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Age and Modified European LeukemiaNet Classification to Predict Transplant Outcomes: An Integrated Approach for Acute Myelogenous Leukemia Patients Undergoing Allogeneic Stem Cell Transplantation

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Abstract

We evaluated the prognostic significance of a modified European LeukemiaNet (ELN) classification for patients with acute myeloid leukemia (AML) undergoing hematopoietic stem cell transplantation (HSCT) while in first complete remission (CR1).

We analyzed 464 AML patients with matched related (n=211, 45.5%), matched unrelated (n=176, 37.9%) and mismatched donors (n=77, 16.6%). Patients were classified into four modified ELN risk groups (favorable, intermediate-I, intermediate-II, and adverse) separately for 354 patients age <60 years and 110 patients age >=60 years. In this modified version of ELN classification,

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patients with normal cytogenetic were classified by FLT3-ITD mutational status; favorable risk if FLT3-ITD*wild* and intermediate-I if FLT3-ITD*mut*.

The best outcomes occurred in the ELN favorable and intermediate-II groups in younger and in the favorable and intermediate-I groups in older AML patients. Older AML patients had worse transplant outcomes within each modified ELN risk group except intermediate-I when compared with younger patients; LFS at 3-year was 67.8% vs. 49.8% in favorable, 53.4% vs. 50.7% in intermediate-I, 65.7% vs. 20.2% in intermediate-II and 44.6% vs. 23.8% in adverse group younger and older patients respectively. Among lesion-specific abnormalities, del5q/−5 and abnl(17p) had the worse transplant outcomes with 3-year LFS of 18.4% and 20% in younger CR1 patients.

In conclusion, the modified ELN prognostic classification developed for chemotherapy outcomes also identifies prognostic groups for HSCT, which is useful for selection of patients for post-transplant strategies to improve outcomes.

INTRODUCTION

Achieving cure in acute myeloid leukemia (AML) depends on successful induction therapy to achieve a complete remission (CR) and subsequent post-remission therapy to prevent relapse. A major treatment decision is whether to recommend allogeneic hematopoietic stem cell transplantation (HSCT) or to continue with consolidation chemotherapy for patients in first complete remission (CR1). The choice of therapy is determined by patient and disease factors affecting the prognosis with each treatment modality. Allogeneic hematopoietic transplantation is an effective treatment but carries a higher risk of treatment related morbidity and mortality; HSCT is indicated for patients in CR1 when the progression free survival exceeds that achieved with conventional chemotherapy. Based upon prospective and retrospective studies as well as metaanalyses, patients with intermediate or high-risk cytogenetics have been considered candidates for hematopoietic transplantation, while patients with favorable risk cytogenetics have been recommended to continue with consolidation chemotherapy(1, 2).

There has been major progress in defining the molecular pathophysiology of AML, and molecular subtypes of the disease have been described which impact prognosis (3). Recently, an international expert panel, working on behalf of the European LeukemiaNet (ELN), proposed a standardized prognostic system, incorporating both cytogenetic and select molecular abnormalities, separating AML patients to four distinct genetic risk groups (4). At least two studies have demonstrated prognostic stratification when ELN criteria were applied to large patient cohorts receiving chemotherapy, and this prognostic system is being used for treatment planning and clinical trials (5, 6). Adults younger than age 60 with favorable, intermediate-I, intermediate-II and high risk AML have 3 year progression free survival of approximately 55%, 23%, 34% and 10% respectively with chemotherapy. Age is also an independent risk factor in AML. Older patients can successfully receive reduced intensity preparative regimens; patients over age 60 have achieved favorable outcomes compared to chemotherapy (7).

The outcomes for patients in ELN risk categories have not been determined for HSCT as well as the impact of age on the transplant outcome in each ELN category. In the present analyses, we aimed to investigate the prognostic significance of the ELN classification and age in a large cohort of adult AML patients who underwent allogeneic HSCT in CR1 at our institution over the last decade.

METHODS

Patient Population and Transplantation Procedure

We retrospectively analyzed the results of allogeneic HSCT in patients with AML 18 years or older transplanted in CR1 at the University of Texas MD Anderson Cancer Center between January 1, 2001 and June 30, 2014. Disease status at HSCT was defined in accordance with the previously published criteria (8). Patients with incomplete hematopoietic recovery (CRi) were not included in the analyses. The evaluation of comorbidities and assignments of scores were done using the consistent definitions for coding the 17 component of the hematopoietic cell transplant (HCT)-comorbidity index (CI) (9).

