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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ABSTRACT

We investigated whether octogenarian patients with acute myeloid leukemia enrolled onto Cooperative Group clinical trials and treated with intensive induction therapy could be cured, and whether karyotype and selected molecular markers had any prognostic significance in these patients. Among 138 patients with cytogenetic information, normal karyotype was the most common (47.1%) followed by complex karyotype (14.5%) and sole +8 (9.4%). Among these patients, the relapse-free survival rate at 1 year was 37% and 13% at 3 years, and the respective overall survival rates were 24% and 8%. Whereas the 90 patients who survived beyond 30 days had the same relapse-free survival rates, their 1-year and 3-year overall survival rates were 36% and 11%, respectively. Of the 66 patients surviving beyond 30 days who could be classified into European LeukemiaNet genetic groups, those in the intermediate-I group had better overall survival than patients in the adverse group (P=0.01). Among patients with cytogenetically normal acute myeloid leukemia who were tested for the European LeukemiaNet-associated molecular alterations, *FLT3*-internal tandem duplication and *NPM1* mutations, it was found that *FLT3*-internal tandem duplication (detected in 29% of patients) did not associate with overall survival (P=0.31), whereas *NPM1* mutations (30%) were associated with a significantly longer overall survival (P=0.002). We conclude that intensive induction is effective and indicated in selected octogenarians with acute myeloid leukemia, that their overall survival varies among the European LeukemiaNet genetic groups and that *NPM1* mutations may be of prognostic significance among octogenarian patients with cytogenetically normal acute myeloid leukemia.

Introduction

Acute myeloid leukemia (AML) is mostly a disease of older adults; 24% of patients are aged 75 to 84 years and 10% are 85 years of age or older.[1] The question arises whether to offer intensive treatment to octogenarian AML patients. The only randomized trial for patients aged ≥65 years (n=60 with only 18 patients aged 76-85 years) evaluating intensive induction therapy *versus* supportive care demonstrated significantly longer overall survival for the intensively treated patients.[2] However, the patients' median age was 72 years in that study, which included only a few octogenarian patients. Two trials[3,4] studying patients aged ≥75 years, comprising 22 and 62 patients, and three trials[5-7] evaluating 29, 24 and 45 patients aged ≥80 years demonstrated a marginal, if any, advantage in overall survival for intensively-treated patients.

For patients aged 75 years or older who are not considered fit for intensive treatment, low-dose cytarabine has been demonstrated to be more beneficial than best supportive care and hydroxyurea.[8] Recently, the efficacy of hypomethylating agents such as azacytidine has been studied in older patients (albeit mostly under the age of 80 years) with mixed results.[9-11] Since the data on clinical outcomes of patients aged 80 years or older and factors influencing their outcomes are scarce, we evaluated the impact of an intensive cytarabine/anthracycline-based therapy along with the effects of karyotype, *FLT3*-internal tandem duplication (*FLT3*-ITD) and *NPM1* mutations in a relatively large cohort of octogenarians treated with this type of regimen.

The prognostic impact of karyotype in AML is well

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known,[12-16] but few groups[6,7,17,18] have studied its effect in octogenarian AML patients and conclusions have been mixed. This may stem from the differences in classification systems among studies, treatments, inadequate numbers of patients or all of the above. We, therefore, evaluated whether the European LeukemiaNet (ELN) classification,[19] a modified ELN classification (i.e., a classification based only on karyotype, without molecular markers), and the ELN-associated molecular alterations *FLT3*-ITD and *NPM1* mutations have prognostic significance in octogenarian AML patients receiving intensive induction treatment.

