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

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To assess the prognostic impact of cytogenetics in elderly patients with acute myeloid leukemia (AML) receiving intensive induction and consolidation treatment according to a single protocol specifically designed for patients above age 60, pretreatment samples from 361 patients registered for the AML HD98-B trial of the German-Austrian AML Study Group were analyzed by chromosome banding and fluorescence in situ hybridization, and cytogenetic findings were correlated with outcome. Using a proportional hazards model with backward selection, 3 prognostic subgroups were identified based on the influence of cytogenetic abnormalities on overall survival (OS): low-risk, t(15;17), and inv(16) in 25 of 361 patients (7%); standard-risk, normal karyotype, t(8;21), t(11q23), +8 within a noncomplex karyotype, and +11 within a noncomplex karyotype in 208 of 361 patients (58%); high-risk, all other aberrations in 128 of 361 patients (35%). On multivariate analysis, high-risk cytogenetics (hazard ratio [HR], 2.24) and age above 70 years (HR, 2.34) were independent prognostic factors affecting OS, and stratification according to these parameters demonstrated that a large subgroup of patients (55%), characterized by age 70 or older or high-risk cytogenetics, or both, had very unfavorable treatment results despite intensive chemotherapy. Thus, karyotype and age are major determinants of outcome in elderly patients with AML. (Blood. 2006;108:3280-3288)

Introduction

Pretreatment karyotype is the most important predictor of outcome in adult acute myeloid leukemia (AML).[1] In younger patients with AML, analysis of chromosome abnormalities allows categorization into favorable, intermediate, and adverse risk groups; most stratification systems distinguish t(8;21), inv(16), and t(15;17) as conferring a significantly better prognosis than normal karyotype, whereas other aberrations, such as −5/del(5q), −7, abn(3q), and complex karyotype, are associated with a high risk for induction failure, relapse, and shortened survival.[2-5]

AML occurring in patients older than 55 to 60 years of age is characterized by profound biologic differences, including the distribution, but not the spectrum, of cytogenetic abnormalities. In particular, favorable-risk aberrations are relatively uncommon in the elderly, as opposed to normal and complex karyotypes.[6-10]

Data regarding the prognostic relevance of cytogenetic abnormalities in older patients with AML receiving intensive chemotherapy are limited, and only 2 studies have assessed the impact of specific chromosome aberrations in elderly patients treated according to a single protocol. Grimwade et al[7] found that diagnostic karyotype was a prognostic factor for outcome in 1065 patients (median age, 66 years) from the United Kingdom Medical Research Council (MRC) AML11 trial designed for patients aged 56 years and older. Based on their results, they proposed a hierarchical cytogenetic classification that identified subgroups with significantly different outcomes: patients with t(8;21), inv(16), or t(15;17) had a favorable prognosis, whereas, in the absence of these changes, the presence of 5 or more abnormalities predicted an adverse prognosis; the remaining patients, by far the largest group and including the patients with normal karyotype, had an intermediate prognosis. Rowe et al[11] assessed the prognostic value of the 3-subgroup cytogenetic risk classification for younger AML patients developed by the Southwest Oncology Group[5] in 213 patients older than age 55 who were entered into a trial conducted by the Eastern Cooperative Oncology Group. This analysis showed that patients with unfavorable karyotypes (n = 88), defined by the presence of inv(3), −5/del(5q), t(6;9), −7/del(7q), t(9;22), abn(9q), abn(11q), abn(17p), abn(20q), abn(21q), or 3 or more chromosome aberrations, had significantly inferior complete remission (CR) rates and median overall survival (OS) than patients with intermediate-risk cytogenetics (n = 122), defined as normal karyotype or the presence of −Y, +6, +8, or del(12p), or favorable cytogenetics (n = 3), defined as the presence of t(8;21), inv(16), or t(15;17).

We analyzed the prognostic value of pretreatment cytogenetic abnormalities, as assessed by chromosome banding and fluorescence in situ hybridization (FISH), in 361 patients older than 60 years registered for the AML HD98-B trial of the German-Austrian AML Study Group (AMLSG).[12,13]

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A complete list of the members of the German-Austrian AML Study Group appears in "Appendix."

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Patients, materials, and methods

Patients and treatment

The study included 361 patients older than 60 years with AML, de novo or secondary (after treatment for a primary malignancy or following myelodysplasia), as defined by the French-American-British (FAB) classification.

