Mitoxantrone Versus Daunorubicin in Induction-Consolidation Chemotherapy—The Value of Low-Dose Cytarabine for Maintenance of Remission, and an Assessment of Prognostic Factors in Acute Myeloid Leukemia in the Elderly: Final Report of the Leukemia Cooperative Group of the European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group Randomized Phase III Study AML-9

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Purpose and Methods: **Optimization of remission-induction and postremission therapy in elderly individuals with acute myeloid leukemia (AML) was the subject of a randomized study in patients older than 60 years. Remission-induction chemotherapy was compared between daunomycin (DNR) 30 mg/m² on days 1, 2, and 3 versus mitoxantrone (MTZ) 8 mg/m² on days 1, 2, and 3, both plus cytarabine (Ara-C) 100 mg/m² on days 1 to 7. Following complete remission (CR), patients received one additional cycle of DNR or MTZ chemotherapy and were then eligible for a second randomization between eight cycles of low-dose (LD)-Ara-C 10 mg/m² subcutaneously every 12 hours for 12 days every 6 weeks or no further treatment.**

Results: **A total of 242 patients was randomized to DNR and 247 to MTZ. Median age of both study groups was 68 years. Secondary AML was documented in 26% and 25% of patients in either arm. The probability of attaining CR was greater (P = .069) with MTZ (47%) than with DNR (38%). Median duration of neutropenia was 19 (DNR) and 22 days (MTZ). The greater response rate to MTZ therapy correlated with reduced occurrence of chemotherapy resistance (32% *v* 47%, P = .001). With a median follow-up of 6 years, 5-year disease-free survival (DFS) is 8% in each arm. Overall survival estimates are not different between the groups (6% *v* 9% at 5 yrs). Poor performance status at diagnosis, high WBC count, older age, secondary AML, and presence of cytogenetic abnormalities all had an adverse impact on survival. Secondary AML and abnormal cytogenetics predicted for shorter duration of CR. Among complete responders, 74 assessable patients were assigned to Ara-C and 73 to no further therapy. Actuarial DFS was significantly longer (P = .006) for Ara-C-treated (13% [SE = 4.0%] at 5 years) versus nontreated patients (7% [SE=3%]), but overall survival was similar (P = .29): 18% (SE = 4.6%) versus 15% (SE = 4.3%). Meta-analysis on the value of Ara-C postremission therapy confirms these results.**

Conclusion: **In previously untreated elderly patients with AML, MTZ induction therapy produces a slightly better CR rate than does a DNR-containing regimen, but it has no significant effect on remission duration and survival. Ara-C in maintenance may prolong DFS, but it did not improve survival.**

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IN RECENT YEARS, there has been an intensified interest in the development of treatment in the elderly with acute myeloid leukemia (AML).[1,2] The outcome of these patients following remission-induction chemotherapy has remained disappointing. While complete remission (CR) rates in middle-aged adults have improved to values of 70% to 80%, response rates in patients of aged ≥ 60 years generally range between 40% and 50%. Overall survival at 2 years following start of treatment is often less than 20%. The results of a palliative wait-and-see approach in patients older than 65 years of age are worse than those of remission-induction chemotherapy.[3] Scarce studies have especially dealt with the question of treatment development in the elderly.[3-9] An important question relates to the choice of drug or the dose applied in remission-induction treatment. Usu-

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ally, a combination of an anthracycline (eg, daunomycin [DNR] or doxorubicin) and cytarabine (Ara-C) has been applied. Variation of the dose of DNR has not brought any significant benefit.[5] In a noncontrolled study, mitoxantrone (MTZ) plus Ara-C yielded promising CR rates of 58%.[6] A phase III study in adults of all ages that compared DNR plus Ara-C versus MTZ plus Ara-C included 99 patients older than 60 years of age.[10] In this cohort of patients, the MTZ chemotherapy regimen was suggested to produce higher CR rates (46% *v* 37%), but the numbers were small and the results were based on a subgroup analysis. Therefore, the question has remained as to whether MTZ would produce greater response rates and also prolonged survival in elderly patients with AML.

Another issue of the therapeutic management of elderly AML concerns the employment of postremission treatment. Should patients of higher age receive additional chemotherapy once a CR has been obtained and, if so, what would be the postremission therapy of choice? The application of repeated cycles of high-dose Ara-C postremission showed efficacy in reducing the recurrence of leukemia and improving survival in a large study of adults, but did not prove successful in elderly patients.[11] Conventional-dose (100 mg/m^2/d), intermediate-dose (400 mg/m^2), and high-dose (3 g/m^2) schedules of Ara-C resulted in approximately equivalent outcome in 60+-year-old patients.[11] High-dose Ara-C was associated with excessive toxicity in the elderly in the latter study. The use of low-dose (LD)-Ara-C (10 mg/m^2/d) has been favored for some time in the treatment of patients with myelodysplastic syndromes and shown to offer active antileukemic therapy.[12-14] It has also been advocated in elderly patients with AML, of whom a significant proportion may have a hidden history of prior myelodysplasia (MDS). LD-Ara-C as post-remission therapy has not been critically evaluated yet.

We report here the results of a phase III study in which MTZ induction therapy was compared with a schedule of DNR. Complete remitters were then eligible for a second randomization and received LD-Ara-C for 12 days for eight cycles as maintenance chemotherapy or no maintenance chemotherapy.