Cytogenetic and Molecular Analyses and Grouping of Patients

Complete cytogenetic information was available in 452 of 464 (97.4%) patients. Evaluable patients with diagnostic cytogenetic abnormalities were assessed for the presence of specific chromosomal abnormalities and, complex karyotype (CK) defined as ≥ three cytogenetic aberrations. Core Binding Factor (CBF) abnormalities include t(8;21), inv(16)/t(16;16) and high risk chromosomal abnormalities include inv3(q21q26.2) or t(3;3) (q21q26.2), t(6;9) (p23;q34), t(v;11)(v;q23), −5/del5q, −7 and abnormalities involving 17p. Ultimately, patients were assigned to 4 prognostic groups: favorable, intermediate-I, intermediate-II and adverse risk using the ELN classification as published in 2010 (4) (Table 1). Of 174 patients with normal cytogenetics (CN), FLT3-ITD mutation was evaluable in 145 (83.3%), NPM1 in 77 (44.3%) and CEBPα in 46 (26.4%) patients. There were 75 (43.1%) CN patients that had both FLT3-ITD and NPM1 mutations were evaluable. Therefore we modified ELN classification and prognostic classification of CN patients was determined only by the presence of FLT3-ITD mutation. Patient with CN was classified as favorable risk group if they had FLT3-ITD*wild* and intermediate-I if FLT3-ITD*mut*.

HSCT Characteristics

Patients with peripheral blood (PB), bone marrow (BM) and cord blood (CB) as the hematopoietic stem cell source were included. Among PB or BM recipients, 211 (45.5%) had matched related donors (MRDs) and 176 (37.9%) matched unrelated donors (MUDs). A total of 5 patients (1.1%) had mismatched related donors (MMRDs) and 27 patients (5.8%) had 1-antigen mismatched unrelated donors (MMUDs). A total of 20 patients (4.3%) received a haploidentical graft. Owing to small sample sizes, recipients of MMRD, MMUD, haploidentical donors and CB units were analyzed together as mismatched donors (MMD).

The impact of conditioning regimens on outcomes was analyzed by their dose intensity, using Center for International Blood and Marrow Transplant Research (CIBMTR) criteria

(10). Tacrolimus and methotrexate were used as graft-versus-host disease prophylaxis in the majority of the patients (n=368, 84.4%).

Statistical Analysis and Endpoints Definitions

Outcomes analyzed included leukemia free survival (LFS), cumulative relapse incidence (RI), transplant-related mortality (TRM) and overall survival (OS). All outcomes were measured from the time of stem cell infusion. LFS was defined as survival without leukemia progression or relapse; patients alive without disease progression or relapse were censored at the time of last contact. OS was based on death from any cause. Surviving patients were censored at the time of last contact. Relapse was defined as leukemia recurrence at any site. LFS and OS were calculated using the Kaplan-Meier method. Univariate comparisons of all end points were completed by the log-rank test. Cumulative incidence was used to estimate the endpoints of RI and TRM. A Cox proportional hazards model (11) or the Fine & Gray method (12) for competing hazards was used for multivariate regression. Variables were included in the multivariate model if they were conceptually important or if they approached ($p<0.2$) or attained statistical significance by univariate analysis. All factors were tested for the proportional hazards assumption. All P values were 2-sided. Analyses were stratified by age HSCT. The analyses were based on follow-up through August 2014.

RESULTS

Median age of all patients at HSCT was 52 years (interquartile range, (IQR) 40–59 years). This patient population comprised 354 (76.3%) adults aged younger than 60 years and 110 (23.7%) patients aged 60 years or older. Baseline clinical features of all patients stratified as younger and older patients are presented in Table 2.

Among all 423 evaluable patients by modified ELN, 92 (19.8%) were classified as favorable, 66 (14.2%) intermediate-I, 120 (25.9%) intermediate-II and 145 (31.2%) adverse risk groups. The distribution of modified ELN classification among younger and older patients was similar (p=0.09).

In the subgroup of 75 CN patients that both FLT3-ITD and NPM1 mutation were evaluable, 9 should be categorized as favorable by ELN as they had NPM1*mut* while FLT3-ITD*wild*. The remaining 65 patients were intermediate-I by ELN; 27 had NPM1*wild* and FLT3-ITD*wild*, 33 NPM1*mut* and FLT3-ITD*mut*, 6 had NPM1*wild* and FLT3-ITD*mut*. The modification of ELN led to 27 (36%) patients with NPM1*wild* and FLT3-ITD*wild* to be classified as favorable rather than intermediate-I risk group.

Of 145 patients with adverse risk by modified ELN classification, 7 (4.8%) had inv3(q21q26.2) or t(3;3)(q21q26.2), 10 (6.9%) t(6;9), 26 (17.9%) t(v;11)(v;q23), 59 (40.7%) −5/del5q, 46 (31.5%) −7 and 16 had (11.1%) abnl(17p). CK was seen in 82 patients (56.2%). Within adverse group, older patients had more del5q/−5 abnormality (55.6% vs. 35.5%, p=0.03) while younger patients had more t(v;11)(v;q23) (21.1% vs. 5.6%, p=0.03). The distribution of other lesion specific abnormalities including −7, abnl(17p), t(6;9) and CK were similar between younger and older patients.

The median time to HSCT was 5.4 months (IQR, 4.2–7.9 months) and did not differ between modified ELN risk groups. The median time to HSCT was 6.4, 5.0, 5.7 and 5.1 months for favorable, intermediate-I, intermediate-II and adverse risk groups respectively. Median time to HSCT was also similar for younger and older patients with 5.2 and 6 months. Older patients were more frequently transplanted after 2008, compared with younger patients (p=0.03).

