

Does Treatment With ARA-C in Low Dosage Cause Differentiation of Leukemic Cells?

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A series of 21 patients (5 refractory anemias with an excess of blasts in transformation and 16 acute leukemias) were treated with small doses of ARA-C (10 mg/sq m/12 hr for 15–21 days). Improvement was noted in 15 cases (71%) and complete remission observed in 12 (57%). Complete remission was obtained after one course of treat-

ment in 8 cases. The fact that these patients entered remission relatively slowly and did not suffer marrow aplasia suggests that low-dose ARA-C may function in vivo as it does in vitro, i.e., by inducing differentiation of leukemic blasts.

COMplete remission in adults with leukemia is generally induced by high-dose antimitotic chemotherapy. However, in cases where this treatment is ineffective (resistance to antimitotic drugs or refractory anemia with an excess of blasts "RAEB" in transformation¹), or contraindicated, other approaches are required to obtain remission.

One possibility that has not been widely explored involves inducing the malignant cells to differentiate. ARA-C is one of the substances that acts as a differentiating agent in in vitro experiments.^{2,3} It has been administered with success to a number of patients: one case of RAEB,⁴ two cases of nonlymphatic leukemia,⁵ one case of RAEB in transformation,⁶ and two myeloblastic (M1 and M2) leukemias.⁶ ARA-C was given continuously in small doses so that it would interfere in the process of cell differentiation without any antimetabolic effect.

Encouraged by our previous results,⁶ we treated 21 patients (16 with acute leukemia, and 5 with RAEB) in order to further evaluate the effectiveness of this procedure.

MATERIALS AND METHODS

The study was comprised of adult patients with acute leukemia for whom other kinds of high-dose antimitotic chemotherapy were ineffective or contraindicated and cases of RAEB in transformation. Three patients who died during the first course of treatment were excluded.

The 21 patients were divided into four categories: (1) 5 elderly cases (70–77 yr) of AML (1 M1, 2 M2, 2 M4); (2) 5 cases of AML secondary to myeloproliferative disorders (3 polycythemia vera, 1 chronic myeloid leukemia, and 1 thrombocytopenia) and 2 cases of leukemia with features of secondary myelodysplastic syndrome¹ (after chemotherapy for multiple myeloma and irradiation for cancer); (3) 2 relapses of AML (M1), 2 leukemias resistant to large doses of anthracycline and ARA-C chemotherapy (1 M2 and 1 ALL with Ph¹ chromosome); and (4) 5 RAEB (in transformation).

ARA-C treatment is given by subcutaneous injection at doses of 10 mg/sq m every 12 hr for 15–21 days. If complete remission was not obtained, additional courses of the same treatment were given at 8–15-day intervals so that one course each month was given. ARA-C was the only drug administered to these patients.

Complete remission was documented by normal hemogram and less than 5% of blasts in a normal bone marrow smear. After complete remission, the same treatment was given 8 days per month.

Table 1. Low-Dose ARA-C (LD ARA-C Treatment) in Leukemia and RAEB (21 Cases)

Categories of Patients	No. of Patients	CR	PR	Duration of CR (mo)
I. AML in elderly persons	5	3	0	2+, 6+, 2‡
II. AML secondary to myeloid proliferative disorder	5	1	2	4+
AML: secondary MDS	2	1*	0	1‡
III. AML and ALL: relapse or resistance to high-dose chemotherapy	4	3	1†	5+, 12, 4+
IV. RAEB in transformation	5	4	0	12, 6, 5, 2+
Total	21	12	3	

CR, complete remission; PR, partial remission; (+) alive; MDS, myelodysplastic syndrome.

*After chemotherapy for multiple myeloma.

†ALL with Ph¹ chromosome: normal hemogram and 7% blasts in the myelogram after 8 courses of treatment.

‡Intercurrent cause of death (death in CR).

RESULTS

The effect of doses of ARA-C treatment is summarized in Table 1. An improvement was recorded in 71% of patients and complete remission was obtained in 57%. The effectiveness of low-dose ARA-C was observed in all proposed subclasses of acute leukemia, even when patients were refractory to classical antimetabolic treatment and in RAEB.

The duration of complete remission was relatively short (5 mo ± 3.6 SD), the maximum being 12 mo. However, 6 patients are still alive, and in 2 cases, death occurred during complete remission, due to intercurrent cause.