MATERIALS AND METHODS

Study Design and Chemotherapy

In a collaborative phase III study of the European Organization for the Research and Treatment on Cancer-Leukemia Cooperative Group (EORTC-LCG) and the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON), patients ≥ 60 years of age were enrolled and randomized to receive as induction therapy either DNR 30 mg/m^2 by intravenous bolus on days 1, 2, and 3 plus Ara-C 100 mg/m^2 by continuous infusion on days 1 through 7, or MTZ 8 mg/m^2 by intravenous bolus on days 1, 2, and 3 plus Ara-C 100 mg/m^2 by continuous infusion on days 1 through 7 (Fig 1). The choice of these dosages was based on a previous pilot study.[3] In case of a partial response (PR) to the latter induction cycle, patients were planned to receive a second identical course of treatment. Complete responders were to receive one cycle of consolidation therapy that consisted of the same agents, but with 1 day of DNR or MTZ depending on the treatment arm. The objective of the study was to compare DNR and MTZ induction chemotherapy as regards the response rate, and in addition, the duration of survival, disease-free survival (DFS), postchemotherapy cytopenia, frequency of infectious complications, and number of days spent in the hospital during and following induction chemotherapy. Patients after consolidation and continuing in CR were eligible for a second randomization between no further therapy (arm A) and LD-Ara-C chemotherapy (arm B) (Fig 1). Arm B patients received LD-Ara-C at 10 mg/m^2 subcutaneously every 12 hours on days 1 through 12 at 42-day intervals for a total of eight cycles or until relapse. The effects of LD-Ara-C maintenance chemotherapy on DFS and overall survival were evaluated.

Eligibility

Patients ≥ 61 years of age with AML were eligible if they had M0-M7 AML according to the French-American-British (FAB) classification.[15,16] Patients with secondary leukemias following MDS or following chemotherapy for solid tumors or lymphomas more than 1 year before entry onto the study were also eligible. They were not eligible if they had been treated with chemotherapy for AML or MDS. They were also not eligible if they were refractory to platelet transfu-

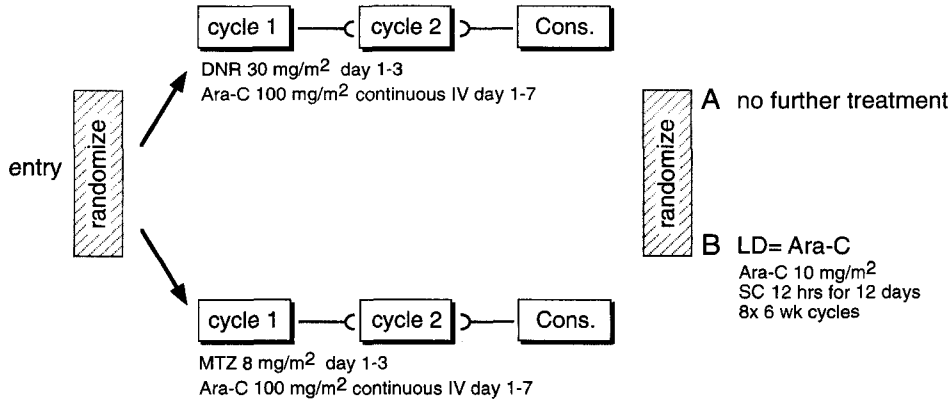

Fig 1. Study scheme.

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sion; had severe hepatic (bilirubin level > three times normal value), pulmonary, or renal disease (serum creatinine concentration > two times normal value or creatinine clearance < 50 mL/min); or had symptomatic heart disease that required therapy.

Criteria of Response and Evaluation of Outcome

CR was defined by a normocellular bone marrow that contained ≤5% blast cells, including monocytoid cells, less than 10% blast cells and promyelocytes, and less than 50% erythroid cells, no evidence of extramedullary leukemia, and recovery of peripheral-blood values to platelet counts of at least 100×10^9/L and neutrophils of at least 1.5×10^9/L. PR was defined by bone marrow smears that contained between 5.1% and 25% blasts and less than 5% circulating blast cells. Failure to respond was classified as treatment resistance when there was no reduction of the leukemic cell infiltration in the marrow or a reduction that would not meet the criteria for a PR or CR. Hypoplasia followed by leukemic regrowth was also classified as treatment failure. Regeneration failure was defined as a prolonged hypoplasia of ≥8 weeks without evidence of medullary leukemia. Early death was defined as death before the completion of the induction cycle of therapy, and hypoplastic death as death during the 4- to 5-week recovery interval after the completion of chemotherapy. Survival duration and DFS were important parameters of evaluation (defined later). Frequencies of excessive toxicities, numbers of nights spent in hospital, frequencies of hemorrhages and infections, number of days to hematopoietic recovery, and duration of fever were evaluated separately. Standard cytogenetic techniques, including direct preparations, incubation of cultures for 24 or 48 hours, and banding techniques, were used at diagnosis to karyotype the leukemia.[17] Normal (NN) cytogenetics (this category included the deletion of the Y chromosome), abnormal cytogenetics (AA), and a mosaicism of abnormal and normal karyotypes (AN) were recorded. Deletions of the long arm of chromosomes 5 and 7 (5q-, 7q-) or the entire chromosomes (-5, -7), and abn 11q23, as well as +8 abnormalities, were regarded as poor-risk abnormalities, whereas inv16(p13q22), t(16;16)(p13q22), t(15;17)(q22;q21), and t(8;21) (q22;q22) were considered as good-risk features. Karyotypic abnormalities that involved three or more chromosomes but without any of the aforementioned specific poor-risk or good-risk aberrations were classified as complex anomalies.[18-20]

Statistical Analysis

The relationship between the initial categorized ordered variables (WBC count, age, and performance status) and the CR rate after induction was statistically tested using the χ^2 test for linear trend.[21] For unordered variables, the usual χ^2 test, with correction for continuity, was used. The relationship between treatment randomized and response (CR, resistance, or death during induction or during the hypoplastic phase) was tested using Fisher's exact test. The 95% confidence interval (CI) of the treatment difference was computed using the Confidence Interval Analysis (CIA) program.[22]

Overall survival was calculated from the date of randomization until the date of death, whatever the reason. DFS was calculated from the date of first CR achieved after the induction course(s), until the date of first relapse or date of death without confirmed relapse. For patients randomized for the second question (Ara-C *v* no Ara-C), the starting point for these analyses was the date of second randomization.