Transplant outcomes by modified ELN classification

Overall 272 of 464 patients were alive at last follow up with a median survival of 37.2 months (IQR, 15.6–74 months). Of 272, 249 (91.5%) were alive and free of disease at their last follow-up. Because of the biological differences and less intensive conditioning regimens received by older patients, we performed outcome analyses separately for younger and older patients. The lowest relapse incidence in younger patients was observed with favorable and intermediate-II groups with 3-year incidences of 15.4% and 14.9% while the highest incidence was 39.8% in adverse risk group (Table 3, Fig 1). Younger intermediate-I risk patients with CN/FLT3-ITD*mut* had high a RI of 36.5% at 3-years which was not different from adverse risk patients (p=0.7). The 3-year RI of 31.1% and 35.5% in older patients with cytogenetic and molecular features consistent with favorable and intermediate-II groups by modified ELN were approximately twice the 3-year RI observed in younger patients though that difference did not reach statistical significance (p=0.1 and p=0.06). However, older patients with intermediate-I and adverse groups had similar RI with the younger patients.

Younger patients in the favorable and intermediate-II groups had the longest LFS with 3-year estimates of 67.8% and 65.7% while those in the adverse risk group the shortest LFS with an estimate of 44.6%. Patients classified in the intermediate-I group had 3-year LFS of 53.4% which was not significantly different than the favorable and intermediate-II groups, but was significantly better than those in the adverse risk group (p=0.003) (Table 3; Fig 1). Older patients had 3-year LFS of 49.8% and 50.7% in the favorable or intermediate-I groups. The 3-year estimates were significantly lower in older patients with intermediate-II and adverse groups at 20.2% and 23.8% respectively. It was striking that older patients had inferior LFS compared with younger patients in each risk group, except the intermediate-I group with CN/FLT3*mut* (Figure1a–1d).

To investigate whether modified ELN groups remain associated with transplant outcomes when controlling for established prognostic factors in AML, we performed multivariable analyses. The results revealed that best outcomes in younger AML patients were observed in favorable and intermediate-II groups while intermediate-I and adverse groups represented the worst prognosis (Table 4). In the younger AML patients, age older than 40 was also associated with increased RI and decreased LFS and OS. For AML patients aged 60 or older, multivariate analyses were not performed for RI, LFS and OS since no other prognostic factor for transplant outcomes, other than modified ELN classification, was identified in the univariate analyses.

Transplant related mortality (TRM) at 1-year was 12.8% in younger and 19.4% in older patients (p=0.05). In younger patients, MMD recipients had higher TRM with 26.4%

compared with 12.9% in MRD recipients (p=0.01). No difference was observed between younger MUD and MRD recipients (p=0.5). In older patients, MUD and MMD recipients had similar TRM as MRD recipients (p=0.7); failure to detect a difference could be due to the small sample size of older MMD recipients.

HCT-CI was also able to identify two different prognostic groups for TRM in younger patients. TRM at 1-year was 7.2% and 11.9% for patients with HCT-CI score of 0 and 1–2 while it was 18.9% and 14.9% in younger AML patients with a score of 3–4 and ≥5 respectively. The difference observed in 1-year TRM between younger patients with HCT-CI < 3 and ≥3 were significant (p=0.02). In older patients, no prognostic separation with HCT-CI was observed (p=0.2).

Transplant Outcomes within modified ELN groups

We analyzed the primary outcome of LFS for specific subsets within each ELN risk group if there was adequate sample size of at least 10 patients.

Favorable and intermediate-I groups by modified ELN—The favorable group by modified ELN included 13 patients with CBF and 76 with CN/FLT3-ITD*wild*. The indication of HSCT in CR1 for CBF patients was the presence of high-risk features including therapy-related AML, central nervous involvement at diagnosis, requirement of at least 2 lines of induction chemotherapy to achieve CR1 and minimal residual disease by molecular studies after consolidation chemotherapy. Patients with CN/FLT3-ITD*wild* were recommended HSCT in CR1 as our institutional policy.

Among younger patients within favorable group by modified ELN, 3-year LFS was 71.3% in 12 patients with CBF and 67.5% in 53 patients with CN/FLT3-ITD*wild* (p=0.9). As indicated, NPM1 mutation analysis was available only on a subset of patients. Therefore we modified ELN classification and prognostic classification of CN patients was determined only by the presence of FLT3-ITD mutation. Patient with CN was classified as favorable risk group if they had FLT3-ITD*wild* and intermediate-I if FLT3-ITD*mut*. Of 53 patients classified in the favorable group by modified ELN since they were CN/FLT3-ITD*wild*, 26 had had NPM1 mutation analysis evaluable and 19 would actually be classified as intermediate-I risk by ELN since they were FLT3-ITD*wild* and NPM1*wild*. However, the 3-year LFS of these 19 patients of 80.5% was comparable with 80.9% in 18 patients with CBF and CN/FLT3-ITD*wild* NPM1*mut* (see supplemental Table 1). Based on these observations and limited sample size of patients with FLT3-ITD and NPM1 evaluable, we did not change our classification and included all CN/FLT3-ITD*wild* as favorable group for our analyses.

