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Treatment of Leukemia with Low Dose Ara-C: A Study of 159 Cases *

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A. Introduction

The management of acute leukemia has been transformed by the advent of major antimitotic agents. Intensive combination drug therapy has given excellent results for many patients, but in certain cases it remains dangerous (acute leukemia in elderly patients) or ineffective (refractory anemia with excess blasts (RAEB), secondary leukemia, leukemic relapse). Allogeneic bone marrow grafts are also limited by the particular conditions required (compatibility of MHC, age).

In vitro studies by Lotem and Sachs [1] demonstrated the differentiation of leukemic cells from normal cells, raising new hopes of therapeutic possibilities. In recognition of this, clinical trials with low dose cytosine arabinoside (LD Ara-C) were undertaken. Success was obtained for one case of RAEB and two cases of acute nonlymphoblastic leukemia (ANLL) unresponsive to combination chemotherapy [2]. The first substantial series (23 patients) showed that it was possible to obtain complete remission in all categories of leukemia [3].

Several clinical trials with LD Ara-C have recently been reported, but the small number of patients in each series (less than 20) and the contradictory results render a conclusive judgement impossible. Thus, a number of questions have yet to be answered. What is the efficacy of LD Ara-C and which category of patients can benefit from it? What is the hematologic and extrahematologic tolerance to the treatment? By what mechanism does LD Ara-C produce its effects? That is why this report presents the results obtained by 12 centers in 159 cases, including some cases which have been published previously [2, 3].

B. Patients and Methods

The series was made up of 159 patients suffering from acute leukemia (AL) or myelodysplastic syndrome (MDS). A total of 12 centers took part in the study: Brest, Dijon, Hamburg, Montpellier, Nantes, Paris Beaujon, Paris Pitié-Salpétrière, Paris St. Louis, Praz Coutant, Rennes, Rouen, and Tours. Patients whose treatment commenced before June 1983 were included in the series.

The aim of the study was first of all to determine the response to the treatment (complete or partial remission, or no response) and to note the main incidents observed. Second, a more detailed questionnaire enabled us to study the results obtained for ANLL in patients over 65 years of age. All patients were treated with Ara-C as the sole agent, administered in two daily subcutaneous injections. The dose was generally 10 mg/m² every 12 h. The duration of treatment varied for the different groups, with a median of 19 days. The treatment was used for cases in which combination drug therapy was contraindicated for various reasons (age, failure of previous treatment, relapse, MDS). One

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Table 1. Results of therapy with low dose cytosine arabinoside[a]

		Number of patients			
		Total	CR	PR	Failure
ANLL	ANLL>65 years	48	24	7	17
	ANLL<65 years	9	1	4	4
No previous treatment	Secondary AL	14	3	4	7
ANLL					
In relapse		13	5	1	7
Unresponsive to previous treatment		15	7	3	5
ALL					
In relapse or unresponsive to previous treatment		7	2	1	4
MDS					
(RAEB, RAEB-T, post-RAEB AL)		38	9	6	23
AT of myeloproliferative disorder		8	1	0	7
Other and unknown		7	1	0	6
		159	53	26	80

[a] ANLL: acute nonlymphoblastic leukemia; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; RAEB: refractory anemia with excess blasts; RAEB-T: refractory anemia with excess blasts in transformation; AT: acute transformation; CR: complete remission; PR: partial remission

Table 2. Tolerance

	Number of patients affected (%)		Total number of patients
	+	–	
Cytopenia (platelets $<20\,000$ mm^3 and/or PN <500 mm^3)	81 (77%)	24	105
Bone marrow aplasia determined by bone marrow aspirates	38 (48%)	40	78
Hemorrhage	65 (47%)	69	134
Infection	72 (52%)	65	137
Home care	37 (33%)	73	110

course of treatment per month was given. No response after three courses was considered as failure of the therapy.

C. Results

The results obtained for all the patients and for the subgroup of elderly AL patients are listed in Tables 1–3.

D. Discussion

Since the first report published by Baccarani and Tura [4], followed by those of Moloney and Rosenthal [5] and Housset et al. [2], LD Ara-C has been extensively used of late to treat malignant blood disorders. By grouping together 159 cases treated in France and Germany it is possible to improve our assessment of the results of LD Ara-C therapy.

1. The effectiveness of the treatment was confirmed, since a response was observed in 49% of the cases, with complete remission (CR) occurring in 33% of the cases.

2. The response varied with the type of illness treated: de novo ANLL was more responsive (response = 59%, CR = 40%) than MDS (response = 39%, CR = 23%).