Actuarial curves were computed according to the Kaplan-Meier technique.[21] The standard error was calculated according to the Greenwood formula.[21] The log-rank test was used to perform the treatment comparison.[21] The prognostic importance of different variables was assessed using the log-rank test (for binary variables) or the log-rank test for linear trend[21] (for ordered variables). The relative risk (RR) of having an event per time unit in the MTZ treatment group versus DNR group, along with its 95% CI, was computed using the odds ratio technique.[22] The intention-to-treat principle was applied in the statistical analyses.

The aim of the trial was to detect a difference in the CR rate from 40% to 55% (using the usual χ^2 test, $\alpha = 0.05$, $\beta = 0.10$) between the two induction arms. The assumption was that such a difference in the CR rate, if it truly existed, would lead to a difference in the survival at 3 years from 10% to 20%. Therefore, it was planned to enter 488 patients, to evaluate their remission status after the induction course, and to monitor them until relapse and death. The final analysis was planned to be performed once 425 deaths had been reported within 3 years from randomization (log-rank test, $\alpha = 0.05$, $\beta = 0.10$).

To detect a 15% difference (10% *v* 25%) in DFS rates at 3 years between the two maintenance groups (LD-Ara-C *v* no Ara-C), a total of 208 patients was required to be randomized. The final analysis was planned once 171 events (relapses/deaths) had been reported (log-rank test, $\alpha = 0.05$, $\beta = 0.10$). As an insufficient number of patients were randomized to address this question in the AML-9 trial (147 in total), 86 additional patients were randomized in the subsequent EORTC-HOVON AML-11 trial in the elderly.[23] Randomization was performed centrally at the EORTC Data Center, based on the minimization technique, with the stratification factors being patient age (60 to 70, 71 to 80, or >80 years) and treating center. For the second randomization, LD-Ara-C versus no maintenance, first treatment allocated by randomization and treating center were used as stratification factors.

RESULTS

A total of 539 patients were registered between April 1986 and November 1993, of whom 270 individuals were randomized to induction therapy with DNR and 269 to treatment with MTZ. Of these, four patients were considered to be nonassessable because of incomplete data (n = 3), and in one case, the dose of Ara-C administered was 10 times greater than the protocol dose. Forty-six subjects were ineligible, of whom 26 had been assigned to DNR and 20 to MTZ treatment. Reasons for ineligibility were incomplete data (n = 18), incorrect or inadequate diagnosis (n = 18), insufficient organ function (n = 8), and exclusions (n = 2) because of chemotherapy for AML or chemotherapy for breast cancer during the year before registration. The clinical and hematologic characteristics are listed in Table 1 for the 242 patients randomized to DNR treatment and the 247 to MTZ treatment who could be evaluated, The median age of the study population was 68 years (range, 60 to 88), of whom only 5% were ≥ 80 years. Less than 10% of patients enrolled had a performance status that kept them in bed for more than 50% of the time.

Response to Remission-Induction Chemotherapy

CR probabilities were 46.6% for patients on MTZ treatment and 38.0% for patients on DNR ($P = .067$) (Table 2). Interestingly, MTZ-treated patients showed a reduced probability of primary resistance to chemotherapy (47% *v* 32%,

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Table 1. Characteristics of Patients by Treatment Arm

	% of Patients	
	DNR (n = 242)	MTZ (n = 247)
Sex, male	53	59
Age, years		
61-69	61	61
70-79	34	35
80-88	5	4
WHO performance status		
Normal	20	18
Ambulatory	52	49
In bed < 50% of time	22	22
In bed > 50% of time	5	10
Entirely disabled	1	1
WBC count ($\times 10^9$/L)		
< 25	59	63
25-99	27	22
≥ 100	14	15
FAB cytology		
M0	0.4	—
M1	18	23
M2	38	36
M3	5	3
M4	14	16
M5	21	19
M6	2	1
M7	1	1
Antecedent history (secondary AML)		
Prior MDS	19	17
Prior hematologic disease or chemotherapy	7	8
Cytogenetics*		
Normal	31	39
t(8;21)	4	2
t(15;17)	1	1
inv/dic(16)	3	0
−5, 5q-	12	12
−7, 7q-	9	7
abn 11q23	2	1
+8	8	14
Complex	4	2
Other abnormalities	26	22

Abbreviation: WHO, World Health Organization.

*Adequate cytogenetic examination was performed in 47.5% of patients (n = 115) assigned to the DNR arm and 38.5% (n = 95) of the MTZ arm. Percentage distributions of specific cytogenetic karyotypes are expressed relative to the subgroup of patients (set at 100%) in whom adequate and assessable chromosome analysis was performed.

$P = .001$) in the context of a slightly greater death rate (21% *v* 15%) (Table 2).

