Intensive induction is effective in selected octogenarian acute myeloid leukemia patients: prognostic significance of karyotype and selected molecular markers used in the European LeukemiaNet classification

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Response Criteria

CR was defined as recovery of morphologically normal bone marrow and blood counts [i.e., neutrophils ≥1.5 x 10^9/L (in all studies but three, i.e., ALFA 9803, BGMT 95 and LAMSA 2002, in which ≥1.0 x 10^9/L was used) and platelets >100 x 10^9/L], and no circulating leukemic blasts or evidence of extramedullary leukemia persisting for at least one month.[35] Relapse-free survival (RFS) was measured from the date of CR until the date of relapse or death; patients alive and in CR were censored at last follow-up. OS was measured from the date of study entry until the date of death from any cause, and patients alive at last follow-up were censored.

Estimated probabilities of RFS and OS were calculated using the Kaplan-Meier method, and the log-rank test evaluated differences between survival distributions. All analyses were performed by the Alliance for Clinical Trials in Oncology Statistics and Data Center.

Supplementary Table 1: Distribution of Genetic Groups, Subsets and more common chromosome abnormalities within the Intermediate-II Genetic Group among 138 octogenarian patients with acute myeloid leukemia classified according to the modified (karyotype only) European LeukemiaNet (ELN) reporting system

Genetic Group	Subsets	All Patients (n = 138) count (%)	Patients who died within 30 days (n = 48)[a] count (%)	Patients alive beyond 30 days (n = 90) count (%)
Favorable[b]		2 (1)	2 (4)	0 (0)
	t(8;21)(q22;q22); *RUNX1-RUNX1T1*	2 (100)	2 (100)	0 (0)
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	0 (0)	0 (0)	0 (0)
Intermediate-I[b]		65 (47)	24 (50)	41 (46)
	Normal karyotype	65 (100)	24 (100)	41 (100)
Intermediate-II[b]		42 (30)	14 (29)	28 (31)
	t(9;11)(p22;q23); *MLLT3-MLL*	0 (0)	0 (0)	0 (0)
	Cytogenetic abnormalities not classified as favorable or adverse	42 (100)	14 (100)	28 (100)
	Including[c]: Sole +8 +8 and other abnormalities Sole –Y Tetraploid clone[d] Other Abnormalities	 13 (31) 5 (12) 3 (7) 3 (7) 18 (43)	 5 (36) 2 (14) 0 (0) 1 (7) 6 (43)	 8 (29) 3 (11) 3 (11) 2 (6) 12 (43)
Adverse[b]		29 (21)	8 (17)	21 (23)
	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*	0 (0)	0 (0)	0 (0)
	t(6;9)(p23;q34); *DEK-NUP214*	0 (0)	0 (0)	0 (0)
	t(v;11)(v;q23); *MLL* rearranged	2 (7)	0 (0)	2 (10)
	–5 or del(5q)	3 (10)	1 (13)	2 (10)
	–7	2 (7)	0 (0)	2 (10)
	abnl(17p)	2 (7)	2 (25)	0 (0)
	complex karyotype (≥3 abnormalities)[e]	20 (69)	5 (62)	15 (70)

[a] Comparing all four Groups, the percent of early death rates is not different among the ELN modified Genetic Groups (*P* = .25).

[b] The percentages in the gray boxes are calculated out of the total number of patients in each column. The percentages in the white boxes below each gray box, represent the percentages within patients in the respective ELN Genetic Group (i.e., Favorable, Intermediate-I, Intermediate-II or Adverse).

[c] The abnormalities listed below do not constitute Genetic Subsets in the ELN reporting system; they belong to the "cytogenetic abnormalities not classified as favorable or adverse" Subset.

[d] Tetraploid clone denotes a cell population with the karyotype 92,XXXX (in women) or 92,XXYY (in men).

