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

By Sylvie Castaigne, Marie Thérèse Daniel, Hervé Tilly, Patrice Hérait, and Laurent Degos

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-

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 transformation), 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 vitro experiments. It has been administered with success to a number of patients: one case of RAEB, two cases of nonlymphatic leukemia, one case of RAEB in transformation, and two myeloblastic (M1 and M2) leukemias. ARA-C was given continuously in small doses so that it would interfere in the process of cell differentiation without any antimitotic effect.

Encouraged by our previous results, 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, 1 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 syndrome (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.

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 antimitotic 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

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

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

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 antimitotic treatment and in RAEB.

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From the Institut des Recherches sur les Maladies du Sang, Hôpital Saint Louis, Paris, France.

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Address reprint requests to L. Degos, Institut de Recherches sur les Maladies du Sang, Centre Hayem, Hôpital Saint Louis, 2, place du Docteur A. Fournier, 75010 Paris, France.

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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. The first effect observed was an increase in
platelet count as previously noted.

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

The dose–response curve of DNA synthesis inhibition
(antimitotic effect) shows a 50% effect at a
concentration of 100 nM ARA-C, 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. The absence of complete
aplasia 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-

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