Methods

Patients, treatment, cytogenetic and molecular analyses

We analyzed octogenarian AML patients treated with intensive induction [cytarabine and anthracycline (7+3) or similar regimens] for whom pretreatment karyotyping information was available. The patients were drawn from the German-Austrian AML Study Group [AMLSG; 5 (0.5%) octogenarian AML patients among 947 patients aged ≥60 years], the German AML Cooperative Group [AMLCG; 35 (2%) octogenarians among 1675 patients aged ≥60 years], Cancer and Leukemia Group B [CALGB; 81 (5%) octogenarians among 1571 patients aged ≥60 years] and the Acute Leukemia French Association [ALFA; 17 (4%) octogenarians among 391 patients aged >65 years] between 1984 and 2010, with the majority of patients (58%) being diagnosed between 2000 and 2010. The patients met ejection fraction criteria to receive an anthracycline-containing regimen and were deemed by their treating physicians otherwise fit to undergo intensive induction. AML was defined according to the French-American-British (FAB) classification[20] in most trials; only the AMLSG 06-04 trial (2 patients) required the use of the World Health Organization (WHO) classification,[21] and the CALGB 10201[22] trial (21 patients) allowed the use of either the FAB or WHO classifications. Approximately half of the trials excluded patients with AML evolving from antecedent myelodysplastic syndromes, namely AMLCG 92[23] (2 patients), AMLCG 99[23] (24 patients), BGMT 95[24] (5 patients), CALGB 8221[25] (1 patient), CALGB 8525[26] (5 patients), CALGB 8923[27] (20 patients), CALGB 9420[28] (1 patient) and LAMSA 2002 (3 patients). Consolidation therapies included intensive chemotherapy (AMLCG 99[23] and CALGB 9720,[29] for a total of 10 patients), intermediate-dose chemotherapy (intermediate-dose cytarabine on CALGB 8923,[27] 6 patients) and low-dose chemotherapy (CALGB 8923 and 9720,[27,29] BGMT 95[24] and ALFA 9803,[30] for a total of 9 patients]. Three patients on AMLCG 99 also received maintenance chemotherapy.

Pretreatment karyotype analyses were performed by the Cooperative Groups' institutional cytogenetic laboratories with the results confirmed by central karyotype review, or were performed centrally. The diagnosis of cytogenetically normal AML (CN-AML) was based on the analysis of ≥20 metaphase cells in bone marrow specimens subjected to short-term culture.[31] We used both a modified, karyotype only, ELN-based classification [including t(8;21) and inv(16)/t(16;16) as favorable; CN-AML as intermediate-I; t(9;11) and all other chromosome abnormalities not classified as favorable or adverse as intermediate-II; and inv(3)/t(3;3), t(6;9), t(v;11)(v;q23), -5 or del(5q), -7, abn(17p) and complex karyotype as adverse] (*Online Supplementary Table S1*) and the standard ELN-based classification[19] (*Online Supplementary Table S2*). Complex karyotype was defined as three or more chromosomal abnormalities in the absence of one of the WHO-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) and inv(3) or t(3;3). *FLT3*-ITD,[32] *NPM1*[33] and *CEBPA*[34] mutations were assessed centrally.

All patients provided informed consent and all study protocols were in accordance with the Declaration of Helsinki and approved by Institutional Review Boards at each center.

Statistical analyses

Estimated probabilities of relapse-free survival and overall survival were calculated using the Kaplan-Meier method, and the log-rank test evaluated differences between survival distributions. Associations for baseline demographic, clinical, and molecular features were compared using the Fisher exact and Wilcoxon rank sum tests for categorical and continuous variables, respectively. All analyses were two-sided, with a *P*-value <0.05 considered statistically significant.

Response criteria are described in the *Online Supplementary Material*.