Among older patients classified as favorable group by modified ELN, all 27 patients but one had CN/FLT3-ITD*wild*. LFS at 3- year was 55.3% and lower compared with outcome estimates in younger favorable group patients (p=0.09). On the other hand, older patients with CN/FLT3-ITD*mut* classified as intermediate-II group by modified ELN had 3-year LFS of 50.8%, which was comparable to LFS estimates in younger patients (p=0.9). We could not perform subgroup analyses for patient with FLT3-ITD and NPM1 mutations evaluable due to small sample size in older AML patient with CN.

Intermediate-II group by modified ELN—Among younger intermediate-II group patients, 23 of 101 (22.8%) had t(9;11)(p22;q23) and this group had 3-year LFS of 70.4% which was comparable to 3-year LFS of 64.2% (p=0.4) in patients with a heterogeneous set of cytogenetic abnormalities not classified as favorable or adverse risk by ELN classification.

In 19 older patients with intermediate-II group, only 2 had t(9;11)(p22;q23) and subgroup analyses were not performed due to small sample size. The 3-year LFS of 20.2 % in older patients with intermediate-II group was significantly lower compared with 65.7% in younger patients (p<0.001). This striking difference in younger and older patients is most likely caused by the heterogeneity of the cytogenetic abnormalities in both age groups.

Adverse Group by modified ELN—In the younger adverse group, 3- year LFS was 44.6%. When lesion specific abnormalities were analyzed, the presence of −5/del5q and abnl(17p) abnormalities were found to decrease the primary outcome of LFS significantly (Figure 2a–b). Three-year LFS was 18.4% in 39 patients with del5q/−5 compared with 58.1% in 70 patients without the abnormality (p<0.001). Similarly 10 patients with abnl17p had 3-year LFS of 20%, which was inferior to 47.3% in 99 patients without this abnormality (p=0.03). The presence of −7 did not decrease LFS in younger adverse risk patients; 3-year LFS of 39.4% in 31 patients with −7 was comparable with 46.8% in patients without −7 (p=0.2) (Figure2c). This finding remained the same when younger adverse risk group patients were categorized based on the presence of −5/del5q, −7 and abnl(17p) as presented in Table 5.

Of 109 younger adverse risk patients, 23 patients with t(v;11)(v;q23) had superior 3- year LFS of 57.6% compared with 41.3% in 86 patients without t(v;11)(v;q23) (p=0.06) (Figure 2d) and this was most likely caused by the exclusive distribution pattern of t(v;11)(v;q23) abnormality. None of the younger adverse group patients with t(v;11)(v;q23) had other high risk cytogenetic abnormalities defined by ELN classification. The presence of CK within adverse group was not associated with inferior outcomes (Figure 2e); the 3-year LFS of 39.2 % in 60 patients with CK was comparable with 51.2% in 49 patients without CK (p=0.2).

In older adverse group patients, only the impact of −5/del5q, −7 and CK were analyzed since other lesion specific abnormalities were not represented in adequate sample sizes. At 3-years, LFS was 6.7% in 15 older adverse group patients with −7 which was lower compared with LFS of 38.7% in 21 patients without −7 (p=0.05). Similarly, older adverse group patients with −5/del5 had lower 3-year LFS of 13.9% compared with 35.2% without −5/del5q but that difference did not reach statistical significance (p=0.1). CK was also associated with lower LFS with 3-year estimated of 15.9% compared with 36.7% in adverse group patients without significance (p=0.1).

DISCUSSION

This large single-center study with prolonged follow-up demonstrated that the modified ELN classification allows prognostic separation of AML patients, both younger and older, undergoing allogeneic HSCT. Similar to the experience with chemotherapy (5, 6), modified

ELN classification in the context of allogeneic transplantation was able to effectively divide younger patients into 2 prognostic groups, with better outcomes in patients with favorable and intermediate-II groups than in the intermediate-I (including CN/FLT3ITD*mut* patients) and adverse groups. In the older AML patients, modified ELN classification was still able to identify two different prognostic groups but the prognostic groups were different than their younger counterparts. Older AML patients with favorable and intermediate-I group had better outcomes than the intermediate-II and adverse risk groups. The modified ELN classification was predictive for RI, LFS and OS in both age groups and was shown to be independent from other prognostic factors by multivariate analyses.

