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High-Dose Daunorubicin in Older Patients with Acute Myeloid Leukemia

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ABSTRACT

BACKGROUND

A complete remission is essential for prolonging survival in patients with acute myeloid leukemia (AML). Daunorubicin is a cornerstone of the induction regimen, but the optimal dose is unknown. In older patients, it is usual to give daunorubicin at a dose of 45 to 50 mg per square meter of body-surface area.

METHODS

Patients in whom AML or high-risk refractory anemia had been newly diagnosed and who were 60 to 83 years of age (median, 67) were randomly assigned to receive cytarabine, at a dose of 200 mg per square meter by continuous infusion for 7 days, plus daunorubicin for 3 days, either at the conventional dose of 45 mg per square meter (411 patients) or at an escalated dose of 90 mg per square meter (402 patients); this treatment was followed by a second cycle of cytarabine at a dose of 1000 mg per square meter for 6 days. The primary end point was event-free survival.

RESULTS

The complete remission rates were 64% in the group that received the escalated dose of daunorubicin and 54% in the group that received the conventional dose ($P=0.002$); the rates of remission after the first cycle of induction treatment were 52% and 35%, respectively ($P<0.001$). There was no significant difference between the two groups in the incidence of hematologic toxic effects, 30-day mortality (11% and 12% in the two groups, respectively), or the incidence of moderate, severe, or life-threatening adverse events ($P=0.08$). Survival end points in the two groups did not differ significantly overall, but patients in the escalated-treatment group who were 60 to 65 years of age, as compared with the patients in the same age group who received the conventional dose, had higher rates of complete remission (73% vs. 51%), event-free survival (29% vs. 14%), and overall survival (38% vs. 23%).

CONCLUSIONS

In patients with AML who are older than 60 years of age, escalation of the dose of daunorubicin to twice the conventional dose, with the entire dose administered in the first induction cycle, effects a more rapid response and a higher response rate than does the conventional dose, without additional toxic effects. (Current Controlled Trials number, ISRCTN77039377; and Netherlands National Trial Register number, NTR212.)

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Most patients with acute myeloid leukemia (AML) are 60 years of age or older, and in this age group, the outcome of treatment is unfavorable. Among these older patients, a combination of daunorubicin plus cytarabine induces a complete remission in 40 to 50% of cases. It is standard practice to treat patients with daunorubicin at doses of 45 to 50 mg per square meter of body-surface area for 3 days, plus cytarabine at a dose of 100 to 200 mg per square meter for 7 to 10 days.[1-11] However, the optimal dose of daunorubicin is unknown.

Maximizing the rate of complete remission among patients with AML is a prerequisite for improving survival and quality of life,[12-14] but maintaining the remission is equally important. We investigated whether an escalation of the dose of daunorubicin is feasible and beneficial in patients 60 years of age or older who have AML or high-risk refractory anemia. We compared the conventional dose of daunorubicin (45 mg per square meter for 3 days) with an escalated dose of 90 mg per square meter for 3 days (each given in combination with cytarabine) in the first induction cycle of the treatment of AML.

Methods

Study Design and Chemotherapy

Previously untreated patients, 60 years of age or older, with a cytologically confirmed diagnosis of AML and at least 20% myeloblasts in the bone marrow or with refractory anemia with excess blasts and an international prognostic score[15] of 1.5 or higher (on a scale of 0 to 3.0, with higher scores indicating a poorer prognosis) and a World Health Organization (WHO) performance status score of 2 or less (on a scale of 0 to 5, with lower numbers indicating better performance status) were eligible for inclusion in the study. The exclusion criteria can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Eligible patients were randomly assigned to receive daunorubicin at a dose of 45 mg per square meter (conventional-dose group) or at a dose of 90 mg per square meter (escalated-dose group) — both administered intravenously over the course of 3 hours on days 1 to 3 of the first cycle of induction treatment — plus cytarabine at a dose of 200 mg per square meter, administered by continuous infusion for 7 days. In the second cycle of treatment, both groups received cytarabine at a dose of 1000 mg per square meter, given intravenously over the course of 6 hours on days 1 through 6. Patients who were in complete remission after the second cycle and who had an HLA-matched donor could undergo allogeneic stem-cell transplantation. Alternatively, they could be randomly assigned to receive either three cycles of treatment with gemtuzumab ozogamicin at a dose of 6.0 mg per square meter or no further maintenance treatment.

The study was designed by the Leukemia Working Group of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group, the data were gathered at the data center of HOVON, and the statisticians in that group conducted the analysis. The study was approved by the ethics committee at each participating institution and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Risk Classification and Clinical Characteristics

Patients were classified into prognostic categories on the basis of the karyotype of the leukemic cells (for details, see the Supplementary Appendix). Favorable risk was defined by the presence of abnormalities in core-binding factors; very unfavorable risk, by the presence of a monosomal karyotype[16]; and unfavorable risk, by the presence of complex cytogenetic abnormalities (at least three unrelated cytogenetic abnormalities), monosomies or partial deletions of chromosome 5 or 7 (del(5q), del(7q), -5, -7), abnormalities of the long arm of chromosome 3 (q21;q26), t(6;9)(p23;q34), t(9;22)(q34;q11.2), or abnormalities involving the long arm of chromosome 11 (11q23)[17] unless the criteria for a monosomal karyotype were fulfilled. Any other cytogenetic abnormalities, as well as AML without cytogenetic abnormalities or with loss of an X or Y chromosome as the only abnormality, were considered to indicate an intermediate risk. Leukemia that developed after chemotherapy or radiation therapy or after a myelodysplastic syndrome was classified as secondary AML. Hepatomegaly and splenomegaly as assessed on physical examination, WHO performance status, extramedullary disease, and white-cell count were recorded at the time of diagnosis (Table 1).