Prognostic Factors for Response to Remission-Induction Chemotherapy

Table 3 lists the factors at diagnosis that showed prognostic value for CR. Age ≥ 80 years, a progressively worse performance status, and high WBC count (>25 × 10^9/L) all predicted for a reduced CR probability. The unfavorable effect of age was associated with a reduced responsiveness of the leukemia to chemotherapy (ie, resistance). In contrast, poor performance status and (hyper)leukocytosis correlated with a greater death rate (Table 4). Secondary leukemia predicted for a greater probability of resistance to chemotherapy (Table 4). Sex of the patient or FAB subtype of AML

Table 2. Response to Induction Chemotherapy

	DNR (n = 242)		MTZ (n = 247)		Difference Between		
Response	No.	%	No.	%	Groups (%)	95% CI	P‡
CR	92	38.0	115	46.6	8.6	−0.2-17.3	.067
Resistance*	114	47.1	80	32.4	−14.7	−23.3-−6.1	.001
Death†	36	14.9	52	21.1	6.2	−0.6-13.0	.079

NOTE. 15 patients who did not receive any chemotherapy following randomization because of early deteriorating condition (3 on DNR arm and 6 on MTZ arm) or subsequent refusal (one on DNR and 5 on MTZ) are included in the analysis based on the intention-to-treat principle.

*Includes absolute resistance, PR (8% and 7%), and transient hypoplasia followed by leukemic regrowth.

†Includes early death during chemotherapy (6% on both arms) and postinduction death (9% and 15%).

‡Fisher's exact test.

Table 3. Analysis of Prognostic Factors for Response to Induction Chemotherapy

Factor	No. of Patients	%CRs	P
Sex			
Male	274	45	.31*
Female	215	40	
Age, years			
60-69	300	44	
70-79	167	43	.074†
80-88	22	14	
WHO performance status			
Normal	94	46	
Ambulatory	247	46	
In bed < 50% of time	107	36	.014†
In bed > 50% of time	36	28	
Entirely disabled	5	20	
WBC count ($\times 10^9$/L)			
< 25	299	48	
25-99	120	32	.006†
≥ 100	70	36	
Antecedent history			
No	365	44	.21*
Secondary leukemia or prior MDS	124	37	
Cytology–FAB type			
M0/M1	101	45	
M2	181	45	
M3	19	32	.4*
M4	74	38	
M5	100	40	
M6/M7	11	55	
Cytogenetics			
NN	73	53	.057*
AN-NN	137	39	

P values according to the *χ^2 test or †χ^2 test for linear trend.

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Table 4. Prognostic Factors for Drug Resistance or Death Following Induction Chemotherapy

Factor	Treatment Resistance %	Treatment Resistance P	Death %	Death P
Age, years				
< 70	39		17	
70-79	38	.02*	19	.89*
≥ 80	68	.14†	18	.68†
WHO performance status				
Normal	49		5	
Ambulatory	40		14	
In bed < 50% of time	36	.12*	28	< .00001*
In bed > 50% of time	25	.01†	47	< .00001†
Entirely disabled	40		40	
WBC count ($\times 10^9$/L)				
< 25	37		14	
25-99	48	.07*	20	.007*
≥ 100	34	.72†	30	.002†
Secondary AML				
No	37		19	
Yes	48	.03*	15	.45*

NOTE. *P* values according to the *χ^2 test or †χ^2 test for linear trend.

showed no predictive value for induction response, nor did cytogenetics. However, of 489 patients, adequate cytogenetic examination was performed in only 210 (43%). Among these, only 12 patients showed the favorable karyotypes t(8;21) or abn16(q22) or t(15;17), 42 had deletions of chromosomes 5 or 7 (-5,5q-,-7,7q-), 25 presented with 11q23 or +8 abnormalities, and seven other patients showed complex chromosomal abnormalities. Because of the limited numbers of the specific cytogenetic subgroups, most of the subsequent analyses are based on the comparison of normal (NN) versus abnormal (AN and AA) cytogenetics.

Toxicities Associated With MTZ Versus DNR Remission-Induction Therapy

Since the great majority of patients (n = 489) received induction cycle no. 1 and only 73 patients received cycle no. 2, the toxicities of DNR and MTZ chemotherapy were directly compared after the first chemotherapy cycle. There were no significant differences between the two treatment groups as regards the frequencies of mild, gross, or debilitating hemorrhages (mean, 6% of cases); serious infections (mean, 22%); liver function abnormalities (bilirubin level > 2.5 times normal; mean, 13%); renal toxicity (serum creatinine concentration > 2.5 times normal; mean, 4%); vomiting and nausea, and severe intractable diarrhea (mean, 2%); or severe oral toxicity that required liquid food intake or parenteral nutrition (mean, 2%). The incidence of severe infections among patients randomized to MTZ treatment exceeded that in patients on DNR therapy: 25.1% versus 18.6% (P = .036). The duration of aplasia for patients who achieved a CR was slightly longer (P = .06) for patients randomized to the MTZ arm (median, 22 days) than for those on the DNR arm (median, 19 days). Patients treated on either arm had fever for a median of 6 days (P = .10). The median number of days spent in the hospital was 31 days in both the MTZ and DNR treatment groups (P = .71).

Survival and DFS

The median follow-up duration at the time of statistical analysis was 6 years. The duration of survival was similar (P = .23) in the two treatment groups (Fig 2), the RR of the death rate per time unit of MTZ group versus DNR group was 0.893 (95% CI, 0.742 to 1.076). Median survival estimates were 36 weeks (DNR) and 39 weeks (MTZ). The percentages of patients still alive at 5 years were 6% and 9%, respectively. For patients who achieved CR after induction, the DFS probabilities between the treatment arms were not different (Fig 3). The median DFS estimates were 39 weeks in both groups. The DFS rate at 5 years was 8%. A total of 174 patients (77 *v* 97) relapsed and 15 patients died without relapse (seven *v* eight). The causes of death of the latter patients in continuous CR were infection (n = 4), cardiac arrest and myocardial infarction (n = 2), hemorrhage (n = 3), and other or unknown cause (n = 6). The duration of survival from CR was slightly longer (P = .29) in the MTZ arm. Median survival estimates for complete responders were 74 weeks (MTZ) versus 55 weeks (DNR), survival estimates at 5 years were 12% versus 16%, and the RR was 0.85 (95% CI, 0.633 to 1.149).