[e] Complex karyotype is defined by ELN as three or more chromosome abnormalities in the absence of one of the World Health Organization designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Supplementary Table 2: Distribution of Genetic Groups and Subsets among 99 octogenarian patients with acute myeloid leukemia classified according to the European LeukemiaNet (ELN) reporting system

Genetic Group	Subsets	All patients (n = 99) count (%)	Patients who died within 30 days[a] (n = 33) count (%)	Patients alive beyond 30 days (n = 66) count (%)
Favorable[b]		8 (8)	4 (12)	4 (6)
	t(8;21)(q22;q22); *RUNX1-RUNX1T1*	2 (25)	2 (50)	0 (0)
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	0 (0)	0 (0)	0 (0)
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)	5 (63)	2 (50)	3 (75)
	Mutated *CEBPA* (normal karyotype)	1 (12)	0 (0)	1 (25)
Intermediate-I[b]		20 (20)	7 (21)	13 (20)
	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)	4 (20)	2 (28)	2 (15)
	Wild type *NPM1* and *FLT3*-ITD (normal karyotype)	5 (25)	2 (28)	3 (23)
	Wild type *NPM1* without *FLT3*-ITD (normal karyotype)	11 (55)	3 (43)	8 (62)
Intermediate-II[b]		42 (42)	14 (43)	28 (42)
	t(9;11)(p22;q23); *MLLT3-MLL*	0 (0)	0 (0)	0 (0)
	Cytogenetic abnormalities not classified as favorable or adverse	42 (100)	14 (100)	28 (100)
Adverse[b]		29 (29)	8 (24)	21 (32)
	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*	0 (0)	0 (0)	0 (0)
	t(6;9)(p23;q34); *DEK-NUP214*	0 (0)	0 (0)	0 (0)
	t(v;11)(v;q23); *MLL* rearranged	2 (7)	0 (0)	2 (10)
	–5 or del(5q)	3 (10)	1 (13)	2 (10)
	–7	2 (7)	0 (0)	2 (10)
	abnl(17p)	2 (7)	2 (25)	0 (0)
	complex karyotype (≥3 abnormalities)[c]	20 (69)	5 (62)	15 (70)

[a] Comparing all four Groups, the percent of early death rates is not different among the ELN Genetic Groups (*P* = .71).

[b] The percentages in the gray boxes are calculated out of the total number of patients in each column. The percentages in the white boxes below each gray box, represent the percentages within patients in the respective ELN Genetic Group (i.e., Favorable, Intermediate-I, Intermediate-II or Adverse).

[c] Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the World Health Organization designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Supplementary Table 3: Treatment outcome of 138 octogenarian acute myeloid leukemia patients classified by a modified European LeukemiaNet (ELN) reporting system (without molecular markers) and 99 such patients classified by the ELN reporting system

Outcome endpoint	All Patients	Favorable[a]	Intermediate-I[b]	Intermediate-II	Adverse	*P*-value
Modified ELN classification (without molecular markers)	n = 138	n = 2	n = 65	n = 42	n = 29	
Complete remission, no. (%)	41 (30)	0 (0)	22 (34)	13 (31)	6 (21)	.53
Relapse-free survival						.11[c]
Median, years	0.5	–	0.6	0.4	0.3	
Relapse-free at 1 year, % (95% CI)	37 (22-51)	–	40 (19-60)	40 (16-63)	17 (1-52)	
Relapse-free at 3 years, % (95% CI)	13 (4-25)	–	25 (9-45)	0	0	
Overall survival						.09[c]
Median, years	0.3	0.1	0.3	0.3	0.2	
Alive at 1 year, % (95% CI)	24 (17-32)	0	30 (19-42)	26 (13-40)	11 (3-27)	
Alive at 3 years, % (95% CI)	8 (4-14)	0	12 (5-22)	7 (1-19)	0	
ELN classification	n = 99	n = 8	n = 20	n = 42	n = 29	
Complete remission, no. (%)	26 (26)	2 (25)	5 (25)	13 (31)	6 (21)	.60
Relapse-free survival						--[d]
Median, years	0.5	–	0.5	0.4	0.3	
Relapse-free at 1 year, % (95% CI)	39 (22-57)	–	40 (5-75)	40 (16-63)	17 (1-52)	
Relapse-free at 3 years, % (95% CI)	10 (2-26)	–	20 (1-58)	0	0	
Overall survival						.30[c]
Median, years	0.3	0.1	0.3	0.3	0.2	
Alive at 1 year, % (95% CI)	23 (15-31)	25 (4-56)	30 (12-50)	26 (13-40)	11 (3-27)	
Alive at 3 years, % (95% CI)	7 (3-14)	25 (4-56)	10 (2-27)	7 (1-19)	0	

