

Prognostic Significance of Karyotype in Octogenarian Patients with Acute Myeloid

Leukemia - an International Study

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Introduction

- Acute myeloid leukemia (AML) is a disease of the elderly
- The first question is whether to offer intensive treatment to octogenarian AML patients
- A randomized study between intensive induction and best supportive care demonstrated longer survival for intensively treated patients
- However the median age was only 72 years
- Four other studies since then showed marginal, if any, advantage, for intensively treated patients but better outcome for those achieving complete remission (CR)
- Since no other treatment to-date offers a better outcome for these patients we evaluated the impact of karyotype in this age group
- The impact of karyotype in AML is well known but only a few groups studied its effect in octogenarian AML patients and demonstrated mixed results
- One explanation for the mixed results may be the classification system used

Question

Does a modified European LeukemiaNet (ELN) karyotype-based classification (Döhner et al, Blood, 115:453, 2010) without molecular markers have prognostic significance in octogenarian AML patients treated with intensive induction on whom conventional karyotype analyses were completed and centrally reviewed

Methods

- Definitions of clinical endpoints [ie, CR, disease-free survival (DFS) and overall survival (OS)] were standard
- We queried the German-Austrian AML Study Group (AMLSG; 5 pts), the Acute Leukemia French Association Group (ALFA; 17 pts), the German AML Cooperative Group (AMLCG; 35 pts) and the Cancer and Leukemia Group B (CALGB; 81 pts) for AML ($\geq 20\%$ blasts) patients treated with intensive induction [cytarabine and an anthracycline (7+3) or similar regimen] on whom conventional karyotype analyses were completed and centrally reviewed
- The diagnosis of normal cytogenetics (CN) was made based on the analysis of ≥ 20 metaphases in bone marrow specimens cultured for 24-48 hours
- 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
- Associations for baseline demographic, clinical, and molecular features were compared using the Fisher's exact and Wilcoxon rank sum tests for categorical and continuous variables, respectively
- Estimated probabilities of DFS and OS were calculated using the Kaplan-Meier method, and the log-rank test evaluated differences between survival distributions

Results

- Of the 138 patients, including 81 (59%) men and 57 (41%) women, with a median age of 82 years (range, 80-89), 115 patients had *de novo* and 23 had secondary or therapy-related AML (s-AML/t-AML)
- There were 2 patients in the modified Favorable Group [t(8;21) and inv(16)], 65 patients in the modified Intermediate-I Group (CN-AML pts), 44 patients in the ELN Intermediate-II Group [t(9;11) and abnormalities (abn) classified as neither favorable nor adverse] and 27 patients in the ELN Adverse Group [inv(3) or t(3;3), t(6;9), t(v;11)(v;q23), -5 or del(5q), -7, abn(17p) and complex karyotype (≥ 3 abn)]
- In order to assess the impact of karyotype on outcome, we eliminated early (<30 days) deaths
- The CR rate for all 90 (65%) patients surviving beyond 30 days was 46% and their median DFS was 6 months; 37% were disease-free at 1 year and 13% at 3 years
- The median OS for patients surviving beyond 30 days was 6 months, with 36% alive at 1 year and 11% at 3 years
- There was no difference in DFS or OS based on AML type (*de novo* v s-AML/t-AML (Table 1)
- Patients in the modified Intermediate-I Group had better OS than patients in the Adverse Group ($P=0.01$) (Table 2)
- Among CN-AML patients with molecular testing completed, 8/20 (40%) were *NPM1*-mutated, 7/24 (29%) had *FLT3*-internal tandem duplication (ITD) and 1/13 (8%) was *CEBPA*-mutated
- *FLT3*-ITD did not have prognostic significance in the CN-AML cohort (data not shown), but *NPM1* mutation resulted in significantly longer OS (92 v 9 mo, $P=0.04$) in the CN-AML cohort (Figure 1)

- There was no difference between the 2 larger cohorts (AMLCG and CALGB) in regards to patient characteristics or outcome in *de novo* pts; there were insufficient numbers of patients with s-AML/t-AML to compare the 2 cohorts

Table 1: Treatment outcome by disease presentation for 90 patients alive beyond 30 d