The following initial factors appeared to relate to a shorter duration of survival from start of treatment (Fig 4): older age (P = .01), poor performance status (P < .001), high WBC count (P < .001), secondary AML (P = .02) (data not shown), and the presence of cytogenetic abnormalities (P = .002). Interestingly, not only patients with a complete or partial deletion of chromosomes 5 and 7 and complex chromosome abnormalities had a poor prognosis, but also 12

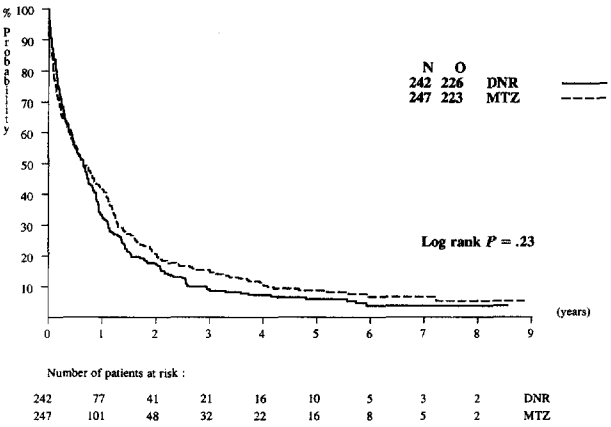

Fig 2. Duration of survival according to induction treatment: DNR versus MTZ.

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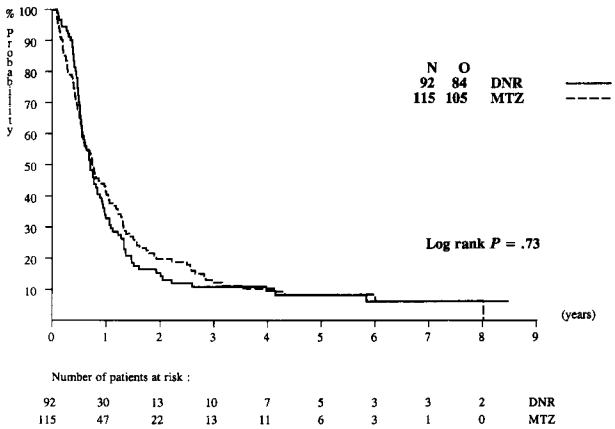

Fig 3. DFS from CR according to treatment: DNR versus MTZ.

patients who presented with good-risk cytogenetic features. The Cox proportional hazards model showed that initial performance status ($P < .0001$) and WBC count ($P = .003$) were the two most important independent prognostic factors. Secondary AML and abnormal cytogenetics predicted for shorter duration of remission. The ability to attain CR after one versus two cycles of induction, or initial leukocytosis, had no predictive value for DFS.

LD-Ara-C Versus No Maintenance Chemotherapy

Of the complete responders, 76 patients were randomized to no further therapy (no Ara-C), and 75 patients to eight cycles of LD-Ara-C. Four patients were ineligible because of no CR at the time of second randomization, so that 73 (no Ara-C) and 74 (LD-Ara-C) patients could be evaluated. Comparative DFS and overall survival are plotted in Fig 5, which shows an advantage of DFS for patients assigned to LD-Ara-C maintenance therapy. The RR estimate was 0.61 (95% CI, 0.43 to 0.87). The median DFS duration following the second randomization was 29 weeks for no-Ara-C and 51 weeks for LD-Ara-C treatment. At 3 years, DFS was estimated at 7% (SE = 3.0%) for no maintenance and 20% (SE = 4.7%) for LD-Ara-C treatment; at 5 years, DFS was estimated at 7% (SE = 3.0%) and 13% (SE = 4.0%), respectively ($P = .006$). Four patients died without relapse: zero (no Ara-C) versus four (LD-Ara-C). The median overall survival estimates were 62 weeks (LD-Ara-C) versus 79 weeks (no Ara-C). The RR was estimated at 0.83 (95% CI, 0.58 to 1.18) for