Table 3. LD Ara-C therapy for elderly de novo ANLL patients with no previous treatment[a]

Number		Mean Age (years)	Dose	Duration (days)	Number of courses		
48		74	10 mg/m² ×2/day	17	1.7		
CR	PR	Failure	Cytopenia	Aplasia	Infection	Hemorrhage	Home care
24/48	7/48	17/48	34/48	18/34	20/48	20/48	14/48

[a] Maintenance therapy: 10 mg/m² Ara-C twice daily for 15 days/month or 15 days/6 weeks (19 patients); mean duration of remission: 8 months; mean survival: 15 months. Correlation: + positive between CR and hypoplasia on aspirates at diagnosis; – no correlation between aplasia following treatment and CR

The good results obtained for the 48 de novo ANLL patients aged over 65 years should be emphasized. CR was achieved in half of the cases and the mean duration of the first remission was 8 months. Mean actuarial survival was 15 months. Fourteen patients were treated entirely at home, nine of whom had CR. These results are worth comparing with those obtained by combination chemotherapy. No comparable series of patients (same age group) treated by combination drug therapy has been reported. Quality of life and cost of treatment must also be taken into account in a comparison between the two types of therapy. The results obtained in secondary leukemias (7/14 responses) or during transformation of MDS (1/8 responses) need to be confirmed by trials with greater numbers of patients.

3. The optimum duration of treatment cannot be established from the data of this study. The best rate of responses was obtained in patients treated for 15–21 days, but the difference was not significant compared with patients treated for shorter (19 patients) or longer periods (48 patients). The need for maintenance therapy and the form it should take could not be determined from this series, as the vast majority of the patients received the same maintenance therapy with LD Ara-C.

4. While extrahematologic tolerance was good, cytopenia was noted in ⅔ cases. It is difficult to assess the toxicity related to the treatment and not to the illness. Nevertheless, when two groups of 52 patients were distinguished on the basis of initial platelet count (platelets < or > 50 000), cytopenia following therapy was equally common in both groups, while severe hemorrhage was more frequent in patients with less than 50 000 platelets/mm³ before treatment. Thus, the appearance of cytopenia does indeed seem to be related to the treatment. On the other hand, the more effective the treatment, the better was the hematologic tolerance. There was a strongly significant relation between obtaining CR and the absence of hemorrhage after treatment for the 48 elderly de novo ANLL patients. Administering the entire treatment in the homes of 14 of the elderly patients shows that the therapy is well tolerated in certain cases, leading to increased patient comfort and suggesting implications for savings in health expenses.

5. The precise mechanism of action of the treatment cannot be deduced solely from the clinical data. Nevertheless, the following observations may contribute to elucidating the mode of action of LD Ara-C. Bone marrow aplasia was noted in half of the cases. However, no correlation was found between the existence of medullary aplasia and CR. This fact was also noted by another group [6]. For elderly ANLL patients, CR was obtained in 10/18 cases when aplasia was observed and in 7/16 cases when aplasia was absent. Thus, in

40% of the cases, CR was obtained without bone marrow aplasia. The therapy seems to be more effective when it is used to treat AL with hypocellular marrow. This observation is comparable to two studies reported in the literature [7, 8]. However, the cellularity of the bone marrow was judged solely from aspirates. The genuineness of this finding would need to be confirmed by the study of bone marrow biopsies. Finally, the fact that Ara-C is more effective in treating de novo AL than MDS is analogous to the results obtained with conventional combination chemotherapy.

The action of LD Ara-C is probably not based on a single mechanism of cytotoxicity bringing on severe aplasia. By its mutagenic action on oncogenes, it might restrain the proliferative capacity of blast cells and permit their maturation, but also repress the clone of leukemic cells sufficiently to liberate the development of normal clones. This phenomenon may perhaps be facilitated when the tumoral mass is small (hypocellular leukemia). The differentiation hypothesis can be viewed in two ways: either as differentiation of the malignant cell from a normal cell, or as the removal of the obstacle to the development of normal cells. No decision between the two is yet possible.

E. Conclusion

The results of the French and German study demonstrate the efficacy of LD Ara-C in the treatment of malignant blood disorders. The treatment can be ethically prescribed for elderly ANLL patients. A randomized trial is currently in progress, comparing conventional combination drug therapy with LD Ara-C. The results obtained in treating MDS and secondary leukemia require confirmation with a large number of cases. Finally, in the light of recent developments in the molecular mechanisms of oncogenesis, clinical trials using agents of differentiation merit attention.

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