Results

The 138 patients had a median age of 82 years (range, 80-89 years); 81 (59%) were male. One-hundred fifteen patients had *de novo* AML, 13 had secondary AML following an antecedent hematologic disorder (s-AML), nine had therapy-related AML (t-AML) and one had both s-AML and t-AML. Because there was no difference in complete response, relapse-free survival and overall survival rates between patients with *de novo* AML and s-AML/t-AML, all patients were considered together for outcome analyses. Thirteen (11%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 71 (58%) had a PS of 1, 31 (25%) had a PS of 2, six (5%) had a PS of 3 and one (1%) patient had a PS of 4; information on PS was not available for 16 of the patients. Normal karyotype was the most common cytogenetic finding (47.1%), followed by complex karyotype (14.5%) and sole +8 (9.4%). We first categorized patients according to the modified ELN classification into favorable (n=2), intermediate-I (n=65), intermediate-II (n=42) and adverse genetic groups (n=29; *Online Supplementary Table S1*). Of all 138 octogenarian AML patients, 41 (30%) achieved a complete remission, their relapse-free survival rates were 37% at 1 year and 13% at 3 years, and the respective overall survival rates were 24% and 8% (*Online Supplementary Table S3*). To assess the impact of karyotype on outcome, we eliminated 48 (35%) patients who died early (within the first 30 days), thus leaving 90 (65%) patients in the modified ELN classification. No significant differences in early death rates were observed (*Online Supplementary Tables S1* and *S2*).

These 90 patients we evaluated for outcome had a complete response rate of 46%, a median relapse-free survival of 6 months, with a relapse-free rate of 37% at 1 year and of 13% at 3 years, and a median overall survival of 6 months, with an overall survival rate of 36% at 1 year and 11% at 3 years. Patients in the modified ELN intermediate-I group had better overall survival than those in the adverse group (*P*=0.003), whereas there were no significant differences in overall survival between intermediate-I and intermediate-II groups or between intermediate-II and adverse groups (Table 1).

Ninety-nine patients had both karyotype and molecular data enabling their classification according to the ELN reporting system.[19] Their median age was 82 years (range,

80-89 years); 60 (61%) were male. The complete response rate for the 66 patients surviving beyond 30 days was 39%. Their median relapse-free survival was 6 months; the relapse-free rate was 39% at 1 year and 12% at 3 years. Their median overall survival was 5 months; with an overall survival rate of 33% at 1 year and 11% at 3 years. As for the modified ELN classification, patients in the ELN intermediate-I genetic group had better overall survival than patients in the adverse group (P=0.01). There were no significant differences in overall survival between patients in the ELN intermediate-II group and adverse group or between patients in the two intermediate genetic groups (Table 2).

Among 21 CN-AML patients surviving beyond 30 days who were analyzed molecularly, 29% (6/21) harbored *FLT3*-ITD, 30% (6/20) *NPM1* mutations and 4% (1/20) double *CEBPA* mutations. Although *FLT3*-ITD were not associated with overall survival (Figure 1A), *NPM1* mutations were associated with a significantly longer overall survival (P=0.002; median, 91 *versus* 10 months; Figure 1B). Table 3 provides the pretreatment characteristics and treatment outcome of patients surviving beyond 3 years and *Online Supplementary Table S3* provides their consolidation regimens. Five of these patients had ECOG performance status data available; three had a PS of 1 and two a PS of 2. Cytogenetically, six patients had a normal karyotype, and all four CN-AML patients with molecular data available harbored an *NPM1* mutation, with (UPN 3 and 7) or without (UPN 5 and 6) *FLT3*-ITD. The only patient who survived 3 years without achieving a complete remission (UPN 1) had an abnormal karyotype with two clones, each containing a different del(7q) as a sole chromosome abnormality, and carried a *FLT3*-ITD without *NPM1* mutation. Molecular data for the octogenarian patient who was cured and survived almost 17 years (UPN 8) were not available.

Discussion

To our knowledge, this is the largest published series of octogenarian patients with AML enrolled onto treatment trials. Our cohort of patients may not be representative of all octogenarian patients with AML because the patients we analyzed were fit enough to be eligible for intensive chemotherapy, and the number of patients with AML evolving from prior MDS is likely lower than that in the total AML population since the eligibility criteria of some

Table 1. Treatment outcome of 90 octogenarian acute myeloid leukemia (AML) patients who survived more than 30 days classified by a modified European LeukemiaNet (ELN) reporting system (without molecular markers).