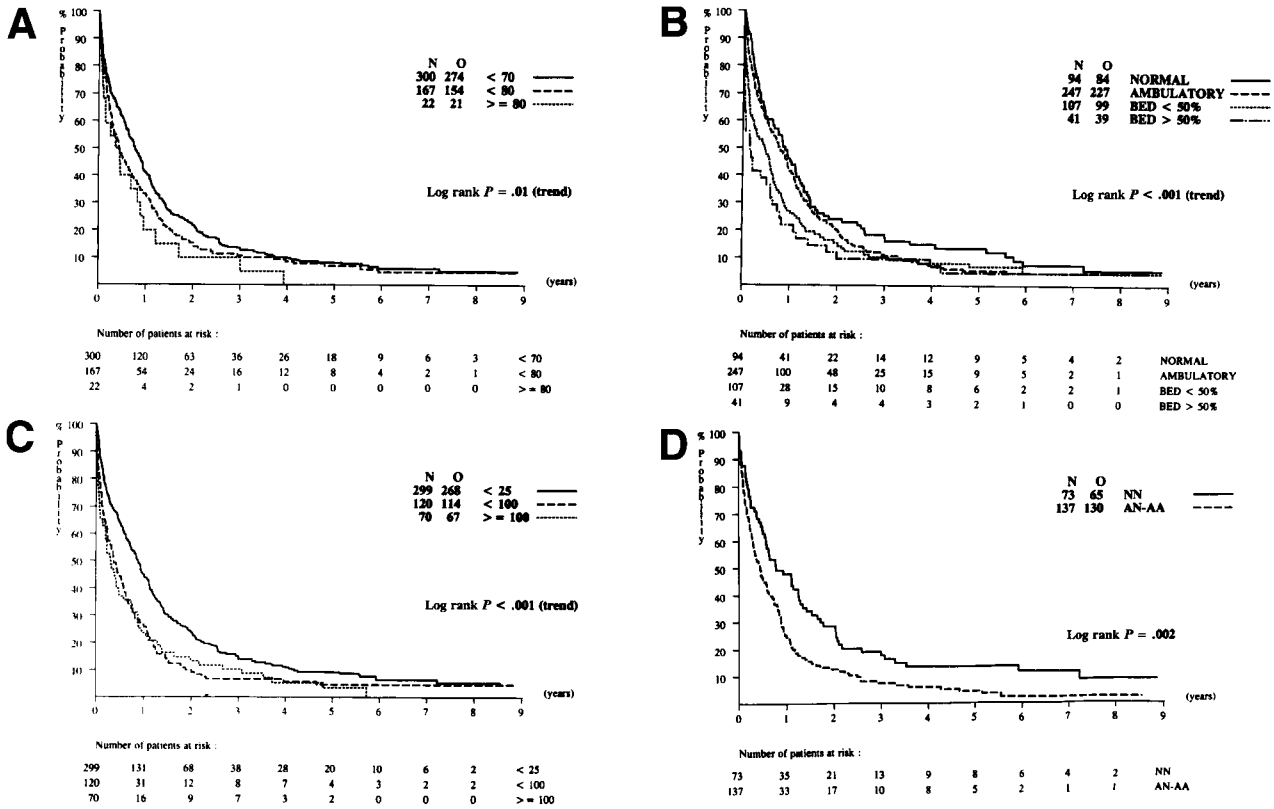

Fig 4. Duration of survival according to age (A), performance status (B), WBC count (C), and cytogenetic abnormalities (D).

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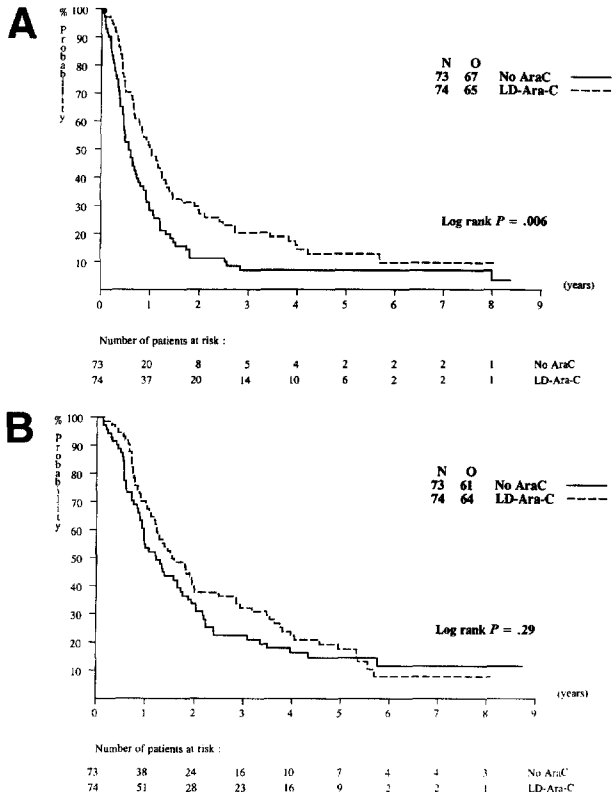

Fig 5. Outcome according to treatment: no maintenance treatment (no Ara-C) versus LD-Ara-C. (A) DFS and (B) overall survival.

LD-Ara-C therapy. Overall survival probabilities at 5 years were 18% (SE = 4.6%) in with LD-Ara-C and 15% (SE = 4.3%) for no-Ara-C maintenance treatment ($P = .29$).

