Prognostic analysis according to the 2017 ELN risk stratification by genetics in adult acute myeloid leukemia patients treated in the Japan Adult Leukemia Study Group (JALSG) AML201 study

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Abstract

The European LeukemiaNet (ELN) first proposed the risk stratification system for AML in 2010 (ELN-2010), and recently published the revised system (ELN-2017). We validated the long-term prognosis and clinical characteristics of each ELN-2017 risk category in Japanese adult AML patients who were enrolled in the Japan Adult Leukemia Study Group (JALSG) AML-201 study. We demonstrated that ELN-2017 successfully discriminated the overall survival in our cohort in comparison with ELN-2010. However, there were still genetic categories in which stratification of patients into favorable or intermediate risk categories was controversial. As many molecular targeting agents, such as FLT3 inhibitors, have been developed, we must continue to modify the genetic risk stratification system to match the progression of therapeutic strategies.

Background

The evaluation of the prognostic risk is clinically important for AML patients to determine the appropriate therapeutic strategy. Although the ELN-2010 based on the cytogenetic and genetic status was useful for further risk stratification of patients, the accumulation of information on the prognostic relevance of recurrent genetic alterations has required further modification to include genetic status [1, 2]. Recently, the ELN published the revised risk stratification system (ELN-2017), in which AML is divided into 3-risk categories [3].

Objective

We validated the long-term prognosis and clinical characteristics of each ELN-2017 risk category in patients who were treated in the JALSG AML-201 study, and evaluated the usefulness of the ELN-2017 risk stratification system in comparison with the ELN-2010 for Japanese AML patients.

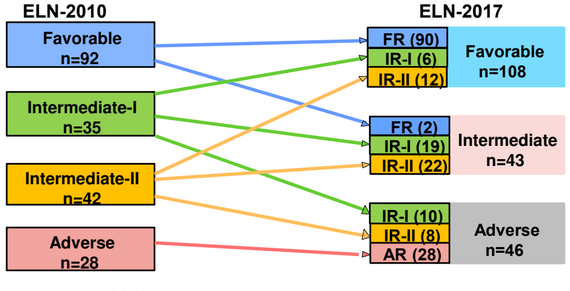
Materials & Methods

The JALSG AML201 study, a multi-center phase 3 randomized study for newly diagnosed *de novo* adult AML patients, except for those of APL. The patients were randomly assigned to receive either idarubicin or daunorubicin in combination with continuous cytarabine daily for 7 days as induction therapy, and those who achieved complete remission were again randomized to receive either 4 courses of conventional consolidation therapy or high-dose cytarabine therapy. The JALSG AML201 study included 1057 patients, 197 of whom were available for comprehensive genetic analysis, and their clinical and genetic data were used for this study.

Distribution of genetic abnormalities according to ELN-2017 risk stratification system

Risk category	Genetic abnormality	Number (%)
Favorable (n=108)	t(8;21)(q22;q22): *RUNX1-RUNX1T1*	41 (20.8)
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22): *CBFB-MYH11*	14 (7.1)
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}	36 (18.3)
	Biallelic mutated *CEBPA*	17 (8.6)
Intermediate (n=43)	Mutated *NPM1* and *FLT3*-ITD^{high}	2 (1.0)
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}	28 (14.2)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*	1 (0.5)
	Cytogenetic abnormalities not classified as favorable or adverse	12 (6.1)
Adverse (n=46)	t(6;9)(p23;q34): *DEK-NUP214*	3 (1.5)
	t(v;11)(v;q23): *KMT2A* rearranged	6 (3.0)
	t(9;22)(q34.1;q11.2); *BCR-ABL1*	2 (1.0)
	-7	1 (0.5)
	Complex karyotype	16 (8.1)
	monosomal karyotype	2 (1.0)
	Wild type *NPM1* and *FLT3*-ITD^{high}	3 (1.5)
	Mutated *RUNX1*	10 (5.1)
	Mutated *ASXL1*	3 (1.5)

Changes in the risk categories between the ELN-2010 and the ELN-2017.



With ELN-2017, the numbers of patients in the favorable and adverse risk group increased due to changes in the risk categories based on genetic status.