All patients were registered for the AML HD98-B trial of the AMLSG.[12,13] Randomized induction therapy consisted of 2 courses of 12 mg/m^2 idarubicin on days 1 and 3, 100 mg/m^2 cytarabine continuously on days 1 through 5, and 100 mg/m^2 etoposide on days 1 and 3 (ICE) with or without all-*trans*retinoic acid (ATRA; 45 mg/m^2 on days 3 through 5 and 15 mg/m^2 on days 6 through 28), followed by first consolidation therapy with a course of 0.5 g/m^2 cytarabine every 12 hours on days 1 through 3 and 10 mg/m^2 mitoxantrone on days 2 and 3 (HAM) with or without ATRA (15 mg/m^2 on days 3 through 28). For further postremission therapy, patients were randomized to intensive second consolidation therapy (12 mg/m^2 idarubicin on days 1 and 3, 100 mg/m^2 etoposide on days 1 through 5) or 12 monthly courses of outpatient maintenance therapy (5 mg idarubicin orally on days 1, 4, 7, 10, and 13 and 100 mg etoposide orally on days 1 and 13). Patients not responding to the first course of induction therapy were assigned to receive a course of 0.5 g/m^2 cytarabine every 12 hours on days 1 through 3, 250 mg/m^2 etoposide continuously on days 4 and 5, 45 mg/m^2 ATRA on days 3 through 5, and 15 mg/m^2 ATRA on days 6 through 28 (A-HAE). Patients with acute promyelocytic leukemia (APL) did not undergo randomization but were treated with a course of 12 mg/m^2 idarubicin continuously on days 2, 4, and 6, 45 mg/m^2 ATRA on days 1 through 6, and 15 mg/m^2 ATRA on days 7 through 35 (AIDA), followed by a course of A-HAM and 6 monthly courses of outpatient maintenance therapy (5 mg idarubicin on days 1, 4, 7, 10, and 13 and 15 mg/m^2 ATRA on days 1 through 28).

The study was approved by the institutional review boards of the participating centers. Informed consent was obtained from all patients according to the Declaration of Helsinki.

Cytogenetic and molecular cytogenetic analysis

All leukemia samples were studied centrally in the Laboratory for Cytogenetic and Molecular Diagnostics of the AMLSG. Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature. Complex karyotype was defined as 3 or more cytogenetic abnormalities in the absence of t(8;21), t(11q23), t(15;17), or inv(16)/t(16;16), unless otherwise stated.

To improve cytogenetic diagnostics, all specimens were also analyzed by FISH using a comprehensive DNA probe set for the detection of the following AML-associated genomic aberrations[14]: inv(3)/t(3;3), t(8;21), t(9;22), t(11q23), t(15;17), inv(16)/t(16;16), +3q, +4q, del(5q), del(7q), +8q, +11q, abn(12p), del(13q)/+13q, del(17p), del(20q), +21q, +22q, and del(Xq).

Criteria for treatment outcomes

Response to induction therapy was assessed after 2 courses of chemotherapy. In accordance with standard criteria,[15] CR was defined as less than 5% bone marrow (BM) blasts, an absolute neutrophil count of 1.0 × 10^9/L or more, a platelet count of 100 × 10^9/L or more, no blasts in the peripheral blood (PB), and no extramedullary leukemia. Therapeutic failures were classified as either refractory disease (RD) or early/hypoplastic death (ED/HD), which was death less than 7 days after completion of the first course of induction therapy/death during the remainder of double-induction therapy. Relapse was defined as more than 5% BM blasts unrelated to recovery from the preceding course of chemotherapy or new extramedullary leukemia in patients with previously documented CR. End points for OS, measured from the date of study entry, were death (failure) and alive at last follow-up (censored). Analyses of cumulative incidence of relapse (CIR) and cumulative incidence of death in CR (CID) included only patients attaining CR, with time calculated from the date of CR to the occurrence of an event (relapse or death).

Statistical analyses

The median duration of follow-up was calculated according to the method of Korn.[16] The Kaplan-Meier method was used to estimate the distribution of OS.[17] Confidence interval (CI) estimation was based on the cumulative hazard using the Greenwood formula for standard error (SE) estimation.[18] Cumulative incidence of relapse, CID, their SEs, and differences between groups were estimated according to Gray.[19] Survival distributions were compared using the log-rank test. A Cox model was used to evaluate prognostic variables.[20] Missing data were estimated with a multiple-imputation technique using predictive mean matching with n = 100 for multiple imputations.[21] Backward selection applying a stopping rule based on the Akaike Information Criterion was used to exclude redundant or unnecessary variables.[21] Testing and estimation of possible cut-off values for continuous variables were done by maximally selected log-rank statistics.[22] To correct for overestimation, a shrinkage procedure and a bootstrap correction of the CIs were applied according to Holländer et al.[23] CIs for binomial probabilities were estimated using the method proposed by Agresti and Coull.[24] All statistical analyses were performed with R software, version 2.1.1, using R packages Design, version 2.0, and cmprsk, version 2.1 (all available at http://www.r-project.org).[25]

Table 1. Clinical characteristics of 361 patients older than 60 with AML

Characteristic	Value
No. of female patients (%)	166 (46)
Median age, y (range)	67 (61-84)
Disease status, no. of patients (%)	
De novo AML	231 (64)
M0	13 (6)
M1	40 (17)
M2	66 (29)
M3	13 (6)
M4	53 (23)
M5	22 (10)
M6	3 (1)
M7	1 (0)
Missing	20 (9)
Secondary AML	119 (33)
Preceding MDS	78 (22)
Preceding malignancy	41 (11)
Missing	11 (3)
Median hemoglobin level, g/L	91 (38-172)
Missing, no. of patients (%)	17 (5)
Median platelet count, × 10^9/L (range)	61.5 (4-848)
Missing, no. of patients (%)	17 (5)
Median WBC count, × 10^9/L (range)	8.4 (0.2-303)
Missing, no. of patients (%)	16 (4)
Median PB blasts, % (range)	31 (0-100)
Missing, no. of patients (%)	66 (18)
Median BM blasts, % (range)	70 (0-100)
Missing, no. of patients (%)	55 (15)
Median LDH level, U/L (range)	358 (57-6623)
Missing, no. of patients (%)	32 (9)
Lymphadenopathy, no. of patients (%)	46 (13)
Missing	42 (12)
Gum hypertrophy, no. of patients (%)	14 (4)
Missing	28 (8)
Extramedullary involvement, no. of patients (%)	16 (4)
Missing	37 (10)

Subheadings under "De novo AML" refer to FAB subtypes. Percentages may not add to 100 because of rounding. MDS indicates myelodysplastic syndrome.