DISCUSSION

We present the results in 489 assessable patients of a prospective randomized study that specifically deals with treatment development in the elderly with AML. The results of this study indicate that specific changes in the choice of induction chemotherapy may affect the effect of treatment in aged patients. They also show that LD-Ara-C maintenance may modify DFS. The dependence of elderly patients on the dose and the choice of the type of chemotherapeutic agents in remission-induction therapy may differ from those in younger adults with AML. In one study of patients ≥ 60 years of age, DNR at a 30-mg/m^2 dose (combined with cytarabine) produced higher response rates than a regimen with DNR 45 mg/m^2 or doxorubicin 30 mg/m^2.[24] In contrast, in patients younger than 60 years, the 45-mg/m^2 DNR dose gave the best response results. In another study, DNR 50 mg/m^2 on day 1 only and DNR 60 mg/m^2 on days 1 to 3 produced differences, but the numbers of patients enrolled in the latter study were small.[5] MTZ has been evaluated in a single-institution study, but induction with MTZ did not result in a greater likelihood of response.[6] A second study in adults with AML that included a considerable number of elderly patients had suggested better response probabilities in case of MTZ induction therapy.[10] The results of the study reported here indicate a slightly improved CR rate following MTZ-based chemotherapy in comparison to DNR treatment, probably due to a better antileukemic effect. The trial was based on a comparatively large number of patients, the patient characteristics in the treatment arms were extremely well balanced, and the analysis showed an improvement of response of approximately 10% (from 38% to 47%). Optimization of induction therapy specific for elderly patients appears of considerable clinical relevance, since more than 50% of all newly diagnosed patients with AML are over 60 years of age. From the results of this study, it is also clear that certain subgroups of patients are notoriously difficult to induce into remission. Poor performance status at diagnosis, high WBC count, and high age were all predictors of poor response. A poor performance condition and high cell counts mainly predicted for toxic deaths and high age and secondary leukemias mainly for resistance to therapy. In a prospective study of 104 patients,[6] secondary leukemia and high blast counts were shown to be unfavorable predictors for response, and in a retrospective study,[25] high age and poor performance status predicted remission failure. In our study, patients ≥ 80 years of age had a probability of attaining a CR of ≤20%, and patients with a World Health Organization (WHO) performance score ≥ 3 had a CR rate of less than 30%. On the other hand, patients with hyperleukocytosis and poor performance status showed greater frequencies of toxic deaths and appeared more prone to early disease-related or treatment-induced complications. Patients with secondary leukemia presented more frequently with treatment refractory disease (Table 4). This was evident both from the failure analysis of induction treatment and also the inferior DFS results. Although the MTZ chemotherapy schedule provided for better response rates, overall survival and DFS probabilities did not improve. Why this effect did not translate into a survival advantage remains unclear. One possible explanation is that the quality of postremission treatment, which is critical for maintaining the remission attained after induction therapy, was inadequate.

A second question addressed in the study was concerned with evaluating eight cycles of LD-Ara-C chemotherapy as postremission therapy. At the time of initiation of the study,

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LD-Ara-C therapy was considered an attractive treatment strategy in the elderly, because it had shown activity in patients with MDS.[12-14] In fact, there may be a considerable proportion of cases with an occult history of MDS among elderly patients with AML. Further, it is of note that high-dose Ara-C schedules, while showing improved activity in middle-aged adults with AML, have failed to produce better outcome in patients ≥ 60 years.[11] An attractive feature of subcutaneous LD-Ara-C therapy is that it can be applied to elderly individuals with limited toxicity and in an outpatient context. The results of the study reported here indicate better DFS for patients randomized to the Ara-C schedule as compared with the group with no postremission therapy. The DFS rate at 3 years of patients on Ara-C maintenance therapy was almost threefold that of patients without Ara-C therapy (20% *v* 7%; $P = .006$). The advantage of LD-Ara-C therapy as regards DFS was expressed and maintained throughout an interval of 5 years at least, even though the LD-Ara-C had been applied during 1 year only. In this respect, it is of note that the improved DFS in LD-Ara-C patients in this study was obtained with induction therapy that included a relatively moderate dose of 100 mg/m^2 Ara-C. It is conceivable that the quantitative impact of LD-Ara-C 10 mg/m^2 applied postremission for preventing recurrence of AML may depend on the dosages of Ara-C used in induction treatment and, for instance, the effect of LD-Ara-C might be less apparent with more intensive Ara-C induction schedules. In the subsequent elderly AML study (EORTC-HOVON AML-11) conducted by our group,[23] Ara-C in induction was applied at 200 mg/m^2 (instead of 100 mg/m^2 for 7 days). However, in the latter study, LD-Ara-C randomized according to exactly the same schedule postremission had a moderate effect on remission duration and no effect on survival.[23] We performed a small meta-analysis of these two EORTC-HOVON studies (AML-9 and AML-11). The meta-analysis provides an indication for a positive effect of LD-Ara-C maintenance on DFS, but not on overall survival (Table 5).

Still, little is known about the prognostic value of distinct clinical and hematologic determinants, especially with respect to outcome of AML in the elderly. This study in a large series of previously untreated patients with AML of higher age has matured to reach a median follow-up duration of 6 years and, therefore, permits an analysis of prognostic factors for survival, DFS, and relapse-free interval. High WBC count, poor performance status, and, to a lesser extent, older age, prior hematologic or oncologic disease (secondary AML), and presence of cytogenetic abnormalities, all independently predicted for poor survival. Although cytogenetic data were available in less than 50% of patients and therefore the analysis of specific cytogenetic features had a limited power, the presence of cytogenetic abnormalities (AA and AN) was indicative of an inferior survival prospect. Secondary AML and abnormal cytogenetics particularly correlated with a higher rate of recurrence. Similarly, in a comparatively small single-center study of 104 patients only, a poor performance status (WHO grades 3 or 4), circulating blasts ≥ 0.2 × 10^9/L, and unfavorable cytogenetics were associated with adverse survival.[6] In another single-center study of retrospective design, poor performance status and high age were associated with shorter survival.[25]

We conclude that a combination of MTZ plus Ara-C might enhance the CR rate in elderly patients with AML. In addition, sequential cycles of LD-Ara-C at 10 mg/m^2 show clinically significant antileukemic activity when applied as postremission therapy, especially following an induction schedule that includes 7 days of 100 mg/m^2 Ara-C.

Table 5. Meta-Analysis of the Effect of LD-Ara-C on DFS and Overall Survival in Elderly Patients With AML: Results From EORTC-HOVON AML-9 and AML-11 Studies

		Comparison for DFS					Comparison for Overall Survival				
		O					O				
Study	No. of Patients	No.	%	RR	95% CI	P*	No.	%	RR	95% CI	P*
AML-9											
No-Ara-C	73	67	92				61	84			
Ara-C	74	65	88	0.607	0.426-0.864	.006	64	86	0.827	0.580-1.178	.293
AML-11											
No-Ara-C	44	35	80				29	66			
Ara-C	42	32	76	0.830	0.513-1.344	.448	27	64	1.153	0.677-1.962	.600
Stratified by study											
No-Ara-C	117	102	87				90	77			
Ara-C	116	97	84	0.677	0.509-0.900	.007	91	78	0.912	0.682-1.230	.558

Abbreviations: O, observed number of events (relapse or death for DFS, death for survival); RR, relative risk.
*(Stratified) log-rank test.