CRITERIA FOR RESPONSE AND END POINTS

The definitions of complete response, disease-free survival, and relapse have been described previously.[11] Event-free survival refers to the interval from randomization to the date of the evaluation of response after the last induction cycle if complete remission had not been achieved by that time, the date of death, or the date of relapse. Overall survival was measured from randomization. Early death refers to death within 30 days after randomization. Time to hematopoietic recovery was measured from the first day of chemotherapy to the time when the neutrophil count reached 0.5×10^9 per liter and the platelet count reached 50×10^9 per liter.

STATISTICAL ANALYSIS

Event-free survival was the primary end point. Randomized assignments to study groups were balanced with the use of a biased-coin minimization procedure, with the bias dependent on the average imbalance between the numbers of patients already assigned to each group overall, within the participating hospital and within the diagnostic subgroup (AML or refractory anemia) of the new patient. The expected complete-remission rate in the conventional-treatment group was 45% and the expected 1-year rate of event-free survival in that group was 22%. With enrollment of 800 patients and an additional follow-up of 1 year after enrollment of the last patient before the final analysis was performed, we estimated that for the analysis of event-free survival, the number of events would be 765, and the study would have 87% power to show an improvement in event-free survival in the escalated-dose group corresponding to a hazard ratio of 0.80 (an increase in the 1-year event-free survival rate from 22% to 30%), at a two-sided significance level of 5% with the use of a log-rank test. All analyses were performed according to the intention-to-treat principle, irrespective of patients' compliance with the protocol, but 15 patients who were ineligible were excluded (6 in the conventional-treatment group and 9 in the escalated-dose group). The reasons for ineligibility included a diagnosis of acute promyelocytic leukemia (six patients), previously treated AML (one), no AML (four), refractory anemia with an international prognostic score of less than 1.5 (one), a history of malignant lymphoma (one), concurrent liver cancer (one), and no provision of informed consent (one). In addition, one eligible patient in the conventional-treatment group, who withdrew after randomization but before the start of treatment, was excluded. To avoid a selection bias in the outcome estimates due to selective reporting, all 33 patients from four hospitals (13 patients in the conventional-treatment group and 20 in the escalated-dose group) were excluded because the appropriate treatment and evaluation forms for more than 25% of the patients at each of these hospitals had not been received.

The effect of treatment group and covariates on the complete-remission rate was analyzed with the use of logistic regression, and the survival end points were analyzed with the use of Cox regression. These analyses were performed with and without adjustment for covariates. The possible heterogeneity of the treatment effects in subgroups was explored in post hoc analyses by estimation of the odds ratios for complete remission and the hazard ratios for survival end points for each subgroup, together with 95% confidence intervals, and performing tests for interaction. Subgroups defined according to age (three groups of similar size: 60 to 65, 66 to 70, and >70 years of age), cytogenetic risk category (favorable, intermediate, unfavorable, or very unfavorable), WHO performance status (0, or 1 or 2), primary AML or secondary AML (the latter after chemotherapy or radiation therapy or after a myelodysplastic syndrome), presence or absence of extramedullary disease, white-cell count ($<20\times10^9$ per liter or $\geq20\times10^9$ per liter), presence or absence of splenomegaly and of hepatomegaly, and sex were considered. The power of these tests of interaction was limited, since the trial was not designed to test for interactions. A competing-risk analysis was performed to calculate the cumulative competing risks of lack of a complete remission during the treatment period, relapse after complete remission, and death during complete remission.

Hematologic recovery after the first cycle was analyzed actuarially and was compared between the groups with the use of a log-rank test. In these analyses, recovery before the start of the next cycle was counted as an event, whereas data were censored at the time of a patient's death or at the start of the next treatment if the patient had not yet recovered at that time. All reported P values are two-sided and have not been adjusted for multiple testing.

Table 1. Characteristics of Patients, Induction and Consolidation Treatments, and Effects of Treatment.*

Variable	Conventional-Dose Group (N=411)	Escalated-Dose Group (N=402)
Age — yr		
Mean	68±4	68±4
Range	60–79	60–83
Median	67	67
Age subgroup — no. (%)		
60–65 yr	149 (36)	150 (37)
66–70 yr	156 (38)	145 (36)
>70 yr	106 (26)	107 (27)
Male sex — no. (%)	233 (57)	215 (53)
Refractory anemia with excess blasts — no. (%)	21 (5)	18 (4)
Extramedullary disease — no. (%)†	59 (14)	33 (8)
Hepatomegaly — no. (%)	39 (9)	38 (9)
Splenomegaly — no. (%)	45 (11)	39 (10)
WHO performance status — no. (%)‡		
0	128 (31)	136 (34)
1	235 (57)	218 (54)
2	43 (10)	42 (10)
Secondary AML — no. (%)	75 (18)	94 (23)
Prior myelodysplastic syndrome	52 (13)	67 (17)
Prior chemotherapy or radiation therapy	23 (6)	27 (7)
White-cell count at diagnosis — no. (%)		
$\leq 20\times10^9$ per liter	270 (66)	274 (68)
$>20–100\times10^9$ per liter	104 (25)	96 (24)
$>100\times10^9$ per liter	37 (9)	32 (8)
Cytogenetic risk — no. (%)§		
Favorable	19 (5)	14 (3)
t(8;21)	11 (3)	6 (1)
inv(16)/t(16;16)	8 (2)	8 (2)
Intermediate		
Normal cytogenetic findings	176 (43)	185 (46)
Cytogenetic abnormalities other than those in favorable, unfavorable, or very unfavorable risk categories	74 (18)	72 (18)
Unfavorable	44 (11)	35 (9)
Very unfavorable	54 (13)	48 (12)
No cytogenetic testing results available¶	44 (11)	48 (12)
Induction treatment — no. (%)‖		
None	5 (1)	5 (1)
One cycle only	116 (28)	104 (26)
Two cycles	290 (71)	293 (73)
Complete remission — no. (%)	221 (54)	259 (64)
After cycle 1	143 (35)	208 (52)
After cycle 2	78 (19)	51 (13)

Table 1. (Continued.)

