Low-Dose Cytarabine Versus Intensive Chemotherapy in the Treatment of Acute Nonlymphocytic Leukemia in the Elderly

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We conducted a randomized multicenter trial comparing low-dose cytarabine (LD ARA-C) (20 mg/m^2 for 21 days) with an intensive chemotherapy (rubidazone [a daunorubicin-derived agent], 100 mg/m^2 for 4 days, ARA-C 200 mg/m^2 for 7 days) in 87 patients over 65 years of age with de novo acute nonlymphocytic leukemia (ANLL). Forty-one patients received LD ARA-C and 46 received intensive chemotherapy. The number of complete remissions (CRs) but also of early deaths was higher in the intensive chemotherapy group, while partial remissions (PRs) and failures were more frequent in the LD ARA-C group ($P < .001$). Infectious complications during induction treatment were more numerous and more severe in the intensive chemotherapy group ($P < .01$). Patients treated with LD ARA-C required fewer RBC transfusions ($P < .02$), fewer platelet transfusions ($P < .01$), and had a shorter hospital stay for induction treatment ($P < .01$). Overall survival and CR duration were not significantly different in either group. In the LD ARA-C group, the survival of patients with PR and those of patients in CRs was identical. We conclude that in a selected group of elderly patients with de novo ANLL a higher number of CRs may be obtained with intensive chemotherapy, but that with LD ARA-C, the number of early deaths is lower, and long-lasting PRs are obtained, resulting in a similar overall survival.

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THE MEDIAN age of patients with acute nonlymphocytic leukemia (ANLL) has been estimated to be between 62 and 64 years, with more than 40% of the patients being over 65 years of age.[1-4] Age is recognized as one of the more adverse prognostic factors in ANLL.[1,3,5-8] Two major factors may explain this finding: first, the incidence of transformation of myelodysplastic syndromes into acute leukemias and of leukemias secondary to treated malignancies increases with age, and both of these conditions are known to respond poorly to conventional chemotherapy.[3,9] Second, aged patients with acute leukemia tolerate poorly the disease and its treatment, especially the prolonged periods of bone marrow hypoplasia induced by therapy.[3,9]

The treatment of ANLL in the elderly is, therefore, controversial. Although the exact proportion has not been clearly established, it is accepted that a number of patients should be given only symptomatic treatment when chemotherapy is contraindicated for one reason or another. However, it is now accepted that purely conservative treatment should not be given systematically to all elderly ANLL patients regardless of age.[10-12] Since the introduction of cytarabine (ARA-C) and anthracyclines and the improvement of supportive care, it has been suggested that intensive chemotherapy be given to ANLL patients over 60 years of age, since complete remission (CR) rates of up to 76% have been reported in some single-center studies.[13-18] In almost all studies, the response rates to therapy steadily decreased with advancing age. In these patients, the major problem encountered after conventional induction chemotherapy is early death due to infections following myelosuppression.[3,9,13,16,17]

Due to its potential action on cellular differentiation in vitro[19] low-dose (LD) ARA-C has been proposed in the treatment of ANLL and myelodysplastic syndromes.[20-23] On the assumption that it is less toxic that conventional intensive treatments, LD ARA-C has been used in the treatment of ANLL in the elderly.[24-27] These retrospective studies have shown CR rates of 30% to 50% and a lower number of early deaths.

We present here a randomized study of 87

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patients over 65 years of age with de novo ANLL, in which the efficacy and toxicity of LD ARA-C was compared with that of intensive chemotherapy.

MATERIALS AND METHODS

Patient Population

Previously untreated patients over 65 years of age with de novo ANLL were eligible for this study. ANLL diagnosis and classification was made according to French-American-British (FAB) criteria.[28] Patients with transformation of myelodysplastic syndrome or myeloproliferative disease were not eligible to enter the study.

The trial was conducted at 15 centers throughout France. In accordance with French regulations no written, informed consent was obtained. The trial lasted from January 1984 to March 1987. Follow-up is complete to June 1988 and all surviving patients have been observed for at least 1 year.

Study Design

All patients who fulfilled inclusion criteria were registered except patients with cardiac, renal, or hepatic failure, with a history of previously treated malignancy, or with a poor performance status not related to ANLL (World Health Organization [WHO] grading over 2, 3 months before diagnosis). These patients were judged to be ineligible to receive intensive chemotherapy and, therefore, were excluded from randomization and treated with LD ARA-C (nonrandomized group). Other patients were randomly allocated to treatment with LD ARA-C or intensive chemotherapy through a centralized procedure. There was no stratification.