Outcome endpoint	All Patients (n = 90)	Favorable[a] (n = 0)	Intermediate-I[b] (n = 41)	Intermediate-II (n = 28)	Adverse (n = 21)	P
Complete remission, n. (%)	41 (46)	NA	22 (54)	13 (46)	6 (29)	0.17
Relapse-free survival						
Median, years	0.5	NA	0.6	0.4	0.3	0.11[c]
Relapse-free at 1 year, % (95% CI)	37 (22-51)	NA	40 (19-60)	40 (16-63)	17 (1-52)	
Relapse-free at 3 years, % (95% CI)	13 (5-25)	NA	25 (9-45)	0	0	
Overall survival						
Median, years	0.5	NA	1.0	0.5	0.3	0.001[d]
Alive at 1 year, % (95% CI)	36 (26-46)	NA	45 (29-59)	37 (20-55)	15 (4-34)	
Alive at 3 years, % (95% CI)	11 (6-20)	NA	18 (8-32)	10 (2-26)	0	

NA: not applicable. [a]The favorable group was excluded from all overall comparisons because no patient was classified in it. [b]For the modified ELN classification, the intermediate-I group comprised all cytogenetically normal AML patients. [c]There were no significant differences in adjusted pairwise comparisons between groups. [d]Adjusted P-values were not significant for the differences between the intermediate-I and intermediate-II groups (P=0.48) or between the intermediate-II and adverse groups (P=0.21). There was a significant difference between the intermediate-I (cytogenetically normal AML) and adverse groups (P=0.003).

Table 2. Treatment outcome of 66 octogenarian acute myeloid leukemia (AML) patients who survived more than 30 days classified by the European LeukemiaNet (ELN) reporting system.

Outcome endpoint	All Patients (n = 66)	Favorable[a] (n = 4)	Intermediate-I[b] (n = 13)	Intermediate-II (n = 28)	Adverse (n = 21)	P
Complete remission, n. (%)	26 (39)	2 (50)	5 (38)	13 (46)	6 (29)	.23
Relapse-free survival						
Median, years	0.5	NR	0.5	0.4	0.3	0.41[c]
Relapse-free at 1 year, % (95% CI)	39 (22-57)	100	40 (5-75)	40 (16-63)	17 (1-52)	
Relapse-free at 3 year, % (95% CI)	12 (3-27)	100	20 (1-58)	0	0	
Overall survival						
Median, years	0.4	NR	1.0	0.5	0.3	0.006[d]
Alive at 1 year, % (95% CI)	33 (22-45)	50 (6-84)	46 (19-70)	37 (20-55)	15 (4-34)	
Alive at 3 years, % (95% CI)	11 (5-20)	50 (6-84)	15 (2-39)	10 (2-26)	0	

NR: not reached. [a]In the ELN classification,[19] the favorable genetic group included patients with t(8;21) or inv(16)/t(16;16) and those cytogenetically normal AML patients who harbored mutated CEBPA, *and/or mutated* NPM1 *without* FLT3-*ITD. The favorable group was excluded from all overall comparisons because of very small numbers of patients. [b]The ELN intermediate-I genetic group included all cytogenetically normal AML patients who were wild-type* CEBPA, *and either wild-type* NPM1 *with or without* FLT3-*ITD or* NPM1-*mutated with* FLT3-*ITD. [c]There were no significant differences in adjusted pairwise comparisons between groups. [d]Adjusted P-values in the following comparisons, intermediate-I* versus *intermediate-II (P=0.98) and intermediate-II* versus *adverse (P=0.09) were not statistically significant. There was a statistically significant difference between the intermediate-I and adverse groups (P=0.01).*

treatment protocols excluded these patients. However, our study demonstrates that intensive induction treatment can result in significantly prolonged (beyond 3 years) relapse-free and overall survival in a select group of patients. It will be of interest to see whether new approaches using, for example, azacytidine or decitabine, produce similar results in this population.