The most common cause of failure in AML after HSCT continues to be the relapse of the disease. Accurate characterization of patients at risk of disease recurrence is central to design of innovative strategies with the potential to reduce relapse. The most commonly used risk classification schemas were developed from cooperative efforts of the Medical Research Council (MRC)(13), Southwest Oncology Group/Eastern Cooperative Oncology Group (SWOG/ECOG(14)), Cancer and Leukemia Group B (CALGB)(15), and the recently described monosomal karyotype categorize AML patients based only on the cytogenetic information available(16, 17). The ELN classification is an integrated approach, combining leukemia associated molecular abnormalities with cytogenetics to provide a more informative characterization of prognosis. The ELN classification divides patients into 4 prognostic risk groups, with patients having normal cytogenetics characterized according to molecular alterations recognized in the WHO classification, namely *NPM1*, *CEBPA*, and *FLT3* mutations. In our analyses, molecular information other than the presence of FLT3-ITD mutation could not be assessed since the information i.e. for NMP1 and CEBPα mutations was not available for the majority of CN patients. This might lead to categorization of CN patients with NPM1*wild* and FLT3-ITD*wild* as favorable risk rather than intermediate-I risk as suggested by ELN and decrease the LFS in the favorable risk group in our analysis. However, CN/FLT3-ITD*wild* (categorized as favorable in modified ELN) had similar LFS with CBF anomalies and superior LFS compared with CN/FLT3-ITD*mut* who were categorized as intermediate-I risk group, suggesting that the risk groups might differ with post-remission therapy approaches applied.

However, our observation of comparable outcomes of CN/FLT3-ITD*wild* with CBF AML after HSCT in small number of patients needs to be validated in larger cohorts before it can be widely accepted. Despite this limitation, which is inherent in retrospective design analyses, we were able to identify prognostic groups for transplant outcomes using a modified ELN classification, confirming the value of combined molecular and cytogenetic information for risk analyses. We believe that addition of further genetic markers, (eg, DNMT3, *TET2*, *ASXL1*, *RUNX* mutations, *FLT3*-ITD allelic ratio) and novel molecular abnormalities emerging from next-generation sequencing may further refine the accuracy of patient risk stratification after transplantation. This information is critical to identify patients for hematopoietic transplantation and potentially post-transplant therapy strategies to prevent relapse.

We showed that for each modified ELN risk group, except the intermediate-I group including CN/FLT3-ITD*mut* patients, LFS was worse for older patients compared with their

younger counterparts. The prognostic significance of the some genetic alterations may vary in younger and older AML patients. In our cohort, older patients had more therapy related AML which independently is a poor prognostic factor. Older patients were also more likely to receive a RIC regimen that might lead a higher risk of relapse. Despite the inferior results in other risk groups, it is notable that for the intermediate-I group, outcome estimates were comparable to younger patients. There has been considerable debate about the prognostic significance of FLT3-ITD in older patients with AML (18–20). Our findings support the use of allogeneic HSCT for older patients with FLT3-ITD mutations. The 3-year LFS of 50.7% in older transplanted patients is very encouraging and significantly better than approximately 20% reported with chemotherapy in this older population (19). On the other hand, our older cohort was limited in number, and our results need to be confirmed in larger studies before modified ELN is accepted as a useful tool for risk classification in older transplant patients.

Of particular interest is the effect of cytogenetically specific abnormalities on the outcome of ELN risk groups after HSCT. We observed that HSCT in CR1 was able to overcome the poor prognosis of adverse group younger patients if they had complex cytogenetics, −7 and t(v;11)(v;q23). On the other hand, among adverse risk group younger patients, −5/del5q and abnl17p represented a very poor prognostic subgroup with 3 year LFS of 18.4% and 20% respectively even if transplanted in CR1; this is similar to previous published reports (21, 22). The inferior outcomes observed with −5/del5q and abnl17p might be related to mutations in the p53 gene (23). In Medical Research Council (MRC) AML trials, TP53 mutations were present in 44% of patients with del(5q) and 66% in patients with a −5 which may explain the poor outcome in this group (24). *M*ore efficient treatment strategies to induce p53-independent cell death are urgently needed.

We could not investigate the chromosome specific effect of other poor risk cytogenetic abnormalities including inv(3)(q21q26.2), t(3;3)(q21q26.2) and t(6;9) due to the small sample size with these abnormalities. We believe that collaborative efforts will enable the investigation of outcome prediction for rare chromosome-specific abnormalities and help tailor treatment for these rare abnormalities.

The selection of patients for hematopoietic transplantation requires consideration for the outcomes of standard chemotherapy and hematopoietic transplantation in each prognostic group, while also considering the impact of age, comorbidities, psychosocial factors and performance status. A recent consensus statement by the ELN (25) proposed that allogeneic HSCT should be favored if projected disease free survival is expected to improve an individual's risk assessment by 10%. In our series, we clearly show that HSCT can provide long-term disease control in each modified ELN group. These data support use of allogeneic HSCT in CR1, particularly for patients with modified ELN intermediate-I, intermediate II and adverse prognostic groups.

In summary, our results demonstrate clear prognostic separation among modified ELN genetic groups for younger and older AML patients after allogeneic HSCT. Therefore the modified ELN classification can possibly be utilized not only for predicting post-transplant outcomes but also for stratifying patients in clinical trials investigating the role of best post-remission therapies in AML CR1 patients. It will require further validation in larger cohorts