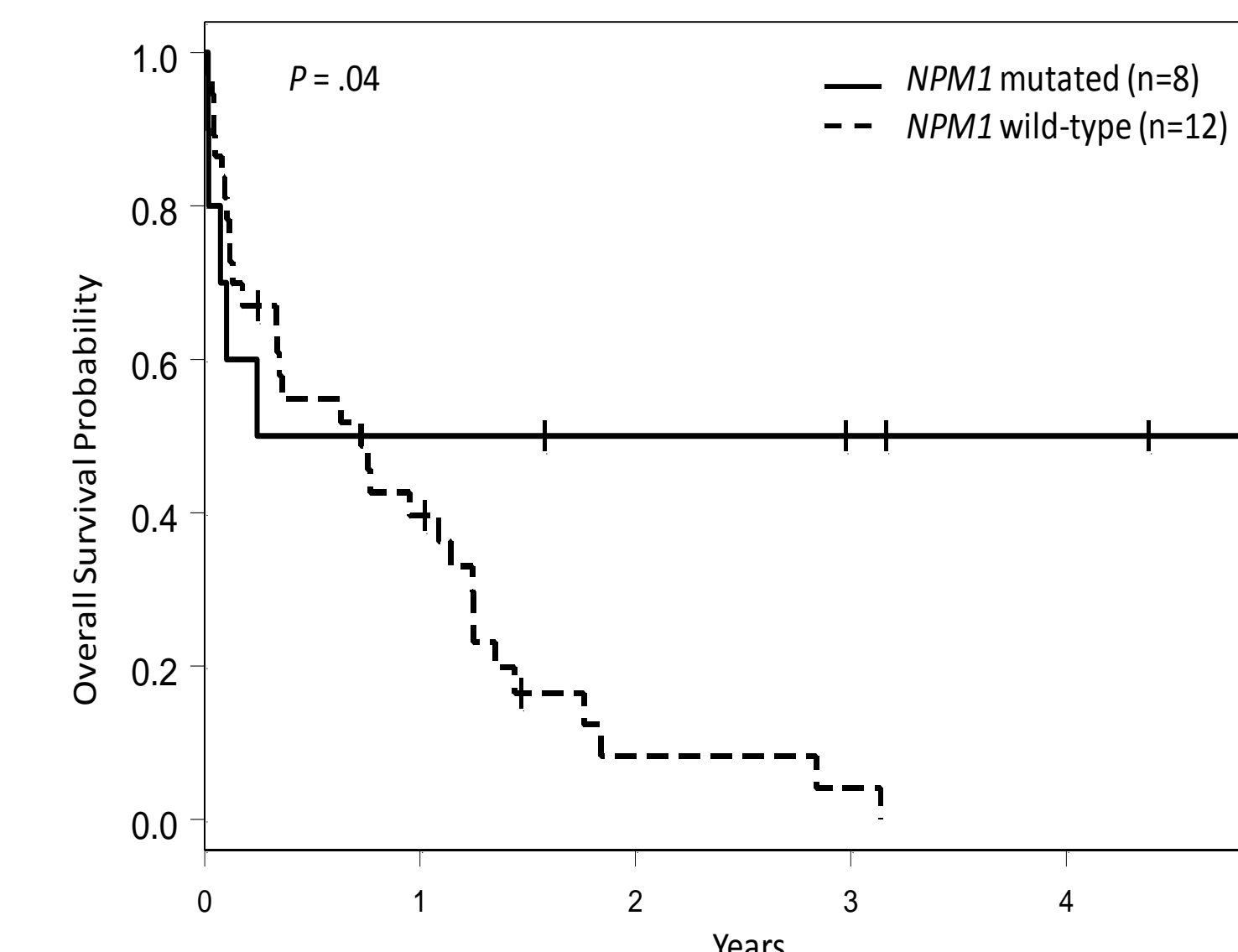
End Point	<i>de novo</i> AML (N=76)	s-AML/t-AML (N=14)	All AML (N=90)	P <i>de novo</i> v s-AML/t-AML
CR, no. (%)	34 (45)	7 (50)	41 (46)	.78
DFS				.67
Median (y)	0.5	0.6	0.5	
% Disease-free at 1 y	38 (22-54)	29 (4-61)	37 (22-51)	
% Disease-free at 3 y	15 (5-30)	0	13 (4-25)	
OS				.25
Median (y)	0.5	0.6	0.5	
% Alive at 1 y	36 (25-47)	36 (13-59)	36 (26-46)	
% Alive at 3 y	14 (7-24)	0	11 (6-20)	

Table 2: Disease outcome by ELN karyotype-based classification without molecular markers for 90 patients alive beyond 30 d

End Point	Intermediate-I (N=41)	Intermediate-II (N=29)	Adverse (N=20)	P
CR, no. (%)	22 (54)	13 (45)	6 (30)	.24
DFS				.11*
Median (y)	0.6	0.4	0.3	
% Disease-free at 1 y	40 (19-60)	40 (16-63)	17 (1-52)	
% Disease-free at 3 y	25 (9-45)	0	0	
OS				.03†
Median (y)	1.0	0.4	0.3	
% Alive at 1 y	45 (29-59)	33 (16-50)	21 (7-41)	
% Alive at 3 y	18 (8-32)	5 (0-20)	5 (0-22)	

* Only Intermediate-I compared to Intermediate-II (too few pts in the Adverse Group)
† This is overall *P*-value. Adjusted *P*-values were not significant for the differences between Intermediate-I and Intermediate-II Groups ($P=.12$) and between Intermediate-II and Adverse Groups ($P=.27$). There was a statistically significant difference between Intermediate-I and Adverse Groups ($P=.01$)

Figure: Overall survival by *NPM1* status in CN-AML patients



Conclusions

- CN-AML patients had better OS in octogenarian AML
- *NPM1* mutation may be of prognostic significance among the CN-AML patients

There are no relevant conflicts of interest to disclose