Our results concerning the role of cytogenetic and molecular markers in octogenarian AML patients are similar to those of previous studies demonstrating that the ELN intermediate-I genetic group has better overall survival than the adverse group in AML patients aged ≥60 years.[36,37] However, we did not detect differences in relapse-free survival and observed only a trend towards better overall survival of the intermediate-II group compared with that of the adverse group. A possible explanation could be the small overall number of patients in our cohort, and potential under-representation of patients classified in the adverse group because of a lower number of patients with AML evolving from an antecedent myelodysplastic syndrome. Moreover, a different composition of specific abnormalities in the cytogenetically heterogeneous intermediate-II group could also influence the observed results.[38] For example, no octogenarian patient had t(9;11) whereas this translocation was detected in 6% of intermediate-II group patients aged 60-79 years and 11% of those under the age of 60 years (P=0.002 for the three-way comparison).[37] Conversely, while isolated trisomy 8 was found in 31% of octogenarians in the intermediate-II group, it was detected in 25% of intermediate-II group patients aged 60-79 years and only 15% of those younger than 60 years (P=0.03; Mrózek *et al.*, unpublished results).

The results of outcome analyses with respect to *FLT3*-ITD status among octogenarian patients with CN-AML are consistent with and extend previous reports showing that *FLT3*-ITD loses its prognostic effect in CN-AML patients who are older than 60 years,[39] and especially in those aged 70 years or older.[40] On the other hand, *NPM1*

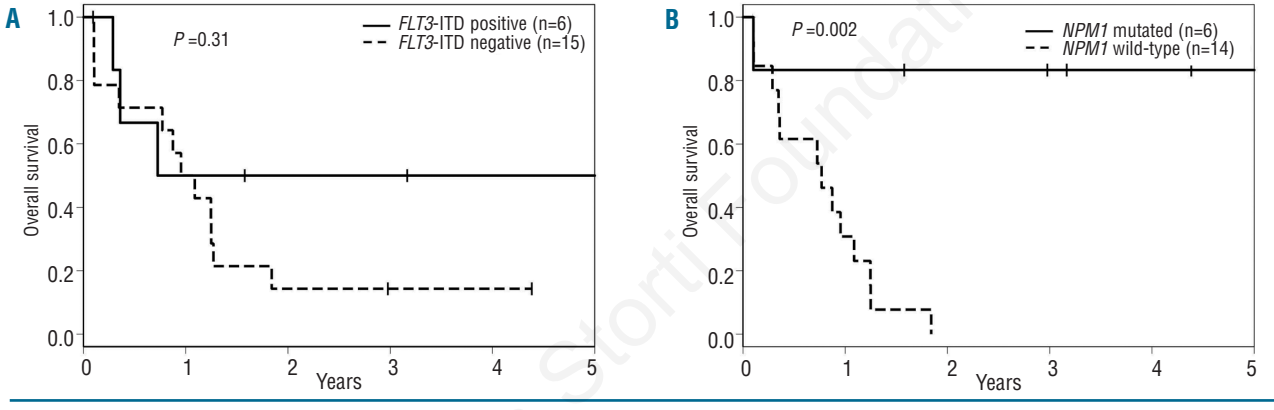

Figure 1. Overall survival of octogenarian patients with cytogenetically normal acute myeloid leukemia who were alive beyond 30 days and for whom data on the molecular markers *FLT3*-ITD and *NPM1* mutation were available. (A) Overall survival by *FLT3*-ITD status. (B) Overall survival by *NPM1* mutation status.

Table 3. Pretreatment clinical and molecular characteristics and treatment outcome of octogenarian patients with AML who survived 3 years or more[a].