Abbreviations: ELN, European LeukemiaNet; –, not applicable.

[a] In the modified ELN classification, the Favorable Genetic Group comprises only patients with t(8;21) and inv(16)/t(16;16), whereas in the ELN classification,[14] the Favorable Genetic Group includes patients with t(8;21) or inv(16)/t(16;16) and those cytogenetically normal AML patients who harbor mutated *CEBPA*, and/or mutated *NPM1* without *FLT3*-ITD. The Favorable group is excluded from all overall comparisons because of very small (or zero) patient numbers.

[b] For the modified ELN classification, the Intermediate-I Group comprises all cytogenetically normal AML patients. The ELN Intermediate-I Genetic Group includes all cytogenetically normal AML patients that are wild-type *CEBPA*, and either wild-type *NPM1* with or without *FLT3*-ITD or *NPM1*-mutated with *FLT3*-ITD.

[c] There are no significant differences in adjusted pairwise comparisons between groups.

[d] Overall *P*-value cannot be calculated due to small cell counts. Intermediate-II and Adverse Groups are not significantly different from each other (*P*=.40).

Supplementary Table 4: Consolidation therapies of octogenarian patients with AML who survived three years or more

UPN	Consolidation
1	No CR
2	No consolidation and no maintenance[a] courses
3	TAD and HAM for consolidation and 6 maintenance[a] courses
4	1 course Idarubicin 9 mg/m^2 day 1 + cytarabine 60 mg/m^2 SC day 1 to 5
5	HIDAC x2
6	TAD and HAM for consolidation and 24 maintenance[a] courses
7	INT ARAC, DHAD x2
8	off protocol-HIDAC, IDA

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; DHAD, mitoxantrone 5 mg/m^2 every 12 hours intravenously x 6 doses; HAM, cytarabine 1 gm/m^2 via 3-hour intravenous infusion every 12 hours on days 1 and 3 with mitoxantrone 10 mg/m^2 via 60 minute intravenous infusion on days 3-5; HIDAC, high-dose (1.5 gm/m^2 intravenously over 3-hour infusion every 12 hours on days 1, 3 and 5) cytarabine; IDA, idarubicin; INT ARAC, intermediate dose cytarabine 500 mg/m^2 every 12 hours for 6 doses intravenously; SC, subcutaneously; TAD, cytarabine 100 mg/m^2 by continuous intravenous infusion on days 1 and 2 and via 30-minute intravenous infusion every 12 hours on days 3-8, daunorubicin 60 mg/m^2 via 60-minute intravenous infusion on days 3-5 and 6-thioguanine 100 mg/m^2 orally every 12 hours on days 3-9; UPN, unique patient number;

[a] Maintenance included monthly courses of cytarabine 100 mg/m^2 every 12 hours subcutaneously on days 1 to 5 and a second agent on a rotating sequence comprising of daunorubicin 45 mg/m^2 via 60-minute intravenous infusion on days 3 and 4, 6-thioguanine 100 mg/m^2 orally every 12 hours on days 1 to 5, or cyclophosphamide 1 g/m^2 by intravenous injection on day 3.