Results

Patient characteristics

The clinical features at presentation of all 361 patients are shown in Table 1. Of the 361 patients, 338 (94%) had adequate results on chromosome banding analysis. In the remaining 23 patients, FISH analyses revealed numerical aberrations in 5 cases and balanced rearrangements in 2 cases.

Frequency of cytogenetic abnormalities

The frequencies of specific cytogenetic abnormalities that were detected in at least 5 patients are shown in Table 2. The distribution of specific cytogenetic abnormalities among different age groups is shown in Table 3.

Of the 361 patients, 161 (45%) had a normal karyotype, whereas 200 (55%) had at least one clonal aberration. The balanced rearrangements t(8;21), t(11q23), t(15;17), and inv(16) were present in 48 (13%) of 361 patients. In the absence of these balanced rearrangements, 73 (20%) patients exhibited a single aberration, 18 (5%) patients had 2 aberrations, and 61 (17%) patients had at least 3 cytogenetic abnormalities, including 44 (12%) patients with 5 or more aberrations. Abnormalities with a frequency above 5% were −5/del(5q) in 16%, −7/del(7q) in 14%, +8 in 13%, abn(12p) in 7%, −17/del(17p) in 7%, −20/del(20q) in 6%, and +11 in 6%.

The balanced rearrangements t(8;21), t(11q23), t(15;17), and inv(16) occurred predominantly as the sole aberration in 25 of 48 cases (52%) or in combination with a single additional abnormality in 13 of 48 cases (27%).

Among the numerical and structural chromosome abnormalities, 4 occurred frequently within a noncomplex karyotype in the absence of a balanced rearrangement: −7/del(7q) in19 of 49 cases (39%), +8 in 19 of 38 cases (50%), +11 in 6 of 20 cases (30%), and

Table 2. Frequency and characteristics of specific cytogenetic abnormalities among 361 AML patients older than 60

Cytogenetic abnormality	No. of patients (%)				
	Total	1 abnormality	2 abnormalities	3 or more abnormalities	5 or more abnormalities
Normal karyotype	161 (45)	NA	NA	NA	NA
−5/del(5q)	57 (16)	2 (4)	4 (7)	51 (89)	39 (68)
−5	16 (4)	0 (0)	0 (0)	16 (100)	15 (94)
del(5q)*	41 (11)	2 (5)	4 (10)	35 (85)	24 (59)
Balanced	3	0	0	3	2
−7/del(7q)	52 (14)	9 (17)	11 (21)	32 (62)	25 (48)
−7	23 (6)	2 (9)	5 (22)	16 (70)	12 (52)
del(7q)†	29 (8)	7 (24)	4 (14)	18 (62)	13 (45)
Balanced	3	0	1	0	2
+8	47 (13)	18 (38)	4 (9)	25 (53)	18 (38)
Balanced	9	0	3	6	2
−17/del(17p)	25 (7)	0 (0)	1 (4)	24 (96)	24 (96)
Balanced	1	0	1	0	0
abn(12p)	25 (7)	3 (12)	2 (8)	20 (80)	15 (60)
Balanced	3	0	1	2	1
−20/del(20q)	23 (6)	3 (13)	2 (9)	18 (78)	13 (57)
Balanced	4	0	0	4	1
+11	20 (6)	4 (20)	2 (10)	14 (70)	13 (65)
+13	17 (5)	8 (47)	0 (0)	9 (53)	8 (47)
+21	17 (5)	2 (12)	2 (12)	13 (76)	8 (47)
Balanced	1	0	0	1	0
+22	17 (5)	0 (0)	1 (6)	16 (94)	12 (71)
Balanced	3	0	1	2	1
del(13q)	15 (4)	1 (7)	1 (7)	13 (87)	12 (80)
Balanced	1	0	0	0	1
abn(3q)	14 (4)	1 (7)	1 (7)	12 (86)	10 (71)
inv(16)	14 (4)	9 (64)	3 (21)	2 (14)	0 (0)
t(8;21)	12 (3)	6 (50)	4 (33)	2 (17)	0 (0)
t(11q23)	11 (3)	3 (27)	3 (27)	5 (45)	3 (27)
t(9;11)	5 (1)	2 (40)	2 (40)	1 (20)	0 (0)
t(11;various)	6 (2)	1 (17)	1 (17)	4 (67)	3 (50)
t(15;17)	11 (3)	7 (64)	3 (27)	1 (9)	0 (0)
+14	9 (2)	0 (0)	1 (11)	8 (89)	6 (67)
−18	9 (2)	0 (0)	0 (0)	9 (100)	9 (100)
−Y	8 (2)	1 (13)	2 (25)	5 (63)	2 (25)
Balanced	4	0	2	2	0
+4	5 (1)	1 (20)	0 (0)	4 (80)	4 (80)
del(11q)	5 (1)	0 (0)	1 (20)	4 (80)	3 (60)
Balanced	2	0	0	2	1

Patients may be counted more than once due to the coexistence of more than one cytogenetic abnormality in the leukemic clone. Percentages may not add to 100 because of rounding.