Variable	Conventional-Dose Group (N=411)	Escalated-Dose Group (N=402)
No complete remission — no. (%)	190 (46)	143 (36)
Early death — no. (%)**	49 (12)	44 (11)
Consolidation therapy for patients in complete remission after cycle 2 — no./total no. (%)		
None	124/205 (60)	144/236 (61)
Gemtuzumab ozogamicin	52/205 (25)	58/236 (25)
Chemotherapy	6/205 (3)	5/236 (2)
Autologous hematopoietic stem-cell transplantation	3/205 (1)	2/236 (1)
Allogeneic hematopoietic stem-cell transplantation	20/205 (10)	27/236 (11)
Events during follow-up period — no.		
Relapse	149	158
Death		
Total	340	325
During first complete remission††	24	46
After cycle 1 or 2	19	32
After allogeneic hematopoietic stem-cell transplantation	1	7
After other post-remission therapy	4	7

* Plus–minus values are means ±SD. Patient characteristics did not differ significantly between the two treatment groups except that there was a higher prevalence of extramedullary disease in the conventional-dose group (P=0.006). AML denotes acute myeloid leukemia, and WHO World Health Organization.

† Extramedullary disease, which was usually identified by means of clinical assessment and sometimes also by means of pathological assessment, included hepatomegaly, lymph-node enlargement, and clinical or pathological evidence of leukemic-cell infiltration in the central nervous system or in the gingivae, skin, or lungs.

‡ The WHO performance status is scored on a scale of 0 to 5, with lower numbers indicating better performance status. The number of patients shown with a score of 2 included two enrolled patients (both in the conventional-dose group) who had a score of 3.

§ Cytogenetic risk was classified as favorable in the case of AML with core-binding–factor chromosomal abnormalities — that is, t(8;21) or inv(16)/t(16;16); as intermediate in the case of AML with normal cytogenetic findings or –X or –Y as single abnormalities only, or in the case of AML with any other abnormal cytogenetic findings not included in the favorable or unfavorable categories; as unfavorable if there were abnormal cytogenetic findings with unfavorable characteristics but not a monosomal karyotype; and as very unfavorable if there were abnormal cytogenetic findings with a monosomal karyotype.

¶ Results were not available either because cytogenetic testing was not performed or because results could not be evaluated.

‖ Ten patients (five in each group) did not receive the assigned study treatment owing to deterioration of their condition or early death. These patients were considered in analyses as not having had a complete remission and as not having reached the end point of event-free survival.

** Early death refers to death within 30 days after randomization.

†† The causes of death during the first complete remission are specified in Table 1 in the Supplementary Appendix.

RESULTS

PATIENTS

From October 27, 2000, through June 9, 2006, a total of 813 eligible patients who could be evaluated were randomly assigned to a treatment group — 411 to the conventional-dose group and 402 to the escalated-dose group. The median follow-up period for patients who were still alive at the date of last contact (148 patients) was 40 months. Table 1 shows the demographic characteristics of the patients. The median age was 67 years (range 60 to 83); 26% of the patients were 71 years of age or older. There were no significant differences between the two groups with respect to clinical and hematologic features at baseline except for a higher prevalence of extramedullary disease in the conventional-dose group (P=0.006).

CYTOGENETIC RISK

Of the 813 patients who were randomly assigned to a study group, 102 had a very unfavorable (monosomal) karyotype. These patients had a low rate of complete remission (34%), a 2-year rate of dis-

Table 2. Treatment Outcome According to Treatment Group and Clinical and Hematologic Factors.

Group or Subgroup	No. of Patients	Complete Remission			
		% of Patients	P Value*	Odds Ratio (95% CI)	P Value†
Treatment group			0.002		0.002
Conventional-dose	411	54			
Escalated-dose	402	64		1.59 (1.18–2.15)	
Age‡			0.15		0.08
60–65 yr	299	62			
66–70 yr	301	58		0.85 (0.60–1.21)	
>70 yr	213	56		0.70 (0.48–1.02)	
Sex			0.28		0.36
Male	448	61			
Female	365	57		0.87 (0.64–1.18)	
WHO performance score§			<0.001		0.003
0	264	69			
1 or 2	549	54		0.61 (0.44–0.84)	
AML			<0.001		<0.001
Primary	644	62			
Secondary					
Prior myelodysplastic syndrome	119	45		0.44 (0.29–0.68)	
Prior chemotherapy or radiation therapy	50	52		0.65 (0.36–1.20)	
Extramedullary disease			<0.001		0.03
Absent	721	61			
Present	92	42		0.59 (0.36–0.96)	
Splenomegaly			<0.001		0.04
Absent	729	61			
Present	84	39		0.57 (0.34–0.96)	
White-cell count			0.02		0.02
≤20×10^9 per liter	544	62			
>20×10^9 per liter	269	54		0.67 (0.48–0.93)	
Cytogenetic risk¶			<0.001		<0.001
Favorable	33	82		2.74 (1.07–6.99)	
Intermediate					
Normal cytogenetic findings	361	65			
Cytogenetic abnormalities other than those in favorable, unfavorable, or very unfavorable risk categories	146	60		0.82 (0.54–1.24)	
Unfavorable	79	56		0.67 (0.40–1.13)	
Very unfavorable	102	34		0.25 (0.15–0.40)	
No cytogenetic testing results available‖	92	58		0.69 (0.43–1.13)	