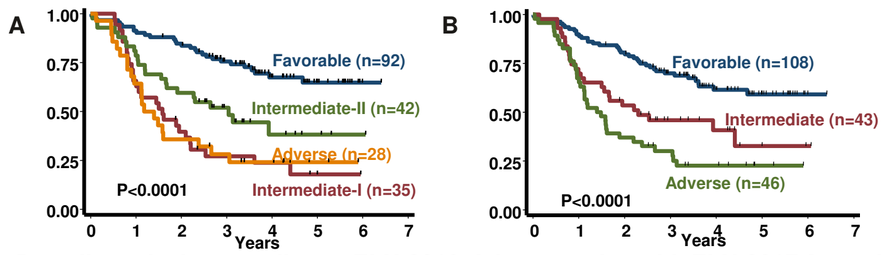
Summary

The OS in the favorable group with the ELN-2017 was lower than that with the ELN-2010 (64.8%). In the favorable risk groups in ELN-2017, the prognosis of patients categorized into IR-I and IR-II by the ELN-2010 was relatively poor, and all IR-I patients had mutated *NPM1* with *FLT3*-ITD^{low}, and all IR-II patients were cytogenetically abnormal and had mutated *NPM1* without *FLT3*-ITD, mutated *NPM1* with *FLT3*-ITD^{low} or bi-allelic mutated *CEBPA*. The allelic ratio of *FLT3*-ITD did not affect the prognosis in patients with *FLT3*-ITD, those with CN-AML, those with wild-type *NPM1* nor those with mutated *NPM1*.

Discussion

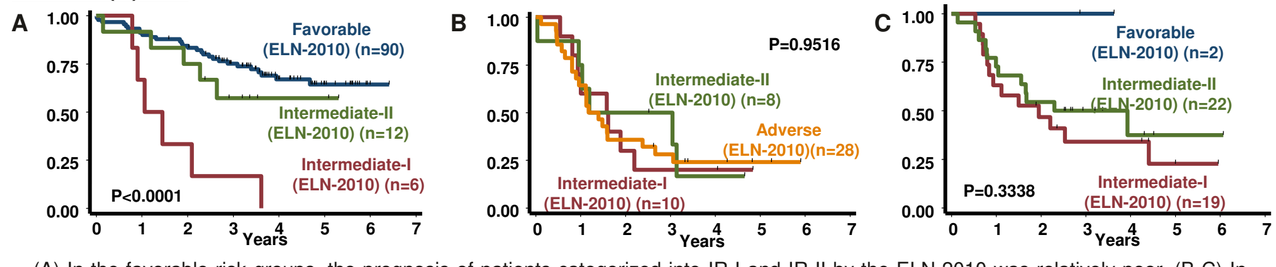
The 3-risk category system of the ELN-2017 successfully discriminated the overall survival in our cohort in comparison with the 4-risk category of the ELN-2010. However, there were still genetic categories in which stratification of patients into favorable or intermediate risk categories was controversial. The low allelic ratio of *FLT3*-ITD was not necessarily associated with a better prognosis in patients with *FLT3*-ITD, and cytogenetic abnormalities may affect the prognosis in patients with favorable genetic lesions such as *NPM1* and *CEBPA* mutations. We must continue to modify the genetic risk stratification system to match the progression of therapeutic strategies.

Overall survivals according to ELN-2010 (A) and ELN-2017 (B) risk categories



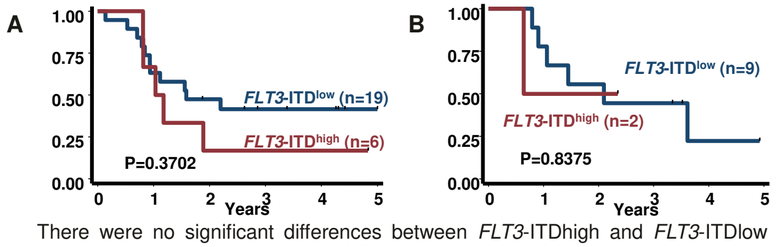
(A) OSs at 5 years in the FR, IR-I, IR-II and AR groups with ELN-2010 were 64.8%, 17.8%, 38.1% and 24.1%, respectively.
(B) OSs at 5 years in the favorable, intermediate and adverse groups with ELN-2017 were 59.1%, 32.6% and 22.6%, respectively.

Overall survivals according to ELN-2010 risk categories with ELN-2017-favorable (A), -intermediate (B) and -adverse (C) risk



(A) In the favorable risk groups, the prognosis of patients categorized into IR-I and IR-II by the ELN-2010 was relatively poor. (B C) In the intermediate and adverse group, there was no prognostic difference among the risk categories with the ELN-2010.

Overall survivals according to the *FLT3*-ITD allelic ratio in patients with wild-type *NPM1* (A) and mutated *NPM1* (B)



There were no significant differences between *FLT3*-ITDhigh and *FLT3*-ITDlow patients with wild-type or mutated *NPM1*.

References

1. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet, *Blood (2010)*.
2. Comprehensive analysis of genetic alterations and their prognostic impacts in adult acute myeloid leukemia patients, *Leukemia (2014)*
3. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel, *Blood (2017)*.