Treatment Regimen

LD ARA-C induction regimen consisted of subcutaneous injections of ARA-C, 10 mg/per square meter of body surface area every 12 hours for 21 days. If CR was not obtained, a second course of the same treatment was given after a 15-day interval. Patients who achieved CR or partial remission (PR) received the same chemotherapy as maintenance at the same dose for 14 days every 6 weeks for 18 months.

Intensive induction chemotherapy consisted of rubidazone (a daunorubicin-derived agent; Zorubicin, Rhone-Poulenc, France) (100 mg per square meter intravenously for 4 days) and ARA-C (200 mg per square meter continuous infusion for 7 days). If leukemic cells were still seen in a bone marrow aspirate 7 days after the end of chemotherapy (day 14) an additional course (rubidazone, same dose for 2 days; ARA-C, same dose for 3 days) was delivered. When a CR or PR was obtained maintenance treatment was started consisting of 5-day courses of ARA-C (100 mg per square meter, subcutaneously) in association with alternating drugs (rubidazone, courses 1-5-9; cyclophosphamide, courses 2-6-10; mercaptopurine, courses 3-7-11; and mitoguazone, courses 4-8-12) every 6 weeks for 18 months.

Patients whose disease progressed despite LD ARA-C treatment, or who did not achieve CR or PR after two cycles, were considered as failures and treated whenever possible with the intensive chemotherapy regimen. Conversely, LD ARA-C was administered whenever possible to patients who failed to respond to intensive chemotherapy.

When feasible, patients in the LD ARA-C group were treated as outpatients, but they were hospitalized in cases of fever, granulocytopenia ($< 1 \times 10^9$/L), or thrombocytopenia ($< 20 \times 10^9$/L). Patients treated with intensive chemotherapy were maintained in conventional hospital isolation rooms during the induction phase. Both groups of patients received RBC and platelet transfusions to maintain the hemoglobin level above 10 g/dL and the platelet count above 20×10^9/L.

Evaluation of Response

Evaluation of response was performed 2 weeks after the end of the induction course of LD ARA-C (or after the second course if this was administered) and 4 weeks after the completion of intensive induction chemotherapy. CR was defined as a normal cellular marrow with normal myeloid and erythroid maturation and less than 5% blasts, and peripheral blood counts showing hemoglobin concentration greater than 12 g/dL, granulocyte count greater than 1.5×10^9/L, and platelet count greater than 100×10^9/L. PR was defined as a bone marrow showing more than 5% blasts but fewer than 25%, and peripheral blood counts showing hemoglobin concentration greater than 9 g/dL, granulocyte count greater than 0.5×10^9/L, and platelet count greater than 25×10^9/L, all criteria lasting for at least 1 month. Induction treatment toxicity was assessed using the WHO grading for toxicity.

Statistical Analysis

Data (except age) are expressed as means ± SD. Initial characteristics and responses to induction treatments were tabulated and compared with Fisher's exact test for discrete variables and by Mann and Whitney's U test for continuous characteristics. Survival was calculated from the beginning of the treatment to death or to the date when the patient was last known to be alive. Remission duration was calculated from the date of remission to relapse or to the date the patient was last known to be free of disease. Survival and remission duration analysis were based on the Kaplan-Meier estimate and compared with the Mantel-Haenszel test. Analyses were performed on a personal computer (software developed by P. Kwiatkowski, Centre Jean Perrin, Clermont-Ferrand, France).

RESULTS

Patient Groups

One hundred twenty-six patients were registered. Thirty-nine patients (31%) were excluded from randomization. The main reasons for exclusion were: cardiac failure, 15; poor performance status, 12; renal or hepatic failure, two; unfavorable social conditions, five; prior malignancy, three; and refusal, two.