Balanced indicates the number of patients exhibiting a given abnormality in combination with t(8;21), t(11q23), t(15;17), or inv(16)/t(16;16); NA, not applicable.

*Four cases detected only by FISH.

†Six cases detected only by FISH.

Table 3. Frequencies of specific cytogenetic abnormalities in different age groups

Cytogenetic abnormality	60-69 y	70-79 y	80 y or older
Normal karyotype	109 (45)	50 (45)	2 (33)
Unbalanced*			
+4	4 (2)	1 (1)	0 (0)
−5/del(5q)	35 (14)	21 (19)	1 (17)
−5	10 (4)	6 (5)	0 (0)
del(5q)	25 (10)	15 (13)	1 (17)
−7/del(7q)	36 (15)	16 (14)	0 (0)
−7	12 (5)	11 (10)	0 (0)
del(7q)	24 (10)	5 (4)	0 (0)
+8	32 (13)	14 (13)	1 (17)
Noncomplex	17 (7)	4 (4)	1 (17)
Complex	15 (6)	10 (9)	0 (0)
+11	13 (5)	7 (6)	0 (0)
Noncomplex	5 (2)	1 (1)	0 (0)
Complex	8 (3)	6 (5)	0 (0)
+13	12 (5)	4 (4)	1 (17)
del(13q)	9 (4)	6 (5)	0 (0)
+14	5 (2)	4 (4)	0 (0)
−17/del(17p)	16 (7)	8 (7)	1 (17)
−17	8 (3)	5 (4)	1 (17)
del(17p)	8 (3)	3 (3)	0 (0)
−18	5 (2)	4 (4)	0 (0)
−20/del(20q)	17 (7)	6 (5)	0 (0)
−20	6 (2)	2 (2)	0 (0)
del(20q)	11 (5)	4 (4)	0 (0)
+21	12 (5)	5 (4)	0 (0)
+22	12 (5)	5 (4)	0 (0)
Balanced†			
t(8;21)	7 (3)	5 (4)	0 (0)
t(11q23)	7 (3)	4 (4)	0 (0)
t(15;17)	7 (3)	4 (4)	0 (0)
inv(16)/t(16;16)	12 (5)	2 (2)	0 (0)
Other‡			
abn(3q)	9 (4)	5 (4)	0 (0)
abn(12p)	10 (4)	14 (13)	1 (17)
Complex			
3 or more unrelated	37 (15)	23 (21)	1 (17)
5 or more unrelated	28 (12)	15 (13)	1 (17)
Total	243 (100)	112 (100)	6 (100)

Values indicates number of patients, with percentage in parentheses. Patients may be counted more than once due to the coexistence of more than 1 cytogenetic abnormality in the leukemic clone.

*In the absence of t(8;21), t(11q23), t(15;17), or inv(16)/t(16;16).

†Irrespective of karyotype complexity.

‡Including cases with unbalanced or balanced abnormalities.

+13 in 8 of 17 cases (47%). All other chromosomal imbalances were seen as part of a complex karyotype, defined as 3 or more aberrations in the absence of a balanced rearrangement, in the majority of cases.

Response to induction therapy according to cytogenetic abnormalities

Of all 361 patients, 155 (43%) achieved CR. The rates of CR after 2 courses of induction therapy, RD, and ED/HD for patients with specific cytogenetic abnormalities are shown in Table 4.

Compared with the normal karyotype group (CR rate, 52%), CR rates were similar or even higher for patients with the following aberrations: t(8;21), t(11q23), t(15;17), inv(16), +8 within a noncomplex karyotype, and +11 within a noncomplex karyotype. All other abnormalities were associated with lower CR rates than normal karyotype, with RD being the predominant cause of therapeutic failure as opposed to ED/HD (Table 4).

Long-term outcome according to cytogenetic abnormalities

OS and CIR for patients with specific cytogenetic abnormalities are summarized in Table 5. The estimated median follow-up duration for survival was 57 months. The median OS for the entire study population was 9.9 months.