Complete remission was generally obtained after one course of treatment (8 cases). A progressive effect was observed in other patients after 2 courses (3 cases) or 3 courses (1 case). One patient reached a normal

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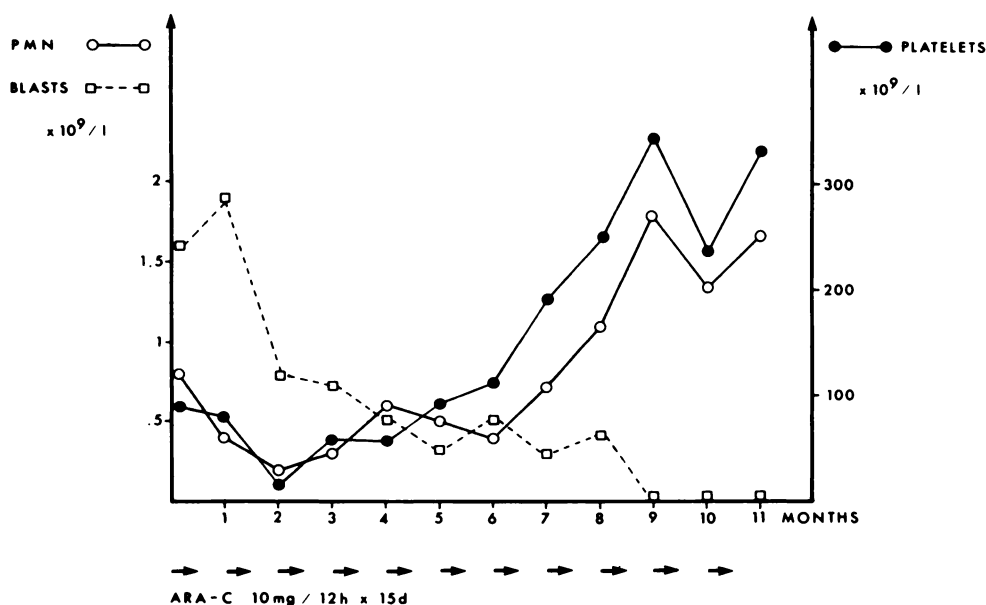


Fig. 1. Hemogram (polymorphonuclear, platelets, and blasts) during 8 courses of low-dose ARA-C treatment. Progressive improvement in one case of ALL with Ph¹ chromosome.

hemogram and persistence of 7% of blasts in bone marrow (partial remission) after 8 courses (see Fig. 1). Platelets were first normalized in 9 of the 12 cases who went into complete remission.

A cytopenic phase was noted in 6 patients after the tenth day of treatment. Two patients with RAEB suffered severe infectious diseases during this phase. The treatment was well tolerated in the 15 other patients.

DISCUSSION

Treatment of acute leukemia and RAEB with low-dose ARA-C (10 mg/sq m/12 hr for 15–21 days) in a series of 21 patients when usual chemotherapy was contraindicated or ineffective induced 12 complete and 3 partial remissions. These results confirm preliminary studies.⁴⁻⁶ The first effect observed was an increase in platelet count as previously noted.⁴⁻⁶

The slow evolution leading to remission in some cases in this series has already been reported^{4,6} and favors a progressive effect of the treatment. Diffusion chamber culture experiments indicated that low-dose ARA-C may enhance differentiation of leukemia cells.⁵

The dose-response curve of DNA synthesis inhibition (antimitotic effect) shows a 50% effect at a concentration of 100 nM ARA-C,⁷ which corresponds approximately to high-dose chemotherapy (200 mg/sq m/24 hr, continuous infusion). One-tenth of this dose induced a concentration of 10 nM, which did not inhibit DNA synthesis.⁸ The absence of complete aplasia⁶ in the effect of low-dose ARA-C confirms this theory. On the other hand, the role of ARA-C (low concentrations) in the in vitro differentiation of leu-

kemic cells was documented by Lotem and Sachs.³ Thus, these data favored the argument of a differentiation of leukemic cells by low-dose ARA-C treatment.

The approach of treatment for leukemia and disorders such as RAEB in transformation by differentiating agents must be encouraged mainly when other chemotherapy cannot be proposed. Low-dose ARA-C treatment brought benefits to this category of patients and was financially beneficial, since patients were treated at home (except for the cytopenic phases) and the total cost of a course of treatment was largely reduced.

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