Eighty-seven patients were randomized: 41 were assigned to LD ARA-C treatment, and 46 to intensive chemotherapy. Patients in both groups were comparable in age, sex ratio, initial mean

Table 1. Initial Characteristics of the 87 Randomized Patients

	Number of Patients (%)	
	LD ARA-C N = 41	Intensive Chemotherapy N = 46
Median age (yr)	71.8	72.8
Range	65-82	65-83
Sex (M/F)	26/15 (63/37)	31/15 (67/33)
Platelets ($\times 10^9$/L)		
<20	4 (10)	8 (17)
20-100	19 (46)	23 (50)
>100	18 (44)	15 (33)
Leukocytes ($\times 10^9$/L)		
<1	3 (7)	5 (11)
1-9.9	23 (57)	22 (48)
10-100	12 (29)	15 (32)
>100	3(7)	4 (9)
Bone marrow		
Hypercellular	17 (41)	20 (43)
Normal	16 (39)	17 (37)
Poor	8 (20)	9 (20)
FAB		
M1	17 (42)	13 (28)
M2	14 (34)	17 (37)
M4	3 (7)	4 (9)
M5	4 (10)	5 (11)
M6	1 (2)	2 (4)
Unclassifiable	2 (5)	5 (11)

leukocyte and platelet counts, and initial bone marrow cellularity (Table 1). The frequencies of different FAB subtypes of the disease were equivalent in both groups and comparable to those described by the Groupe Français de Morphologie Hématologique[4] for patients of the same age.

No randomized patient refused therapy. The LD ARA-C 21-day course was discontinued in four patients, one because of uncontrolled disseminated intravascular coagulopathy at day 8, two because of severe sepsis at day 12 and day 13, and one because of progression at day 19. Except for three patients who died during the first week, all patients assigned to intensive therapy received the full dose.

Response to Induction Treatments

After completion of the first cycle of LD ARA-C, eight patients (20%) achieved CR and three patients died. Of the remaining 30 patients, four were evaluated to be in PR and placed on a maintenance program, eight were switched to intensive therapy because of progression, and 18 were given a second 21-day course of LD ARA-C. Of these eighteen patients, five achieved CR, five PR, seven failed to achieve CR or PR, and one patient died. These data yielded a CR rate of 13 of 41 (32%) and a PR rate of nine of 41 (22%).

In the intensive therapy group, at the time of the bone marrow examination (day 14), three patients were dead, 31 patients had an aplastic marrow without leukemic cells, and 12 patients had persistent leukemic cells. Of the 31 patients, 24 entered CR (52%), one entered PR, and six patients died. In the group with persistent leukemic infiltration at day 14, nine patients had severe sepsis and did not receive the intended additional course of chemotherapy, and five patients died during the following days. Only three patients received this additional course but without success.

Results in both groups, at the time of evaluaton, are shown in Table 2. The number of CRs as well as that of early deaths was higher in the intensive chemotherapy group, while PRs and failures were more frequent in the LD ARA-C group ($P < .001$). Response to therapy in both groups was independent of age, sex, initial blood counts, FAB classification, and bone marrow cellularity.

Induction Treatment Toxicity

All patients treated with intensive chemotherapy developed severe granulocytopenia ($< 0.5 \times 10^9$/L) and thrombocytopenia ($< 20 \times 10^9$/L) (Table 3). Platelet and RBC transfusions were given to all patients in this group. In the LD ARA-C group, 12 patients did not develop severe granulocytopenia and eight did not receive platelet transfusion (of whom four received no RBC transfusion). The mean number of platelet transfusions was 10.0 ± 7.4 in the intensive chemotherapy group and 5.6 ± 6.1 in the LD ARA-C group ($P < .01$). The mean number of RBC transfusions was 10.1 ± 5.2 in the intensive chemotherapy group and 7.2 ± 5.2 in the LD ARA-C group

Table 2. Results of Induction Treatment in the 87 Randomized Patients ($P < .001$)

	Number of Patients (%)	
	LD ARA-C N = 41	Intensive Chemotherapy N = 46
CR	13 (32)	24 (52)
PR	9 (22)	1 (2)
Failure	15 (36)	7 (15)
Early death	4 (10)	14 (31)