When we analyzed the impact of specific chromosome aberrations on OS, we noted a pattern that was very similar to the one we had observed during assessment of the influence of karyotype on the response to induction therapy: t(8;21), t(11q23), t(15;17), inv(16), +8 within a noncomplex karyotype, and +11 within a noncomplex karyotype were associated with OS comparable to or higher than that of patients with normal karyotype. The highest 3-year OS rates were observed in patients with t(15;17) (55%, $P = .02$), followed by inv(16) (26%, $P = .13$), and +8 within a noncomplex karyotype (26%, $P = .40$). Low 3-year OS rates were seen in patients with noncomplex cytogenetic abnormalities, defined

Table 4. Response to induction therapy according to cytogenetic abnormalities

Cytogenetic abnormality	No. of patients	CR, %	95% CI	ED/HD, %	RD, %
Normal karyotype	161	52	44-60	11	37
Unbalanced*					
+4	5	40	11-77	20	40
−5/del(5q)	54	7	3-18	26	67
−5	16	0	0-19	38	63
del(5q)	38	11	5-27	21	68
−7/del(7q)	49	6	2-17	18	76
−7	22	9	3-28	18	73
del(7q)	27	4	0-20	19	78
+8	38	32	19-47	26	42
Noncomplex	19	53	32-73	16	32
Complex	19	11	3-31	37	53
+11	20	30	12-49	30	40
Noncomplex	6	83	38-99	0	17
Complex	14	7	0-31	43	50
+13	17	18	6-41	24	59
del(13q)	14	0	0-22	21	79
+14	9	22	6-55	22	56
−17/del(17p)	24	4	0-20	29	67
−17	14	0	0-22	21	79
del(17p)	9	11	0-43	33	56
−18	9	0	0-30	33	67
−20/del(20q)	19	0	0-17	21	79
−20	7	0	0-35	29	71
del(20q)	12	0	0-24	17	83
+21	16	19	7-43	13	69
+22	14	14	4-40	14	71
Balanced†					
t(8;21)	12	58	32-81	17	25
t(11q23)	11	55	28-79	18	27
t(15;17)	11	73	43-90	27	0
inv(16)/t(16;16)	14	86	60-96	14	0
Other‡					
abn(3q)	14	0	0-22	14	86
abn(12p)	22	18	7-39	23	59
Complex					
3 or more unrelated	61	10	5-20	28	62
5 or more unrelated	44	7	2-18	25	68
All patients	361	43	38-48	14	43

Patients may be counted more than once due to the coexistence of more than 1 cytogenetic abnormality in the leukemic clone. Percentages may not add to 100 because of rounding.

*In the absence of t(8;21), t(11q23), t(15;17), or inv(16)/t(16;16).

†Irrespective of karyotype complexity.

‡Including cases with unbalanced or balanced abnormalities.

Table 5. Long-term outcome according to cytogenetic abnormalities

Cytogenetic abnormality	CR, no. of patients	2-y CIR (SE)*	P†	No. of patients	Median OS, mo	3-y OS (95% CI)	P†
Normal	83	0.72 (0.05)	NA	161	12.4	0.19 (0.13-0.26)	NA
Unbalanced‡							
+4	2	—	—	5	12.1	0.20 (0.03-1.0)	.95
−5/del(5q)	4	—	—	54	2.7	0	< .001
−7/del(7q)	3	—	—	49	5.2	0	< .001
+8	12	0.83 (0.12)	.94	38	7.5	0.16 (0.07-0.33)	.22
Noncomplex	10	0.80 (0.15)	.94	19	14.2	0.26 (0.12-0.56)	.40
Complex	2	—	—	19	2.7	0.05 (0.01-0.35)	< .001
+11	5	1.0	.05	20	5.0	0.07 (0.01-0.41)	.02
Noncomplex	5	1.0	.1	6	15.1	0.20 (0.03-1.0)	.76
Complex	1	—	—	14	2	0	< .001
+13	3	—	—	17	3.1	0.06 (0.01-0.39)	< .001
del(13q)	0	—	—	14	2.3	0	< .001
+14	2	—	—	9	5.9	0.11 (0.02-0.70)	.08
−17/del(17p)	1	—	—	24	2.1	0	< .001
−18	0	—	—	9	2.2	0	< .001
−20/del(20q)	0	—	—	19	5.7	0	.006
+21	3	—	—	16	5.6	0	< .001
+22	2	—	—	14	5.7	0.10 (0.02-0.59)	.05
Balanced§							
t(8;21)	7	1.0	.04	12	12.8	0.10 (0.02-0.65)	.67
t(11q23)	6	0.83 (0.2)	.92	11	11.7	0.18 (0.05-0.64)	.95
t(15;17)	8	0.29 (0.19)	.03	11	NR	0.55 (0.32-0.94)	.02
inv(16)	12	0.75 (0.14)	.83	14	21	0.26 (0.10-0.66)	.13
Other‖							
abn(3q)	0	—	—	14	4.9	0	< .001
abn(12p)	4	—	—	22	4.1	0.05 (0.01-0.31)	< .001
Complex							
3 or more unrelated	6	1.0	.009	61	3.1	0.04 (0.01-0.15)	< .001
5 or more unrelated	3	—	—	44	2.7	0.03 (0.01-0.20)	< .001
All patients	155	0.74 (0.03)	NA	361	9.9	0.15 (0.11-0.19)	NA

Patients may be counted more than once due to the coexistence of more than 1 cytogenetic abnormality in the leukemic clone.
NA indicates not applicable; —, not determined; NR, not reached.
*Determined for abnormalities present in 5 or more patients.
†For comparison of a given abnormality with normal karyotype.
‡In the absence of t(8;21), t(11q23), t(15;17), or inv(16).
§Irrespective of karyotype complexity.
‖Including cases with unbalanced or balanced abnormalities.

by fewer than 3 or fewer than 5 chromosome aberrations, in the absence of t(8;21), t(11q23), t(15;17), or inv(16) (6% and 6%, respectively).