of patients before being widely implemented. We believe further studies to assess the prognostic significance of recently defined molecular abnormalities and minimal residual disease testing will enable us to better determine prognosis with each form of treatment and provide an improved basis for selection of patients for hematopoietic transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ, Wadleigh M, DeAngelo DJ, Stone RM, Sakamaki H, Appelbaum FR, Dohner H, Antin JH, Soiffer RJ, Cutler C. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. Jun 10; 2009 301(22):2349–61. [PubMed: 19509382]
2. Oliansky DM, Appelbaum F, Cassileth PA, Keating A, Kerr J, Nieto Y, Stewart S, Stone RM, Tallman MS, McCarthy PL Jr, Hahn T. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myelogenous leukemia in adults: an evidence-based review. Biol Blood Marrow Transplant. Feb; 2008 14(2):137–80. [PubMed: 18215777]
3. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Lowenberg B, Bloomfield CD, European L. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. Jan 21; 2010 115(3):453–74. [PubMed: 19880497]
4. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Lowenberg B, Bloomfield CD. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. Jan 21; 2010 115(3):453–74. [PubMed: 19880497]
5. Rollig C, Bornhauser M, Thiede C, Taube F, Kramer M, Mohr B, Aulitzky W, Bodenstein H, Tischler HJ, Stuhlmann R, Schuler U, Stolzel F, von Bonin M, Wandt H, Schafer-Eckart K, Schaich M, Ehninger G. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. J Clin Oncol. Jul 10; 2011 29(20):2758–65. [PubMed: 21632498]
6. Mrozek K, Marcucci G, Nicolet D, Maharry KS, Becker H, Whitman SP, Metzeler KH, Schwind S, Wu YZ, Kohlschmidt J, Pettenati MJ, Heerema NA, Block AW, Patil SR, Baer MR, Kolitz JE, Moore JO, Carroll AJ, Stone RM, Larson RA, Bloomfield CD. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. J Clin Oncol. Dec 20; 2012 30(36):4515–23. [PubMed: 22987078]
7. Farag SS, Maharry K, Zhang MJ, Perez WS, George SL, Mrozek K, DiPersio J, Bunjes DW, Marcucci G, Baer MR, Cairo M, Copelan E, Cutler CS, Isola L, Lazarus HM, Litzow MR, Marks DI, Ringden O, Rizzieri DA, Soiffer R, Larson RA, Tallman MS, Bloomfield CD, Weisdorf DJ. Acute Leukemia Committee of the Center for International B, Marrow Transplant R, Cancer, Leukemia Group B. Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60–70 years with acute myelogenous leukemia in first remission. Biol Blood Marrow Transplant. Dec; 2011 17(12):1796–803. [PubMed: 21699879]
8. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, Schiffer CA, Doehner H, Tallman MS, Lister TA, Lo-Coco F, Willemze R, Biondi A, Hiddemann W, Larson RA,

Lowenberg B, Sanz MA, Head DR, Ohno R, Bloomfield CD. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. Dec 15; 2003 21(24):4642–9. [PubMed: 14673054]

9. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. Oct 15; 2005 106(8):2912–9. Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S. [PubMed: 15994282]
10. Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M, Sandmaier B. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. Mar; 2009 15(3):367–9. [PubMed: 19203728]
11. Cox DR. Regression models and life-tables. Journal of the Royal Statistical Society Series B (Methodological). 1972:187–220.
12. Fine JPGR. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94(446):496–509.
13. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, Rees J, Hann I, Stevens R, Burnett A, Goldstone A. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood. Oct 1; 1998 92(7):2322–33. [PubMed: 9746770]
14. Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A, Paietta E, Willman CL, Head DR, Rowe JM, Forman SJ, Appelbaum FR. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood. Dec 15; 2000 96(13):4075–83. [PubMed: 11110676]
15. Byrd JC, Mrozek K, Dodge RK, Carroll AJ, Edwards CG, Arthur DC, Pettenati MJ, Patil SR, Rao KW, Watson MS, Koduru PR, Moore JO, Stone RM, Mayer RJ, Feldman EJ, Davey FR, Schiffer CA, Larson RA, Bloomfield CD. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. Dec 15; 2002 100(13):4325–36. [PubMed: 12393746]
16. Oran B, Dolan M, Cao Q, Brunstein C, Warlick E, Weisdorf D. Monosomal karyotype provides better prognostic prediction after allogeneic stem cell transplantation in patients with acute myelogenous leukemia. Biol Blood Marrow Transplant. Mar; 2011 17(3):356–64. [PubMed: 20553926]
17. Breems DA, Van Putten WL, De Greef GE, Van Zelderen-Bhola SL, Gerssen-Schoorl KB, Mellink CH, Nieuwint A, Jotterand M, Hagemeijer A, Beverloo HB, Lowenberg B. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol. Oct 10; 2008 26(29):4791–7. [PubMed: 18695255]
18. Ferrara F, Criscuolo C, Riccardi C, Izzo T, Pedata M, Copia C, Vicari L, Tarsitano M, Palmieri S, Pane F. FLT3 mutations have no prognostic impact in elderly patients with acute myeloid leukemia and normal karyotype. Am J Hematol. Aug; 2009 84(8):532–5. [PubMed: 19562748]
19. Whitman SP, Maharry K, Radmacher MD, Becker H, Mrozek K, Margeson D, Holland KB, Wu YZ, Schwind S, Metzeler KH, Wen J, Baer MR, Powell BL, Carter TH, Kolitz JE, Wetzler M, Moore JO, Stone RM, Carroll AJ, Larson RA, Caligiuri MA, Marcucci G, Bloomfield CD. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood. Nov 4; 2010 116(18):3622–6. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. [PubMed: 20656931]
20. Breccia M, Latagliata R, Carmosino I, Guarini A, Diverio D, De Cuia R, Cimino G, Alimena G. Negative impact of FLT3 abnormalities in elderly acute myeloid leukemia patients. Leukemia & lymphoma. May; 2008 49(5):994–7. [PubMed: 18464120]
21. Middeke JM, Fang M, Cornelissen JJ, Mohr B, Appelbaum FR, Stadler M, Sanz J, Baurmann H, Bug G, Schafer-Eckart K, Hegenbart U, Bochtler T, Rollig C, Stolzel F, Walter RB, Ehninger G, Bornhauser M, Lowenberg B, Schetelig J. Outcome of patients with abnl(17p) acute myeloid