Table 3. Induction Treatment Toxicity

	Number of Patients (%)		
	LD ARA-C N = 41	Intensive Chemotherapy N= 46	P Value
Cytopenias			
Granulocytes < 0.5 × 10^9/L	29 (71)	46 (100)	$P < .01$
Platelets < 20 × 10^9/L	34 (83)	46 (100)	$P < .05$
Infectious complications			
None	18 (44)	5 (11)	
Moderate (grade 1–2)	10 (24)	16 (35)	
Severe (grade 3–4)	9 (22)	17 (37)	
Fatal	4 (10)	8 (17)	
			$P < .01$
Bleeding complications			
None	32 (78)	26 (57)	
Moderate (grade 1–2)	5 (12)	13 (28)	
Severe (grade 3–4)	4 (10)	4 (9)	
Fatal	0 (0)	3 (6)	
			$P < .1$
	Mean ± SD		
Transfusions (U)			
Platelet	5.6 ± 6.1	10.0 ± 7.4	$P < .01$
Red cell	7.2 ± 5.2	10.1 ± 5.2	$P < .02$
Hospital stay (days)*	27.5 ± 18.6	33.6 ± 7.6	$P < .01$

*Early deaths are excluded from this comparison.

($P < .02$). Severe cytopenia was not a prerequisite to achieve CR in the group treated with LD ARA-C since four of the seven patients whose platelet counts remained greater than 20 x 10^9/L entered CR.

The frequency of early deaths was higher in the intensive chemotherapy group (31% *v* 10%). Infectious complications were more frequent and more severe in the group treated with intensive chemotherapy ($P < .01$). In this last group, two patients died from acute cardiac failure in the first week of induction treatment and one died from acute renal failure on day 17.

The mean hospital stay for patients who survived the period of induction treatment was 33.6 ± 7.6 days in the intensive chemotherapy group, and 27.5 ± 18.6 days in the LD ARA-C group ($P < .01$). The duration of hospitalizations was much more variable in the LD ARA-C group, ranging from a few days to more than 2 months for some patients who required two cycles of LD ARA-C. Two patients treated with LD ARA-C entered CR without a hospital stay.

Treatment of Failures

Among the 15 patients who did not respond to LD ARA-C and were still alive after one (eight patients) or two cycles (seven patients), 13 could be treated with intensive chemotherapy, four of whom entered CR. Among the seven patients who failed to respond to intensive therapy, six were treated with LD ARA-C, one of whom entered CR.

Maintenance Treatment

Six of the 24 patients in CR with intensive therapy required a dose reduction of maintenance treatment, five because of severe cytopenia, and one because of posttransfusional hepatitis. Median CR duration in this small group was 6 months. One patient mistakenly received twice the dose of ARA-C during the first year of maintenance; she experienced several cytopenic episodes and a CR duration of 33 months.

In the LD ARA-C group, all patients in CR received the scheduled maintenance program while three patients in PR were given shortened courses because of poor hematologic tolerance.

Survival

There was no difference in overall survival between the two groups ($P > .12$) (Fig 1). The median survival was 8.8 months in the LD ARA-C group and 12.8 months in the intensive therapy group. At the time of this analysis, six patients are still alive more than 2 years from the

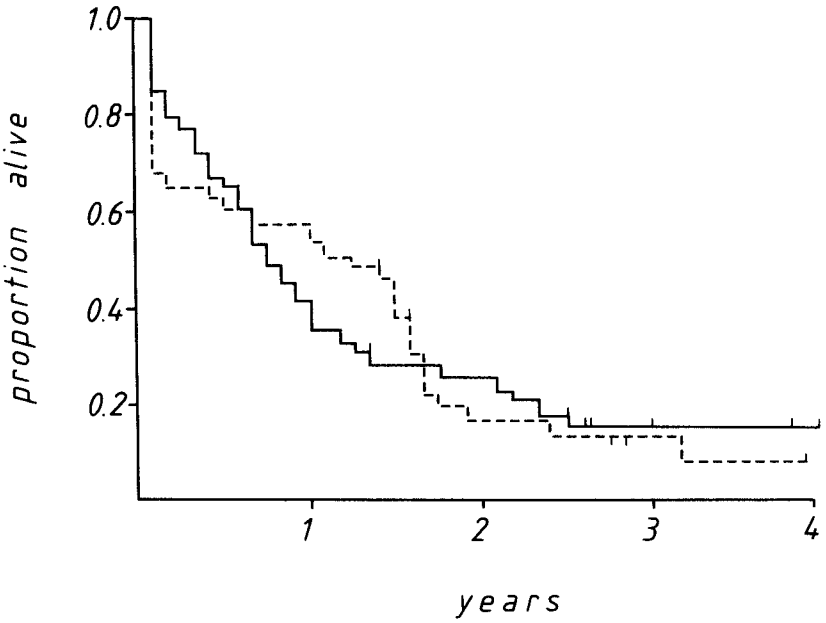

Fig 1. Overall survival (Kaplan-Meier estimate; $P > .12$). The (——) indicates the LD ARA-C group (41 patients), and the (-----) the intensive chemotherapy group (46 patients).

