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

By Sylvie Castaigne, Marie Thérèse Daniel, Hervé Tilly, Patrice Herait, 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 treatment 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.

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>5</td>
<td>4</td>
<td>0</td>
<td>12, 6, 5, 2+</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>12</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

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.

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

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

Submitted October 18, 1982; accepted January 5, 1983.

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.

© 1983 by Grune & Stratton, Inc.

0006-4971/83/6106-0010$01.00/0
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 leukemic cells was documented by Lotem and Sachs. 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.

**REFERENCES**

Does treatment with ARA-C in low dosage cause differentiation of leukemic cells?

S Castaigne, MT Daniel, H Tilly, P Herait and L Degos