* These P values were calculated by means of likelihood-ratio tests in univariate models without adjustment for the other variables.
† The odds ratios (with 95% confidence intervals [CIs]) and hazard ratios (with 95% CIs) and associated P values were calculated by means of multivariate logistic regression or Cox regression for each category as compared with the reference category. The multivariate models all include the following variables: treatment group, age, WHO performance status, primary or secondary acute myeloid leukemia (AML), presence or absence of extramedullary disease, presence or absence of splenomegaly, white-cell count (>20×10^9 per liter vs. ≤20×10^9 per liter), and cytogenetic risk.
‡ In the case of age, the P values in both univariate and multivariate analyses are based on likelihood-ratio tests for trend with age as a continuous variable.
§ The WHO performance status is scored on a scale of 0 to 5, with lower numbers indicating better performance status.
¶ Cytogenetic risk was classified as favorable in the case of AML with chromosomal abnormalities in core-binding factors — that is, t(8;21) or inv(16)/t(16;16); as intermediate in the case of AML with normal cytogenetic findings or –X or –Y as single abnormalities only or in the case of AML with any other abnormal cytogenetic findings not included in the favorable or unfavorable categories; as unfavorable if there were abnormal cytogenetic findings with unfavorable characteristics but not a monosomal karyotype; and as very unfavorable if there were abnormal cytogenetic findings with a monosomal karyotype.
‖ Results were not available either because cytogenetic testing was not performed or because results could not be evaluated.

Disease-free Survival				Event-free Survival				Overall Survival			
% at 2 yr	P Value*	Hazard Ratio (95%)	P Value†	% at 2 yr	P Value*	Hazard Ratio (95% CI)	P Value†	% at 2 yr	P Value*	Hazard Ratio (95% CI)	P Value†
	0.77		0.57		0.12		0.16		0.16		0.34
29				17				26			
30		1.06 (0.87–1.30)		20		0.90 (0.78–1.04)		31		0.93 (0.80–1.08)	
	0.04		0.06		0.006		0.002		0.007		0.01
34				21				31			
29		1.12 (0.88–1.43)		18		1.14 (0.96–1.35)		29		1.08 (0.90–1.30)	
24		1.31 (1.00–1.70)		14		1.36 (1.12–1.64)		24		1.31 (1.08–1.59)	
	0.03		0.003		0.57		0.21		0.85		0.38
25				16				27			
36		0.72 (0.58–0.89)		21		0.91 (0.78–1.06)		30		0.93 (0.79–1.09)	
	0.77		0.92		0.004		0.04		<0.001		0.002
31				22				36			
29		1.01 (0.82–1.25)		17		1.18 (1.00–1.38)		25		1.30 (1.10–1.53)	
	0.27		0.42		0.003		0.003		0.01		0.006
31				20				30			
18		1.24 (0.91–1.71)		9		1.45 (1.18–1.79)		22		1.39 (1.13–1.72)	
30		1.04 (0.67–1.61)		16		1.14 (0.85–1.55)		22		1.28 (0.94–1.76)	
	0.29		0.32		0.17		0.64		0.13		0.63
29				19				29			
32		0.82 (0.54–1.23)		14		1.06 (0.83–1.36)		22		1.06 (0.83–1.37)	
	0.54		0.97		0.001		0.05		0.002		0.16
30				19				30			
27		1.01 (0.67–1.51)		11		1.29 (1.01–1.66)		15		1.21 (0.93–1.56)	
	0.31		0.04		0.009		<0.001		0.004		<0.001
30				20				31			
28		1.28 (1.02–1.62)		16		1.34 (1.13–1.58)		22		1.38 (1.16–1.64)	
	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
47		0.44 (0.26–0.77)		41		0.45 (0.29–0.71)		60		0.44 (0.27–0.72)	
31				21				34			
35		0.85 (0.64–1.12)		22		0.95 (0.77–1.17)		31		0.94 (0.76–1.17)	
27		1.10 (0.76–1.58)		15		1.22 (0.94–1.58)		19		1.31 (1.00–1.70)	
3		2.99 (2.03–4.41)		1		2.41 (1.91–3.05)		4		2.43 (1.91–3.09)	
26		1.04 (0.74–1.48)		15		1.20 (0.93–1.54)		25		1.32 (1.02–1.71)	

ease-free survival after complete remission of 3%, and a 2-year rate of overall survival of only 4%. Patients with an unfavorable karyotype but no monosomal karyotype (79 patients) had a complete-remission rate of 56% and 2-year rates of disease-free survival and overall survival of 27% and 19%, respectively. The 33 patients with abnormalities in core-binding factors had a complete-remission rate of 82% and 2-year rates of disease-free survival and overall survival of 47% and 60%, respectively.

TREATMENT, RESPONSE, AND OUTCOME

Of 813 patients, 803 received treatment in the first induction cycle, and 583 (72%) received treatment in the second induction cycle; the proportions of patients who received treatment were similar for the two study groups (Table 1). Ten