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APPENDIX

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REFERENCES

1. Löwenberg B: Treatment of the elderly patient with acute myeloid leukemia, in Löwenberg B (ed): Acute Myelogenous Leukemia and Myelodysplasia (vol 9). London, United Kingdom, Saunders, 1996, pp 147-159

2. Liu Yin JA: Acute myeloid leukaemia in the elderly: Biology and treatment. Br J Haematol 83:1-6, 1993

3. Löwenberg B, Zittoun R, Kerkhofs H, et al: On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: A randomized phase III study of the EORTC Leukemia Group. J Clin Oncol 1:1268-1274, 1989

4. Keating MJ, McCredie KB, Benjamin RS, et al: Treatment of patients over 50 years of age with acute myelogenous leukemia with a combination of rubidizone and cytosine arabinoside, vincristine and prednisone (ROAP). Blood 58:584-590, 1981

5. Kahn SB, Begg CB, Mazza JJ, et al: Full dose versus attenuated dose daunomycin, cytosine arabinoside and 6-thio-guanine in the treatment of acute nonlymphocytic leukemia in the elderly. J Clin Oncol 2:865-870, 1984

6. Liu Yin JA, Johnson PRE, Davies JM, et al: Mitozantrone and cytosine arabinoside as first-line therapy in elderly patients with acute myeloid leukemia. Br J Haematol 79:415-420, 1991

7. Stone RM, Berg DT, George SL, et al: Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. N Engl J Med 332:1671-1677, 1995

8. Dombret H, Chastang C, Fenaux P, et al: A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. N Engl J Med 332:1678-1683, 1995

9. Rowe JM, Andersen JW, Mazza JJ, et al: A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (>55 to 70 years of age) with acute myelogenous leukemia: A study of the Eastern Cooperative Oncology Group (E 1490). Blood 86:457-462, 1995

10. Arlin Z, Case DC, Moore J, et al: Randomised multicenter trial of cytosine arabinoside with mitoxantrone or daunorubicin in previously untreated adult patients with acute nonlymphocytic leukemia (ANLL). Leukemia 4:177-183, 1990

11. Mayer RJ, Davis RB, Schiffer CA, et al: Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 331:896-903, 1994

12. Housset M, Daniel MT, Degos L: Small doses of Ara-C in the treatment of acute myeloid leukemia: Differentiation of myeloid leukemia cells. Br J Haematol 51:125-129, 1982

13. Winter JN, Variakojis D, Gaynor ER, et al: Low dose cytosine arabinoside therapy in the myelodysplastic syndromes and acute leukemia. Cancer 56:443-449, 1985

14. Baccarini M, Zaccaria A, Bandini G, et al: Low dose arabinosyl cytosine for treatment of myelodysplastic syndromes and subacute myeloid leukemia. Leuk Res 7:539-545, 1983

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15. Bennett JM, Catovsky D, Daniel MT, et al: Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British group. Ann Intern Med 103:620-625, 1985

16. Bennett JM, Catovsky D, Daniel MT, et al: Proposal for the recognition of minimally differentiated acute myeloid leukemia (AML-M0). Br J Haematol 78:325-329, 1991

17. Mitelman F (ed): Guidelines for Cancer Cytogenetics, Supplement to An International System for Human Cytogenetic Nomenclature. Basel, Switzerland, Karger, 1991

18. Keating MJ, Smith TL, Kantarjian H, et al: Cytogenetic pattern in acute myelogenous leukemia: A major reproducible determinant of outcome. Leukemia 2:403-412, 1988

19. Schiffer CA, Lee EJ, Tomiyasu T, et al: Prognostic impact of cytogenetic abnormalities in patients with de novo acute nonlymphocytic leukemia. Blood 73:263-270, 1989

20. Dastugue N, Payen C, Lafage-Pochitaloff M, et al: Prognostic significance of karyotype in de novo adult acute myeloid leukemia. Leukemia 9:1491-1498, 1995

21. Buyse ME, Staquet MJ, Sylvester RJ (eds): Cancer Clinical Trials: Methods and Practice. Oxford, UK, Oxford University Press, 1992

22. Gardner MJ, Altman DG (eds): Statistics with confidence—Confidence intervals and statistical guidelines. Br Med J 1989

23. Löwenberg B, Suciu S, Archimbaud E, et al: Use of recombinant granulocyte-macrophage colony-stimulating-factor (GM-CSF) during and after remission induction chemotherapy in patients aged 61 years and older with acute myeloid leukemia: Final report of AML-11, a phase III randomized study of the Leukemia Cooperative Group of the European Organization for the Research and Treatment of Cancer (EORTC-LC6) and the Dutch-Belgium Hemato-Oncology Cooperative Group (HOVON). Blood 90:2952-2961, 1997

24. Yates J, Glidewell O, Wiernik P, et al: Cytosine arabinoside with daunomycin or Adriamycin for therapy of acute myelocytic leukemia: A CALGB study. Blood 60:454-463, 1982

25. Baudard M, Marie JP, Cadiou M, et al: Acute myelogenous leukaemia in the elderly: Retrospective study of 235 consecutive patients. Br J Haematol 86:82-91, 1994

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