leukemia after allogeneic hematopoietic stem cell transplantation. Blood. May 8; 2014 123(19): 2960–7. [PubMed: 24652988]

22. Middeke JM, Beelen D, Stadler M, Gohring G, Schlegelberger B, Baurmann H, Bug G, Bellos F, Mohr B, Buchholz S, Schwerdtfeger R, Martin H, Hegenbart U, Ehninger G, Bornhauser M, Schetelig J. Outcome of high-risk acute myeloid leukemia after allogeneic hematopoietic cell transplantation: negative impact of abnl(17p) and −5/5q. Blood. Sep 20; 2012 120(12):2521–8. [PubMed: 22855604]
23. Rucker FG, Schlenk RF, Bullinger L, Kayser S, Teleanu V, Kett H, Habdank M, Kugler CM, Holzmann K, Gaidzik VI, Paschka P, Held G, von Lilienfeld-Toal M, Lubbert M, Frohling S, Zenz T, Krauter J, Schlegelberger B, Ganser A, Lichter P, Dohner K, Dohner H. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood. Mar 1; 2012 119(9):2114–21. [PubMed: 22186996]
24. Bowen D, Groves MJ, Burnett AK, Patel Y, Allen C, Green C, Gale RE, Hills R, Linch DC. TP53 gene mutation is frequent in patients with acute myeloid leukemia and complex karyotype, and is associated with very poor prognosis. Leukemia. Jan; 2009 23(1):203–6. [PubMed: 18596741]
25. Cornelissen JJ, Gratwohl A, Schlenk RF, Sierra J, Bornhauser M, Juliusson G, Racil Z, Rowe JM, Russell N, Mohty M, Lowenberg B, Socie G, Niederwieser D, Ossenkoppele GJ. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. Nature reviews Clinical oncology. Oct; 2012 9(10):579–90. Review.

- A Modified European LeukemiaNet (ELN) classification using only FLT3-ITD mutational status as the molecular marker divides AML patients into two prognostic groups after transplantation.
- The best outcomes occurred in the modified ELN favorable and intermediate-II groups in younger and in the favorable and intermediate-I groups in older AML patients. Even the worst prognostic groups enjoyed prolonged leukemia free survival if transplanted in first complete remission.
- Modified ELN classification can be utilized not only for predicting post-transplant outcomes but also for stratifying patients in clinical trials investigating the role of best post-remission therapies in AML first complete remission patients.

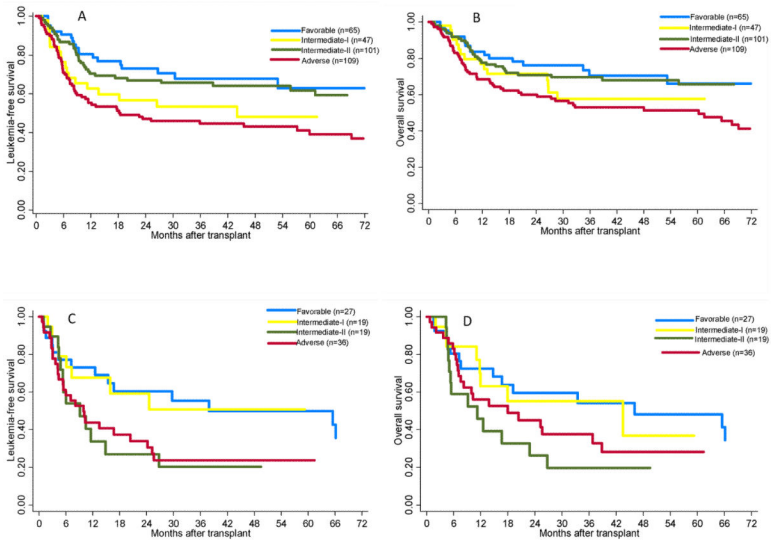

Figure 1.