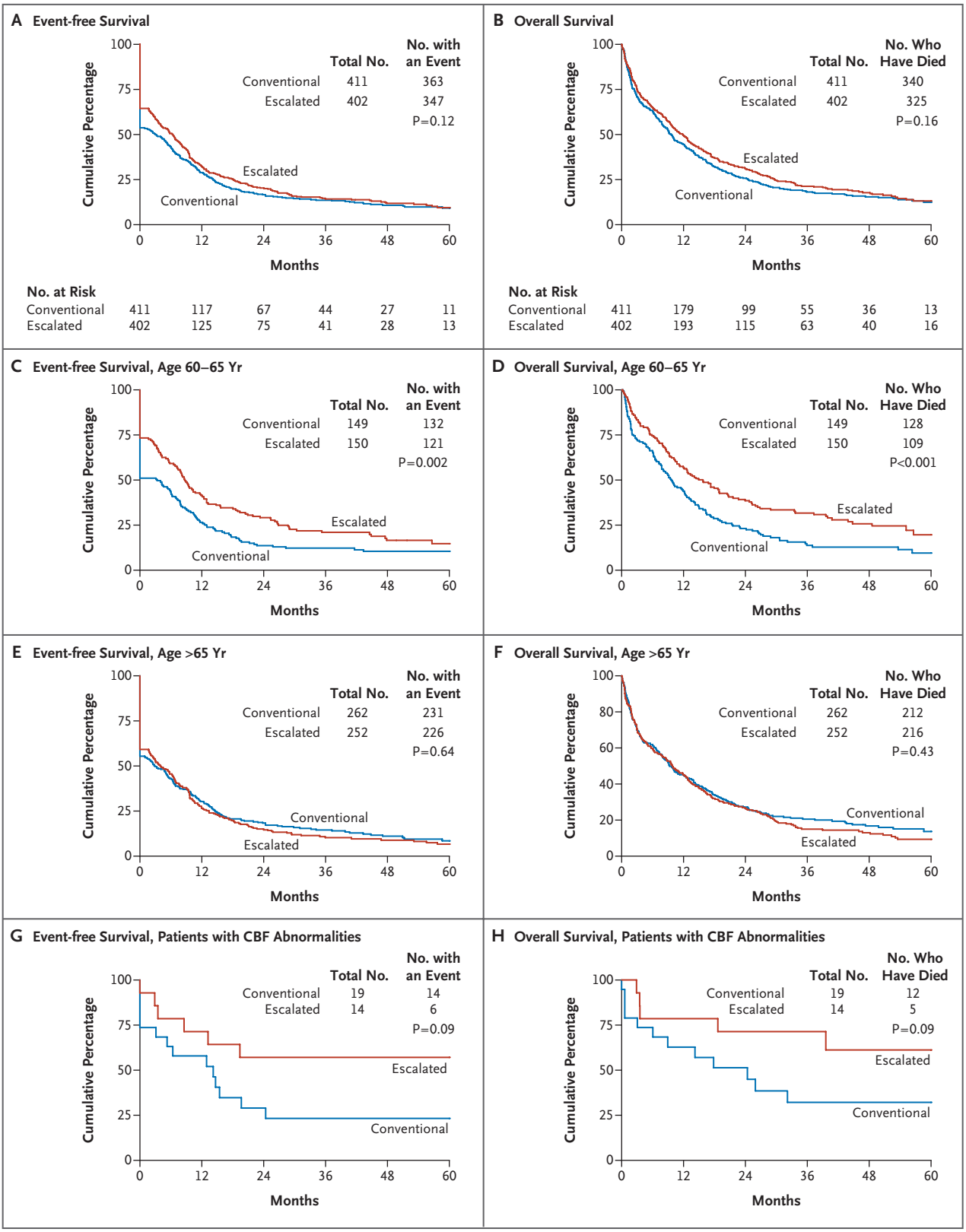

Figure 1 (facing page). Effect of Remission-Induction Chemotherapy with an Escalated Dose of Daunorubicin versus a Conventional Dose on Event-free Survival and Overall Survival in Patients 60 years of Age or Older with Acute Myeloid Leukemia.

Patients were randomly assigned for their first induction cycle of combination chemotherapy to receive daunorubicin at a dose of 45 mg per square meter of body-surface area (conventional-dose group) or 90 mg per square meter (escalated-dose group) on 3 successive days. The top row of panels shows data for all patients, the second row, data for patients 60 to 65 years of age; the third row, data for patients older than 65 years of age; and the bottom row, data for patients with abnormalities in core-binding factors (CBF).

patients (five in each group) did not receive the assigned study treatment owing to deterioration of their condition or early death. Patients assigned to the escalated-dose group had a significantly higher complete-remission rate than patients in the conventional-dose group (64% vs. 54%, P=0.002) (Table 2). There were more complete remissions after the first induction cycle in the escalated-dose group than in the conventional-dose group (52% vs. 35%, P<0.001) (Table 1).

Of the patients in whom complete remission was achieved, 25% received treatment with gemtuzumab ozogamicin, 11% received an allograft, and 4% received chemotherapy or underwent autologous transplantation as consolidation treatment (Table 1). In the conventional-dose group, 149 patients had a relapse, and 340 died, of whom 24 were in complete remission. Of those who died while in complete remission, 3 died after the first cycle, 16 after the second cycle, 1 after receiving an allograft, and 4 after receiving other therapies. In the escalated-dose group, 158 patients had a relapse and 325 died, including 46 who were in complete remission. Of these 46 deaths, 4 occurred after the first cycle, 28 after the second cycle, 7 after receipt of an allograft, and 7 after other treatments (Table 1, and Table 1 in the Supplementary Appendix). There were no significant differences between the two groups in event-free survival (P=0.12) (Fig. 1), disease-free survival (P=0.77), or overall survival (P=0.16) (Fig. 1). The cumulative 2-year probabilities for the competing risks of relapse after complete remission and of death during complete remission in the conventional-dose group as compared with the escalated-dose group were 61% versus 54% for relapse and 10% versus 16% for death.

PROGNOSTIC FACTORS

Table 2 shows the probabilities of complete remission and the actuarial 2-year probabilities of disease-free survival, event-free survival, and overall survival according to treatment group and characteristics of patients, along with the results of univariate and multivariate analyses. Cytogenetic risk category, age, white-cell count, presence or absence of splenomegaly, presence or absence of extramedullary disease, WHO performance status, and primary or secondary AML were all significantly associated with the rate of complete remission (Table 2); cytogenetic risk category and age were associated with disease-free survival; and cytogenetic risk category, age, white-cell count, WHO performance status, primary or secondary AML, and presence or absence of splenomegaly were associated with event-free and overall survival. After adjustment for these factors, the difference in the complete-remission rate between the conventional-dose group and the escalated-dose group remained significant (P=0.003), whereas there were no significant differences in event-free survival, overall survival, or disease-free survival.