Risk stratification according to cytogenetic abnormalities

We used a proportional hazards model to identify prognostic subgroups based on the influence of cytogenetic abnormalities on OS and to generate a cytogenetic stratification system for patients older than 60 years with AML. Cytogenetic categories were defined as follows: normal karyotype, t(8;21), t(11q23), t(15;17), inv(16), −7/del(7q), +8, +11, +13, and other. The category "other" included complex karyotype as well as the following individual chromosome aberrations in the absence of a balanced rearrangement that in the majority of cases were part of a complex karyotype: +4, −5/del(5q), abn(12p), del(13q), +14, −17/del(17p), −18, −20/del(20q), +21, and +22 (Table 2).

Using this approach, we identified 3 prognostic subgroups: a low-risk group including t(15;17) and inv(16) (25 of 361 patients, 7%), a standard-risk group including t(8;21), t(11q23), normal karyotype, +8 within a noncomplex karyotype, and +11 within a noncomplex karyotype (208 of 361 patients, 58%), and a high-risk group including all other aberrations (128 of 361 patients, 35%). The CR rates, median OS, and 3-year OS rates that resulted from the application of this stratification system are given in Table 6; the corresponding OS curves are shown in Figure 1.

Multivariate analysis

To develop a clinically meaningful system that can be used to identify patients who are likely to benefit from intensive chemotherapy as well as those who are better suited for investigational treatment or supportive care, assessment of prognostic factors was performed for OS.

The following variables were evaluated: sex, age, disease status (de novo AML versus secondary AML), hemoglobin level, platelet count, white blood cell (WBC) count, percentage of PB blasts, percentage of BM blasts, lactate dehydrogenase (LDH) level, extramedullary involvement, and cytogenetic risk group as defined

Table 6. CR rates, median OS, and 3-year OS rates resulting from cytogenetic risk stratification of 361 patients older than 60 with AML

Cytogenetic risk group	No. of patients	CR, %	Median OS, mo	3-y OS (95% CI)
Low	25	80	26.4	0.38 (0.19-0.57)
Standard	208	53	12.5	0.18 (0.13-0.24)
High	128	19	5.1	0.05 (0.02-0.10)

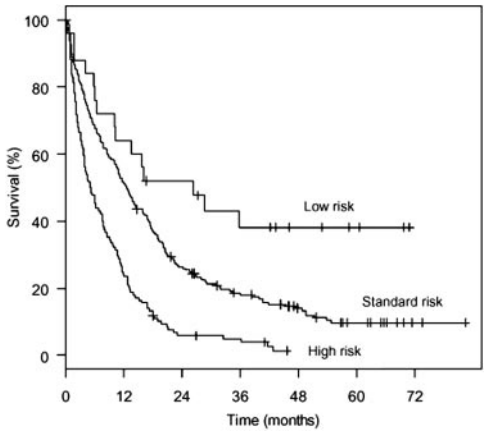

Figure 1. OS based on cytogenetic risk stratification. OS of 361 patients older than 60 years with AML according to the system for cytogenetic risk stratification generated in this study.

(see "Risk stratification according to cytogenetic abnormalities"). Age at diagnosis was the only continuous variable for which a clear cut point was evident on maximally selected log-rank statistics (70 years; $P < .001$; Figure 2). Therefore, age was included as a dichotomized variable in the model.

The multivariate model for OS was built using limited backward selection. To correct for overestimation of hazard ratios (HRs), a shrinkage procedure and a bootstrap correction of CI were applied. The final model included age above 70 years (HR, 2.34; 95% CI, 1.77-3.08), cytogenetic high-risk group (HR, 2.24; 95% CI, 1.74-2.88), and logarithm of LDH level (HR, 2.49; 95% CI, 1.66-3.74) as prognostic factors. Stratification of the patients according to the variables "cytogenetic high-risk group" and "dichotomized age" showed that younger patients (60-70 years) without high-risk cytogenetics had the best outcome (3-year OS, 26%), followed by younger patients with high-risk cytogenetics and patients older than 70 years without high-risk cytogenetics (3-year OS, 6%), and older patients with high-risk cytogenetics (3-year OS, 2%; Table 7 and Figure 3)

Table 7. Outcome of 361 patients older than 60 with AML according to cytogenetic risk group and age

AMLSG score	No. of patients	CR, %	Median OS, mo	3-y OS (95% CI)
Younger than 70 y				
Not high risk	161	62	17.5	0.26 (0.20-0.33)
High risk	82	21	7.2	0.06 (0.02-0.13)
70 y or older				
Not high risk	72	39	6.3	0.06 (0.02-0.13)
High risk	46	15	3.1	0.02 (0.00-0.10)

Cytogenetic risk stratification according to the system proposed in this study.

Discussion

To determine the value of cytogenetics for identifying older patients with AML who are likely to benefit from intensive chemotherapy, we assessed the prognostic impact of pretreatment chromosome aberrations in a prospective series of 361 elderly patients with de novo or secondary AML receiving induction and consolidation treatment according to a single protocol specifically designed for patients above the age of 60.[12,13] Cytogenetic diagnostics was performed by chromosome banding and FISH using a comprehensive DNA probe set that was previously shown to enhance the sensitivity of conventional cytogenetics.[14] The most important finding of our study was that a substantial proportion of patients (55%), characterized by high-risk cytogenetics or age 70 years or older, or both, had very poor outcomes with a median OS not exceeding 7.2 months and 3-year OS rates of 6% or less.

