed in 23 patients. In 12 patients bone marrow cellularity did not decrease during the follow-up period, while a marked hypoplasia was found in the 11 other cases; CR rates were similar within the two groups (6/12 and 7/11, respectively). Thus, in patients who achieved CR with no aplasia, bone marrow pictures showed a progressive change with a decrease in blast populations and an increase in mature cells with appearance of normal granulocytes.

Severe decrease in platelets (<20 × 10^9/l) and/or granulocytes (<0.5 × 10^9/l) was noted in 21 patients. A bleeding tendancy occurred in 15 patients, 9 of whom required platelet transfusions. No cases of death due to hemorrhage were recorded. Fever occurred in 14 patients; this was associated with a severe sepsis in 7 cases and was responsible for the death of 3 of these patients.

Mild nausea was reported by two patients and was described as discomfortable because of the duration of the treatment courses. No impairment of renal or hepatic function reliable to treatment was detected. Patient 4 died of a myocardial infarction during the second month of CR.

Twenty-two patients were initially treated as outpatients; 6 of these patients were referred to hospital because of hemorrhage or infection. The other eight patients followed all the treatment courses at the hospital because of initial evidence of bleeding or sepsis, or because of social isolation.

Tolerance to maintenance therapy was excellent, and no severe decrease in blood counts was noted during this treatment. Patients 10 and 14 did not follow mainte-

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nance treatment, and both relapsed during the fourth month of CR.

Discussion

The question is no longer "to treat or not to treat" ANLL in elderly patients.[2] Several publications[4,5,14-18] have reported high CR rates and improved survival in patients receiving intensive induction chemotherapy. However, major problems associated with these intensive regimens are drug toxicity and severe myelosuppression, which is responsible for hemorrhage and infection, and explain the high frequency of early deaths in older patients.[4,5,16,17]

We have treated 30 patients with ANLL older than 65 years of age with LD Ara-C; 15 patients achieved CR. This result can be compared to the recent reported series using intensive chemotherapy in patients older than 50[4,18] or 60[5,16,17] years of age. A high response rate was observed in patients with low initial bone marrow cellularity. This fact was never reported with intensive therapy and could be a useful indication in the choice of LD Ara-C treatment. It is of interest that complete or partial remission can be induced by LD Ara-C in patients with secondary ANLL, and that the two patients who achieved CR are still free of disease 6 and 10 months, respectively, after the beginning of the therapy. This kind of ANLL is known to be resistant to conventional intensive therapy,[19-21] but seems to have a high responsiveness to high-dose Ara-C therapy.[22]

Toxicity of the regimen is low: nausea was rare and no hepatic, neurologic or ocular disorder appeared. Myelosuppression is reduced, resulting in decreased needs for platelet transfusions and few early deaths due to infection. However, severe cytopenia occurred in the majority of patients and certainly indicated the need for regular medical overview, especially during the third week of treatment.

The relatively good tolerance allowed us to treat 16 patients as outpatients, and it must be noted that 9 patients achieved CR without spending one day in hospital. Thus, one of the main advantages of LD Ara-C treatment appears to be the improvement in the quality of life[23] in these elderly patients. It is of additional interest that the cost of treatment is largely reduced when avoiding protective environments and prophylactic platelet transfusions.

LD Ara-C was empirically used as maintenance therapy and provided remission duration for over 6 months in a substantial proportion of patients who continued on a regular treatment. Other studies are needed to evaluate the possible benefit of the introduction of other drugs in maintenance therapy.

Ara-C is an S-phase specific antileukemic agent acting as a competitive inhibitor of DNA polymerase.[24] Wide variations in cell sensitivity to Ara-C *in vitro*,[25] however, lead to questioning cell kill as the only mechanism for its effect *in vivo*.[26] In this study some patients (6/12) achieved CR with no evidence of bone marrow aplasia. This fact suggests that the mechanism of action of LD Ara-C could be due to its effect on leukemic cells differentiation, but certainly does not permit its affirmation. Lotem and Sachs[6] have shown the differentiating effect of Ara-C low concentrations on mouse leukemic cells *in vitro*. Other data suggest that Ara-C induces differentiation of human leukemia cell lines—HL-60 (promyelocytic),[27] ML-1 (myeloblastic),[28] or U-937 (histiocytic lymphoma)[29]—into monocytic cells as judged by morphologic, functional, or antigenic criteria. Success of LD Ara-C in the three patients with myelomonocytic leukemia we have treated may provide some support for this view.

Differentiation of leukemic cells could be associated with expansion of normal cells. Gordon *et al.*[30] showed that conditioned media from leukemic cells inhibit colony formation by normal bone marrow and decrease the sensitivity of normal colony forming cells to Ara-C. As supposed with high-dose therapy,[22] leukemic cells could reduce the number of normal hematopoietic progenitors in S-phase and therefore decrease their sensitivity to Ara-C.[9] Thus, mature cells could originate either from leukemic clones after a differentiation effect or from normal remaining colony forming cells after a derepression process.

Whatever the mechanism of action of LD Ara-C is, this therapy represents a promising approach for ANLL treatment and could serve as a useful tool in cases where intensive chemotherapy is contraindicated or inefficient.

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