EXPLORATORY ANALYSES OF SUBGROUPS

Exploratory post hoc analyses (Table 3) showed that patients who were 60 to 65 years of age had the greatest benefit from an escalated dose of daunorubicin with respect to the complete-remission rate (51% in the conventional-dose group vs. 73% in the escalated-dose group), the 2-year rate of event-free survival (14% vs. 29%), and the 2-year rate of overall survival (23% vs. 38%) (Fig. 1). Tests for an interaction between age and treatment were significant with respect to complete remission, event-free survival, and overall survival. Tests for an interaction between cytogenetic risk category and treatment were not significant except with respect to disease-free survival (Table 3), but in the subgroup with abnormalities in core-binding factors, the escalated dose was associated with an increased rate of complete remission and with reduced hazard ratios for disease progression or death (Table 3 and Fig. 1). None of the tests for interaction with respect to the other factors were significant.

ADVERSE EVENTS

The two groups were compared with respect to adverse events associated with the first induction

Table 3. Effect of Treatment with a Conventional Dose versus an Escalated Dose of Daunorubicin on Outcome, According to Age, Performance Status, and Cytogenetic Risk Category.*

Group	Complete Remission				Disease-free Survival			
	Conventional Dose	Escalated Dose	Odds Ratio (95% CI)†	P Value	Conventional Dose	Escalated Dose	Hazard Ratio for Event (95% CI)‡	P Value
	%				%			
Overall	54±2	64±2	1.56 (1.17–2.06)		29±3	30±3	1.03 (0.84–1.26)	
Age				0.02				0.43
60–65 yr	51±4	73±4	2.64 (1.63–4.29)		27±5	39±5	0.89 (0.64–1.24)	
66–70 yr	58±4	59±4	1.04 (0.66–1.64)		33±5	25±5	1.21 (0.87–1.69)	
>70 yr	52±5	60±5	1.38 (0.82–2.37)		25±6	23±5	1.08 (0.72–1.62)	
WHO performance status§				0.07				0.50
0	59±4	77±4	2.32 (1.36–3.95)		32±5	29±5	1.13 (0.81–1.58)	
1 or 2	51±3	58±3	1.32 (0.93–1.83)		27±4	31±4	0.98 (0.76–1.27)	
Cytogenetic risk¶				0.37				0.12
Favorable	74±10	93±7	4.64 (0.48–45.21)		31±13	62±13	0.52 (0.17–1.56)	
Intermediate	60±3	66±3	1.28 (0.89–1.84)		32±4	32±4	1.06 (0.83–1.36)	
Unfavorable	48±8	66±8	2.10 (0.84–5.24)		14±8	39±10	0.61 (0.31–1.17)	
Very unfavorable	28±6	42±7	1.86 (0.81–4.25)		7±6	0	1.85 (0.89–3.87)	
No cytogenetic testing results available‖	45±8	69±7	2.64 (1.13–6.18)		34±11	21±8	1.38 (0.71–2.67)	

* For complete remission, the percentages are means ±SE. The percentages in the case of disease-free survival, event-free survival, and overall survival are actuarial probabilities ±SE at 2 years. Exploratory subgroup analyses combined with tests for interaction between covariates and treatment group were performed to determine whether the higher rate of complete remission in the dose-escalated group was restricted to or more pronounced in particular subgroups or whether differences in survival end points were apparent in particular subgroups. P values are for the interaction between treatment group and covariate for each end point.

† Odds ratios are for the escalated-dose group as compared with the conventional-dose group within the subgroup.

‡ Hazard ratios for events are for the escalated-dose group as compared with the conventional-dose group within the subgroup.

§ The WHO performance status is scored on a scale of 0 to 5, with lower numbers indicating better performance status.

¶ Cytogenetic risk was classified as favorable in the case of AML with core-binding–factor chromosomal abnormalities — that is, t(8;21) or inv(16)/t(16;16); as intermediate in the case of AML with normal cytogenetic findings or –X or –Y as single abnormalities only or in the case of AML with any other abnormal cytogenetic findings not included in the favorable or unfavorable categories; as unfavorable if there were abnormal cytogenetic findings with unfavorable characteristics but not a monosomal karyotype; and as very unfavorable if there were abnormal cytogenetic findings with a monosomal karyotype.

‖ Results were not available either because cytogenetic testing was not performed or because results could not be evaluated.

cycle. There were no significant differences between the two groups in 30-day mortality (12% in the conventional-dose group and 11% in the escalated-dose group), the number of nights spent in the hospital, and the time to recovery of neutrophil or platelet counts (Table 4). There were also no significant differences with respect to the rate of death during induction or the incidence of serious adverse events after the first two cycles overall. In the escalated-dose group, as compared with the conventional-dose group, there were more infections of grade 2 to 4, slightly more platelet transfusions were given, and the time to the beginning of the second cycle was, on average, 3 days longer. The difference in the time to the second cycle probably reflects the higher rate of complete remission after the first cycle in the escalated-dose group; among patients with no response, the second cycle was frequently started as soon as possible because hematologic recovery was not expected. There was no significant difference in the rate of grade 2 to 4 (i.e., moderate, severe, or life-threatening) side effects between the two groups (74% in the conventional-dose group and 80% in the escalated-dose group, P=0.08).