We identified 3 prognostic categories based on the influence of pretreatment cytogenetic parameters on OS. The cytogenetic high-risk group included abn(3q), abn(12p), and the vast majority of unbalanced aberrations. Whereas most chromosomal imbalances were almost invariably part of a complex karyotype, the 47 patients with +8 could be divided into 2 similarly sized and prognostically different subgroups: 22 (47%) patients had +8 as the sole abnormality or in combination with a single additional aberration, and their prognosis was comparable to that of patients with normal

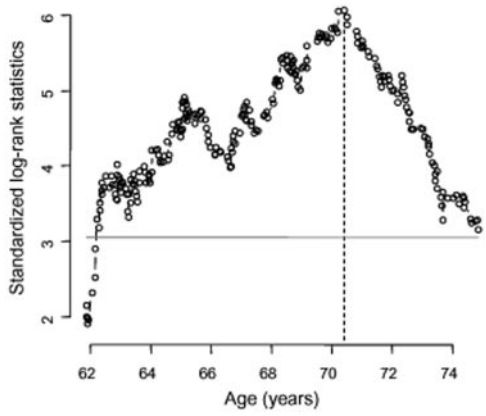

Figure 2. Maximally selected log-rank statistics for age. Maximally selected log-rank statistics performed for age to test for a potential cut point separating 2 groups with different survival distributions. Age is shown on the x-axis, corresponding standardized log-rank statistics are shown on the y-axis. The estimated cut-off point was 70.42 years with an M statistics of 6.06 and a corresponding corrected $P < .001$. Vertical dashed line represents the age cut point evident on maximally selected log-rank statistics and the corresponding M statistics. Horizonal line represents the minimal level of significance based on M statistics.

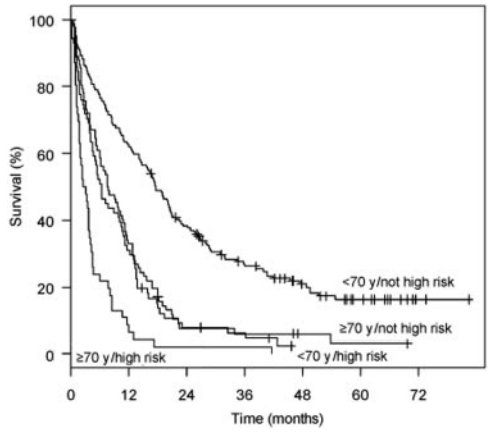

Figure 3. OS based on cytogenetic stratification system and age. OS of 361 patients older than 60 years with AML according to cytogenetic risk group, as assessed using the stratification system generated in this study, and age. Stratification of patients according to the 2 strongest prognostic factors for OS that were evident on multivariate analysis showed that younger patients without high-risk cytogenetics had the best outcome, followed by younger patients with high-risk cytogenetics, older patients without high-risk cytogenetics, and older patients with high-risk cytogenetics.

cytogenetics; in 25 (53%) patients, +8 was detected within a complex karyotype, and the prognosis of these patients was extremely poor. These findings extend previous data obtained in patient populations that were more heterogeneous with regard to age and treatment showing that +8 as the sole abnormality was associated with an intermediate prognosis similar to that of patients with normal karyotype.[26,27] In contrast, Byrd et al found that in patients with de novo AML (median age, 52 years; proportion of patients older than 60, 36%) who were enrolled on 5 different Cancer and Leukemia Group B (CALGB) trials, sole +8 or +8 with one additional abnormality other than t(8;21), inv(16), or t(9;11) were also associated with significantly inferior OS compared with normal karyotype.[2] Similar to our observations in patients with +8, the prognosis of patients with +11 as part of a complex karyotype was significantly worse than that of patients with +11 within a noncomplex karyotype or normal cytogenetics, although reliability was limited by small sample size.

In addition to +8 and +11 within a noncomplex karyotype, and consistent with the study by Grimwade et al,[7] OS of patients with t(11q23) was also not significantly different from that of patients with normal karyotype. However, the frequency of t(11q23) in our cohort of elderly patients was low (11 of 361 patients, 3%), which is in keeping with previous observations.[7,9,28] As a consequence, we were not able to compare the impact of different types of t(11q23), such as t(6;11), t(9;11), t(10;11), and t(11;19).