beginning of the treatment in the LD ARA-C group, and three are alive in the intensive chemotherapy group. Survival of patients in CR and PR was not different in the LD ARA-C group, (median, 11 months and 11.5 months respectively). The median survival of patients who did not achieve CR was 7 months in the LD ARA-C group and less than 1 month in the intensive chemotherapy group.

Remission Duration

The median CR duration was 8.3 months for the patients treated with LD ARA-C and 13.8 months for those treated with intensive chemotherapy, but overall CR duration did not differ between the two groups ($P > .31$) (Fig 2). The median PR duration in the LD ARA-C group was 10.5 months.

Nonrandomized Group

The 39 patients who were not randomized were older than those who were randomized (median, 76 years; range, 65 to 95; $P < .01$), but their other initial clinical and hematological characteristics were not different. All were treated with LD ARA-C: 13 entered CR, five entered PR, 12 failed to respond to treatment, and nine died during induction phase. The median survival was 3.2 months. Four patients are still alive more than 2 years from the beginning of the treatment.

DISCUSSION

Two major obstacles must be overcome in the study of ANLL treatment in elderly patients. The first is the heterogenous nature of the disease, since 10% to 30% of ANLL occurs during the course of a myelodysplastic syndrome or after previous cytotoxic therapy.[3,9] This type of ANLL ususally responds poorly to all forms of chemotherapy.[29] For this reason, these patients were not included in the present study. The second obstacle relates to the selection of patients who will be able to tolerate the various therapeutic regimens.[1] Studies in which all ANLL patients are taken into account show that 15% to 25% of the elderly patients could not be given any chemotherapy or could only receive partial treatment.[7,12] In our study, intensive chemotherapy was considered unsuitable in 31% of the patients who were, therefore, excluded from randomization. In this group, however, LD ARA-C treatment appeared to be beneficial, since some patients subsequently experienced a long survival.

For these reasons, it is difficult to assess the results of intensive chemotherapy in elderly patients in the literature who have CR rates varying between 14% and 76% and median survival is from 1 to 22 months.[12-18,30] Rubidazone is a daunorubicin-derived agent that is widely used in France for the treatment of ANLL.[31] A theoreti-

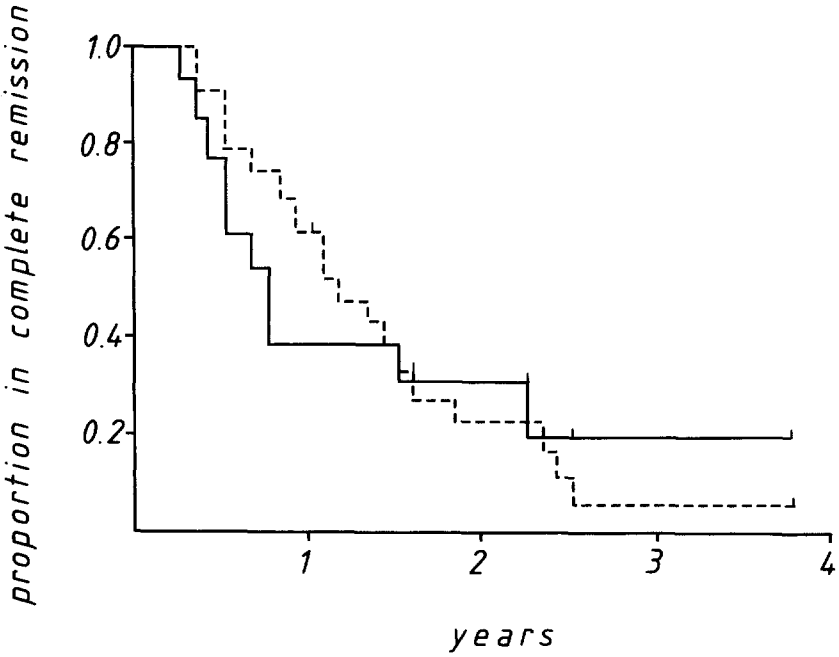

Fig 2. Complete remission duration (Kaplan-Meier estimate; $P > .31$). The (——) indicates the LD ARA-C group (13 patients), and the (-----) the intensive chemotherapy group (24 patients).