DISCUSSION

There is evidence that in the fit elderly, the outcome after intensive chemotherapy to induce a

Event-free Survival				Overall Survival			
Conventional Dose	Escalated Dose	Hazard Ratio for Event (95% CI)‡	P Value	Conventional Dose	Escalated Dose	Hazard Ratio for Event (95% CI)‡	P Value
%				%			
17±2	20±2	0.89 (0.77–1.03)		26±2	31±2	0.90 (0.77–1.05)	
			0.02				0.007
14±3	29±4	0.68 (0.53–0.87)		23±3	38±4	0.65 (0.50–0.84)	
21±3	15±3	1.11 (0.87–1.41)		29±4	29±4	1.11 (0.87–1.43)	
14±3	15±3	0.96 (0.72–1.27)		24±4	24±4	1.04 (0.78–1.39)	
			0.83				0.70
20±4	24±4	0.87 (0.67–1.13)		33±4	39±4	0.94 (0.72–1.24)	
15±2	18±2	0.91 (0.76–1.08)		22±3	27±3	0.88 (0.74–1.06)	
			0.15				0.02
29±11	57±13	0.45 (0.17–1.17)		51±12	71±12	0.41 (0.15–1.18)	
21±3	22±3	0.98 (0.82–1.19)		31±3	36±3	0.96 (0.79–1.25)	
7±4	25±7	0.58 (0.36–0.93)		11±5	28±8	0.52 (0.32–0.85)	
2±2	0	0.98 (0.66–1.46)		8±4	0	1.34 (0.89–2.02)	
15±6	15±5	0.82 (0.52–1.28)		21±6	28±7	0.91 (0.57–1.43)	

remission is superior to that with a wait-and-watch approach or dose-attenuated cytoreductive treatment.[12-14] Our results make a case for intensified initial treatment in older patients. Induction treatment with twice the usual dose of daunorubicin (90 mg per square meter on each of 3 days, all administered in the first induction cycle) was not associated with an increase in serious side effects or with an increase in early mortality or a decrease in overall survival. The escalated-dose regimen did not prolong marrow suppression, a finding that suggests that the customary dose of daunorubicin is too low. Moreover, not only was the rate of complete remission higher with the escalated dose than with the conventional dose but also remissions were achieved earlier, with a higher rate of remission after the first cycle with the escalated dose than with the conventional dose (52% vs. 35%). The increase in the rate of remissions was independent of the cytogenetic risk category; however, it was particularly apparent in the subgroup of patients who were 60 to 65 years of age. Notwithstanding the increased rate of complete remission with the higher dose of daunorubicin, there was no improvement in overall survival or event-free survival. In the escalated-treatment group, as compared with the conventional-dose group, more patients died while they were in complete remission after the second induction cycle or after further consolidation treatment, suggesting that there may be some cumulative toxic effects after successive therapies, but there was no significant difference between the two groups in disease-free survival after complete remission (Table 2).

When daunorubicin was first introduced, it was administered at a dose of 30 mg per square meter, since early experience indicated that induction therapy with 60 mg per square meter for 3 days was not feasible in older persons.[18] Subsequently, a dose of 45 to 50 mg per square meter became widely accepted. Virtually all major cooperative groups have adopted this dose as the standard dose for treating AML in patients 55 to 60 years of age or older.[4-11] A dose of 60 mg per square meter has not been evaluated in direct comparisons.[19] Prospectively evaluated regimens of mitoxantrone–etoposide[9] or combinations of cytarabine with either idarubicin (12 mg per square meter) or mitoxantrone (12 mg per square meter)[10] did not appear to be superior to a regimen of 45 to 50 mg of daunorubicin per square meter

Table 4. Adverse Events during and after the First Cycle of Remission Induction.*

Event	Conventional Dose (N=406)	Escalated Dose (N=397)	P Value†
Maximal-grade side effects — no. of patients (%)‡			0.08
Grade 0 or 1	109 (27)	80 (20)	
Grade 2	100 (25)	101 (25)	
Grade 3	124 (31)	142 (36)	
Grade 4	73 (18)	74 (19)	
Maximal grade infections — no. of patients (%)‡			0.005
Grade 0 or 1	78 (19)	51 (13)	
Grade 2	6 (1)	2 (1)	
Grade 3	290 (71)	302 (76)	
Grade 4	32 (8)	42 (11)	
Early death — no. of patients (%)§	49 (12)	44 (11)	0.59
Neutrophil recovery >0.5×10^9 per liter			
Recovery by day 30 — %	65	73	0.07
Median duration — days	26	26	
Platelet recovery >50×10^9 per liter			
Recovery by day 30 — %	71	71	0.37
Median duration — days	25	25	
No. of platelet transfusions			0.08
Mean	8.7±6.9	9.1±6.7	
Median	7	8	
No. of days from start of chemotherapy to last platelet transfusion			0.004
Mean	21.6±10.8	22.1±9.4	
Median	19	20	
No. of nights in hospital			0.13
Mean	30±11	31±12	
Median	28	29	
Interval between beginning of first cycle and beginning of second cycle — days			0.001
Mean	38±15	43±17	
Median	36	39	

* Ten patients (five in each group) did not receive the assigned study treatment owing to deterioration of their condition or early death. Plus–minus numbers are means ±SD.
† P values were calculated with the use of the Kruskal–Wallis test, except for comparisons of the actuarial probabilities of neutrophil and platelet recovery, for which the log-rank test was used. For these analyses, data from patients in whom recovery had not occurred at the time of death or at the start of the next cycle were censored at that time.
‡ Side effects and infections were graded according to the Common Terminology Criteria for Adverse Events.
§ Early death refers to death that occurred within 30 days after randomization.

plus cytarabine. Furthermore, in another study, treatment with daunorubicin at a dose of 50 mg per square meter for 3 days during each of two successive induction cycles of daunorubicin–cytarabine, with a total dose of daunorubicin of 300 mg per square meter, conferred no more benefit than a dose of 35 mg of daunorubicin per square meter, with a total dose after two successive induction cycles of 210 mg per square meter.[20] This lack of a benefit of 300 mg per square meter administered over two cycles suggests that the advantage of the dose level of 90 mg per

square meter (and a total dose of 270 mg per square meter) given in a single cycle, as reported here, is probably due to the higher peak exposure levels of the intensified dose of daunorubicin, not an increase in the cumulative dose.