Among the 2 low-risk aberrations that were identified in our study, t(15;17) and inv(16), the former was associated with particularly favorable outcome (median OS, not reached; 3-year OS, 55%). This observation reflects that (15;17)-positive APL is a distinct disease entity,[29] and it confirms the high antileukemic efficacy, low toxicity, and high degree of compliance of protocols using ATRA in combination with chemotherapy for induction and consolidation therapy in elderly patients with APL.[7,9,30]

In contrast to t(15;17) and inv(16), long-term outcome of patients with t(8;21) was not better than that of patients with normal karyotype. This result is in line with 2 recent reports. Marcucci et al found that older age was an independent negative prognostic factor for survival in patients with t(8;21), whereas this was not the case when the analysis was restricted to patients younger than 60 years[31]; Schoch et al observed that t(8;21) was not predictive of favorable OS in patients older than 59 years with de novo AML who were treated according to various protocols of the AML Cooperative Group (AMLCG).[9] In the study by Grimwade et al,[7] on the other hand, patients with t(8;21) had a relatively high OS rate (35% at 5 years) despite a 5-year relapse rate of 84%. Similar results were recently reported by Farag et al who demonstrated that t(8;21) and inv(16) were associated with comparable 5-year OS rates (20% and 19%, respectively) in patients 60 years of age or older entered into the CALGB cytogenetic study 8461.[10] Considering that t(8;21)-positive AML in younger patients is highly sensitive to intensive chemotherapy, in particular high cumulative doses of cytarabine,[32-35] it is possible that the worse outcome of our patients was related to the less aggressive treatment that was given in the AML HD98-B trial. Although previous studies have shown that the administration of intensive therapy to older patients was associated with excessive toxicity,[36] improvements in supportive care have increased the tolerability of regimens such as repetitive courses of high-dose cytarabine. Therefore, studies using similar treatment approaches for younger and older patients with t(8;21)-positive AML might be warranted. Alternatively, novel approaches targeting leukemogenic mechanisms, such as aberrant recruitment of histone deacetylase activity, may prove therapeutically useful.[37-40] Clearly, our results regarding the prognostic relevance of t(8;21) need to be interpreted with caution because they are based on a small cohort of patients. This limitation is related to the rarity of this aberration in older patients that has also been noted in previous studies.[7,9,10]

In addition to individual chromosome aberrations, we were also interested in the prognostic impact of karyotype complexity. Although it is commonly accepted that the presence of a complex karyotype predicts an unfavorable clinical course, varying definitions are being used. In the MRC study, complex karyotype was defined by the presence of at least 5 chromosome aberrations in the absence of a prognostically favorable balanced rearrangement.[7] Similarly, Farag et al reported that the long-term outcome of patients with 5 or more cytogenetic abnormalities was significantly worse than that of patients with 3 or 4 aberrations.[10] In contrast, we found that the prognosis of patients with complex karyotype was extremely poor, regardless of definition, and we observed no clinically meaningful difference between patients with 3 or 4 aberrations and patients with 5 or more aberrations. Therefore, our results suggest that discriminating cases with 3 or 4 aberrations from cases with a more complex karyotype does not contribute to the identification of patients who benefit from chemotherapy regimens currently used to treat elderly patients with AML. The reasons that account for the disparity between our findings and previous observations are currently unknown.

When we compared our cytogenetic classification to the MRC stratification system for elderly patients with AML,[7] we noted 2 important differences. First, our system did not identify t(8;21) as a favorable risk abnormality. Second, using our system, 35% of the patients were assigned to the unfavorable risk category, as opposed to 14% in the MRC study,[7] because we identified a large number of patients who had significantly worse OS than patients with normal karyotype but would have been placed in the intermediate-risk category using MRC criteria. This result is in accordance with the most recent CALGB cytogenetic study,[10] in which the majority of patients benefited minimally from chemotherapy.

Our system for outcome prediction using genetic parameters is based solely on the analysis of pretreatment cytogenetic abnormalities, as assessed by conventional chromosome banding and FISH. In younger patients with AML, a number of molecular genetic abnormalities, such as *FLT3* internal tandem duplications, *CEBPA* mutations, or the recently discovered *NPM1* mutations, have been demonstrated to be of prognostic relevance, especially in the large subgroup of patients with normal karyotype.[41-46] Due to the lack of systematic studies in adequately sized patient populations receiving intensive therapy, it remains unclear whether the assessment of molecular disease markers can also improve prognostication and risk stratification in elderly patients with AML.

In many clinical trials, age 60 is arbitrarily used to define "older" patients although it is unknown whether this cut-off actually discriminates patient subgroups with different outcomes. In our cohort of elderly patients, we identified age 70 as a prognostically significant cut-off, and multivariate analysis revealed age above 70 as the other major negative prognostic factor for OS besides high-risk cytogenetics. Stratification of patients according to these 2 parameters demonstrated that a large subgroup of patients, characterized by age 70 or older or high-risk cytogenetics, or both, had very unfavorable long-term outcomes, with patients above age 70 with high-risk cytogenetics showing a particularly poor prognosis. We believe that these findings are of potential relevance for the design of future clinical trials as well as for individual treatment decisions. It is possible that a higher age

cut-off point, for example, 80 years, is even more discriminating.[10] However, the number of patients older than 80 years in our series was too small to draw definitive conclusions.

Collectively, our results demonstrate the clinical importance of cytogenetics and age in patients older than 60 years with AML. In addition, our observations also highlight the dilemma that more than half of the elderly patients who are treated according to current protocols have a very unfavorable prognosis despite intensive chemotherapy. Although it remains to be determined whether the overall prognosis of AML in older patients can be improved by risk-adapted treatment strategies, our findings underscore the need for trials of novel investigational therapies in patients with poor-risk disease.[47]

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Appendix

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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

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