cal advantage could be taken of an improved therapeutic index over daunorubicin.[32] The association of rubidazone (200 mg/m^2 for 4 days) and ARA-C (200 mg/m^2 for 7 days) has been shown to induce CR in 81% of 444 patients under the age of 65.[33] The dose of 100 mg of rubidazone that we used could be considered as the equivalent of 50 mg of daunorubicin.[32] CR and survival rates obtained in our patients treated with this intensive chemotherapy were close to those found in multicenter trials in ANLL patients in the same age.[6,16]

In a randomized trial conducted by the Eastern Cooperative Oncology Group, Kahn et al[17] compared attenuated-dose daunorubicin, ARA-C, and thioguanine (AtDAT) with a standard DAT in patients over 69 years of age. This dose reduction resulted in a reduced early death rate, similar CR rate, and a longer survival. AtDAT yielded 30% of CR, a percentage that is similar to that of LD ARA-C in the present study. However, early deaths were more frequent (25%) and the median survival was approximately 5 months.

The efficacy of LD ARA-C in ANLL treatment is still unclear, since many reports that have been published, usually retrospectively, include patients with heterogenous forms of leukemia or myelodysplastic syndrome. In their comprehensive review of the literature, Cheson et al[34] stated that the CR rate of first intention treatment of acute myelogenous leukemia (AML) with LD ARA-C could be 30%. Two recent reports[35,36] have shown a CR rate of 23%. In these reports, as well as in the present study, no initial characteristics of the disease could be found that predicted the efficacy of LD ARA-C.

Myelosuppression and subsequent risk of infections are the limiting factors of intensive chemotherapy in the elderly. Although patients in the intensive therapy group were otherwise healthy, 31% died during induction phase. Kahn et al[17] observed a percentage of early deaths as high as 60% and a median survival of approximately 1 month in the group treated with full-dose DAT. Myelosuppression induced by this schedule of LD ARA-C appears definitely less severe than that following intensive chemotherapy. This explains the significant reduction of the infections that are the most frequent cause of early deaths during induction chemotherapy.[3,9,13,16,17] This could also explain the decrease in transfusion requirements and in mean hospital stay in the group treated with LD ARA-C. However, most patients became cytopenic and only two patients of 41 included in this series entered CR as outpatients without any transfusions. This proportion is lower than those we have found in previous estimates.[26] As suggested by the prospective study of Powell et al,[36] prolongation of exposure

to LD ARA-C could result in prolonged cytopenia and increased mortality without improvement in CR rate.

It is noteworthy that 22% of the patients treated with LD ARA-C experienced a PR of median duration similar to that of CR. PR duration is difficult to assess precisely, but survival of patients who achieve PR, which was equal to that of patients in CR, is a much more reliable criteria. Using glucose-6-phosphate deshydrogenase isoenzymes[37] or DNA-probes,[38] it has been demonstrated that CRs after intensive therapy were heterogeneous, with, in some cases, persistence and expression of the abnormal clone. These "clonal" remissions, mimicking a preleukemic state, might be more frequent in elderly patients.[37] Although the specific mechanism of action of LD ARA-C, if any, is unknown, it is conceivable that remissions induced by this treatment might be more heterogeneous. Persistence of a clonal chromosomal abnormality during long-lasting clinical CR has been documented.[39] We could only speculate that the PR induced and maintained by LD ARA-C is a relatively stable state, intermediate between CR and overt leukemia.

In conclusion, the absence of a significant difference in survival between both groups may be related to the population size, but it may also be due to the lower number of early deaths, the larger number of patients in PR with a survival equal to that of the patients in CR, and some long-lasting CRs found in the LD ARA-C group.

Based on our experience, we suggest that the treatment of ANLL in the elderly could be improved in two ways: first, by reducing the toxicity of intensive chemotherapy, perhaps with an additional treatment with growth factors, or second, by increasing the efficacy of LD ARA-C through its association with either cytotoxic substances or drugs acting on cellular differentiation.[40]

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