UPN	Age (year)	Sex	PS	Race	Karyotype	*NPM1*	*FLT3*-ITD (+/-)	Plts (x10⁹/L)	WBC (x10⁹/L)	PB blasts (%)	BM blasts (%)	CR (+/-)	Died in CR	RFS (year)	OS (year)	Protocol[b]
1	82	F	NA	White	46,XX,del(7)(q22q34)[12]/46,XX,del(7)(q32q34)[8]	wt	+	25	74.2	76	78	-	No	No CR	3.1	CALGB 9720
2	80	M	2	NA	92,XXYY[8]/46,XY[6]	ND	ND	59	34.9	77	95	+	No	3.0	3.1	AMLCG 92
3	85	M	NA	NA	46,XY[25]	mut	+	7	0.5	NA	91	+	A	0.4+	3.2+	AMLCG 99
4	81	F	1	NA	46,XX[20]	ND	ND	75	1.8	0	38	+	Yes	3.1	3.3	BGMT 95A
5	81	F	1	Black	46,XX[20]	mut	-	19	3.3	71	50	+	Yes	4.3	4.4	CALGB 10201
6	80	M	2	NA	46,XY[25]	mut	-	25	10.3	31	80	+	A	5.4+	5.5+	AMLCG 99
7	80	F	1	Black	46,XX[20]	mut	+	87	83.3	88	87	+	U[c]	5.3	7.6	CALGB 8923
8	81	F	NA	White	46,XX[20]	ND	ND	50	2.0	33	45	+	Yes	16.7	16.8	CALGB 9191[d]

A: alive; BM: bone marrow; CR: complete remission; F: female; FAB: French-American-British classification; FLT3-ITD: internal tandem duplication of the FLT3 gene; Hb: hemoglobin; M: male; mut: mutated; NA: not available; ND: not done; OS: overall survival; PB: peripheral blood; Plts: platelets; PS: Eastern Cooperative Oncology Group performance status; RFS: relapse-free survival; U: unknown; UPN: unique patient number; WBC: white blood count; wt: wild-type. [a]All eight patients had de novo AML. [b]Details of the treatment protocols onto which the patients were enrolled are reported as follows: for CALGB 9720 in Baer et al.,[29] AMLCG 92 and AMLCG 99 in Creutzig et al.,[23] BGMT 95 in Pigneux et al.[24] CALGB 10201 in Marcucci et al.,[22] CALGB 8923 in Stone et al.,[27] and CALGB 9191 in Tallman et al.[45] [c]Last follow-up prior to death with CR status known was 5.3 years. The patient died at 7.6 years with CR status unknown. [d]The patient received induction treatment on CALGB 9191 [cytarabine and anthracycline (7+3)], but was taken off protocol following the result of RT-PCR analysis that was negative for the presence of the PML-RARA fusion gene. The patient received consolidation treatment with high-dose cytarabine and idarubicin.

mutations maintain their positive effect on clinical outcome in this age group.[41] Notably, all four molecularly analyzed CN-AML patients who survived beyond 3 years had an *NPM1* mutation. However, because the number of octogenarians we analyzed is still relatively small, our results concerning the prognostic impact of *FLT3*-ITD and *NPM1* mutations are preliminary and should be corroborated by future, larger studies.

Finally, we noted differences in the number of octogenarian patients accrued to AML clinical trials among the four cooperative groups. While this may reflect both patients' and physicians' choices, a prospective analysis of the attitudes of patients and physicians may help to explain these differences, especially in light of our findings that eight of the 90 patients considered were alive at 3 years, and at least four of them never relapsed.

We conclude that intensive induction treatment is effective in select octogenarian AML patients. The definition of "fit" to undergo intensive induction treatment has not been established and accrual to these protocols was mainly based on the choices of physicians and patients. Current scoring systems such as the Charlson comorbidity index[42] and the hematopoietic cell transplantation comorbidity index[43] are not widely accepted. Cytogenetic and molecular alterations have prognostic significance in intensively treated octogenarian patients: patients in the ELN intermediate-I genetic group had better overall survival than those in the adverse group, and CN-AML patients harboring *NPM1* mutations had a superior outcome compared to patients without an *NPM1* mutation. It may, therefore, be worthwhile awaiting the results of cytogenetic and molecular studies before assigning treatment in this group of patients.[44]

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