In our study, as in previous studies, younger age,[4,6,9,21,22] better performance status,[6,21-23] primary rather than secondary leukemia,[6,9,21] more favorable cytogenetic risk group,[4,6,17,19,21,23] and absence of splenomegaly and of extramedullary disease were independently associated with a higher rate of complete response. A monosomal karyotype distinguished patients with particularly low rates of complete remission, overall survival, and event-free survival, findings that are similar to those from a large series of patients with AML who were younger than 60 years of age.[16] Furthermore, the 33 patients with cytogenetic abnormalities in core-binding factors[17,21,23-25] (67% of whom were 65 years of age or older) had the best outcome, irrespective of age; however, this subgroup was small. In accordance with findings in other studies, older age,[6,9,21,22,24,26] reduced performance status,[6,9,21,22,26] presence of splenomegaly,[21] increased white-cell count,[6,9,21,26] and an unfavorable cytogenetic risk category[6,9,21-24,26] were associated with decreased overall and event-free survival.

In our study, it is apparent that the subgroup of patients who were 60 to 65 years of age benefited the most from intensified doses of daunorubicin. In this subgroup, the rate of complete remission among patients who received the escalated dose, as compared with those who received the conventional dose, was 73% versus 51%; this subgroup, as compared with all other cytogenetic subgroups, also had the highest rates of overall survival (Table 3 and Fig. 1). Patients in the escalated-dose group with a core-binding–factor karyotype also had a survival advantage. Although these differences could be due to chance findings in post hoc analyses, the data and the strong interaction effects between treatment and age with respect to complete remission, event-free survival, and overall survival support a true and consistent effect in favor of the escalated dose of daunorubicin in patients who are 60 to 65 years of age. This outcome is of clinical interest, since our results suggest that high-dose daunorubicin could be an alternative therapy to high-dose cytarabine (up to 3000 mg per square meter), which is an effective treatment for AML in patients younger than 60 years of age but is far too toxic in patients 60 years of age or older.[27]

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APPENDIX

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REFERENCES

1. Löwenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N Engl J Med 1999;341:1051-62. [Erratum, N Engl J Med 1999;341:1484.]
2. Estey E. Acute myeloid leukemia and myelodysplastic syndromes in older patients. J Clin Oncol 2007;25:1908-15.
3. Erba HP. Prognostic factors in elderly patients with AML and the implications for treatment. Hematology Am Soc Hematol Educ Program 2007:420-8.
4. 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 1995; 332:1678-83.
5. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study (9031). Blood 1998;91: 3607-15.
6. Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: results of the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1302-11.
7. Stone RM, Berg DT, George SL, et al. Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with standard-dose cytarabine. Blood 2001; 98:548-53.
8. Baer MR, George SL, Dodge RK, et al. Phase 3 study of the multidrug resistance modulator PSC-833 in previously untreated patients 60 years of age and older with acute myeloid leukemia: Cancer and Leukemia Group B Study 9720. Blood 2002; 100:1224-32.
9. Anderson JE, Kopecky KJ, Willman CL, et al. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. Blood 2002;100: 3869-76.
10. Rowe JM, Neuberg D, Friedenberg W, et al. A phase 3 study of three induction regimens and priming with GM-CSF in older adults with AML: a trial by the Eastern Cooperative Oncology Group. Blood 2004;103:479-85.
11. van der Holt B, Löwenberg B, Burnett AK, et al. The value of the MDR1 reversal agent PSC-833 in addition to daunorubicin and cytarabine in the treatment of elderly patients with previously untreated acute myeloid leukemia (AML), in relation to MDR1 status at diagnosis. Blood 2005; 106:2646-54.
12. 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 European Organization for Research and Treatment of Cancer Leukemia Group. J Clin Oncol 1989;7:1268-74.
13. López A, de la Rubia J, Martín G, et al. Recent improvements in outcome for elderly patients with de novo acute myeloblastic leukemia. Leuk Res 2001;25:685-92.
14. Baz R, Rodriguez C, Fu AZ, et al. Impact of remission induction chemotherapy on survival in older adults with acute myeloid leukemia. Cancer 2007;110:1752-9.
15. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-88. [Erratum, Blood 1998;91:1100.]
16. Breems DA, Van Putten WL, De Greef GE, et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol 2008;26:4791-7.
17. van der Holt B, Breems DA, Berna Beverloo H, et al. Various distinctive cytogenetic abnormalities in patients with acute myeloid leukaemia aged 60 years and older express adverse prognostic value: results from a prospective clinical trial. Br J Haematol 2007;136:96-105.
18. Kahn SB, Begg CB, Mazza JJ, Bennett JM, Bonner H, Glick JH. Full dose versus attenuated dose daunorubicin, cytosine arabinoside, and 6-thioguanine in the treatment of acute nonlymphocytic leukemia in the elderly. J Clin Oncol 1984;2:865-70.
19. Büchner T, Hiddemann W, Berdel WE, et al. 6-Thioguanine, cytarabine, and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) for induction, TAD for consolidation, and either prolonged maintenance by reduced monthly TAD or TAD-HAM-TAD and one course of intensive consolidation by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia (AML): a randomized trial of the German AML Cooperative Group. J Clin Oncol 2003;21:4496-504.
20. Burnett AK, Milligan D, Goldstone A, et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. Br J Haematol 2009;145:318-32.
21. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006;106: 1090-8.
22. Löwenberg B, Suciu S, Archimbaud E, et al. 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. J Clin Oncol 1998;16:872-81.
23. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute leukemia. Blood 2006;107:3481-5.
24. Fröhling S, Schlenk RF, Kayser S, et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. Blood 2006;108:3280-8.
25. Büchner T, Berdel WE, Haferlach C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. J Clin Oncol 2008;27:61-6.
26. Wheatley K, Brookes CL, Howman AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. Br J Haematol 2009;145:598-605.
27. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 1994;331:896-903.