Leukemia-free and overall survival after HSCT by modified ELN classification in younger and older AML CR1 patients. (A) LFS for patients age <60 (B) OS for age <60. In younger patients, 3-year LFS and OS are 67.8% and 70.4% in favorable; 53.4% and 57.6% in intermediate-I; 65.7% and 69.6% in intermediate-II and 44.6% and 52.9% in adverse risk groups. (C) LFS for patients age ≥60 (D) OS for age ≥60. LFS and OS at 3-years for patients age ≥60 are 49.8% and 54.3% in favorable; 50.7% and 55.3% in intermediate-I; 20.2% and 19.7% in intermediate-II and 23/8% and 37.6% in adverse risk groups.

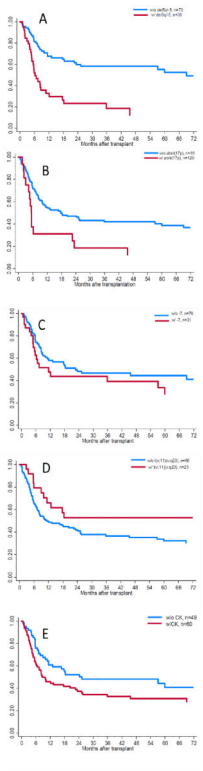

Figure 2.

Leukemia-free survival by lesion specific abnormalities in adverse group younger AML patients after HSCT. Presence of (A) del5q/−5 and (B) abnl 17p were associated with lower LFS. Three-year LFS was 18.4% vs. 58.1% with and without del5q/−5 ($p<0.001$) and 20% vs. 47.3% with and without abnl17p ($p=0.03$). (C) The presence of −7 did not decrease LFS in younger AR patients while (D) t(v;11)(v;q23) was associated with superior 3-year LFS within adverse group (E) The presence of CK within adverse group was not associated with inferior outcomes.

Table 1

Standardized Reporting for Correlation of Cytogenetic and Molecular Genetic Data in Acute Myeloid Leukemia with Clinical Data According to the ELN Guideline

ELN Genetic Risk Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3-ITD* (normal karyotype)
	Mutated CF6Pα(normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3-ITD* (normal karyotype)
	Wild-type *NPM1* and *FLT3-ITD* (normal karyotype)
	Wild-type *NPM1* without *FLT3-ITD* (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*t(6;9)(p23;q34); *DEK-NUP214*t(v;11)(v;q23); *MLL* rearranged−5 or del(5q); −7; abnl(17p); complex karyotype

Table 2

Patient and disease characteristics by disease status at HSCT

	All patients N=464		Age <60 N=354		Age >=60 N=110		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	
Median age (years, IQR)	52 (40–59)		47 (35–55)		64 (61–67)		0.01
AML-t	74	16%	49	13.8%	25	22.7%	0.03
Modified ELN subsets							
Favorable	92	19.8%	65	18.4%	27	24.6%	
CBF	*13*		*12*	*18.5%*	*1*	*3.7%*	
FLT3-ITDwild	*79*		*53*	*81.5%*	*26*	*96.3%*	
Intermediate-1*	66	14.2%	47	13.3%	19	17.3%	
Intermediate-2	120	25.9%	101	28.3%	19	17.3%	
Adverse	145	31.2%	109	31.1%	36	32.7%	0.09
CN/FLT3-ITD-unknown	29	6.2%	25	7.1%	4	3.6%	
Cytogenetics-unknown	12	2.6%	7	2%	5	4.6%	
CN with FLT3-ITD & NPM1 available	75/174				26/49		
NPM1mut FLT3-ITDwild	9	12%	6	12%	3	12%	
NPM1mut FLT3-ITDmut	33	44%	21	42%	12	48%	
NPM1wild FLT3-ITDmut	6	8%	4	8%	2	8%	
NPM1wild FLT3-ITDwild	27	36%	19	38%	8	32%	0.9
Lesion specific abnormalities within AR	145		109		36		
CK	82	56.2%					
inv3(q21q26.2) or t(3;3)(q21q26.2)	7	4.8%	6	5.5%	1	2.8%	NT
t(6;9)	10	6.9%	9	8.3%	1	2.8%	NT
t(v;11)(v;q23)	26	17.2%	23	21.1%	2	5.6%	0.03
del5q/−5	59	40.4%	39	35.5%	20	55.6%	0.03
−7	46	31.5%	31	28.2	15	41.7	0.1
abnl (17p)	16	11%	10	9.2%	6	16.7%	0.2
Cell type							
PB	277	59.7%	215	60.7%	62	56.4%	
BM	162	34.9%	118	33.3%	44	40%	
CB	25	5.4%	21	6%	4	3.6%	0.3
Donor type							
MRD	211	45.5%	164	46.3%	47	42.7%	
MUD	176	37.9%	127	35.9%	49	44.6%	
MMD	77	16.6%	63	17.8%	14	12.7%	0.2
Conditioning intensity							
MAC	376	81%	315	89%	61	55%	
RIC	88	19%	39	11%	49	45%	<0.001

	All patients N=464		Age <60 N=354		Age >=60 N=110		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	
HCT-CI	430/464		323/354		107/110		
0	127	29.5%	108	33.4%	19	17.8%	
1–2	122	28.4%	96	29.7%	26	24.3%	
3–4	104	24.2%	73	22.6%	31	39%	
>=5	77	17.9%	46	14.2%	31	29%	<0.001
Median time to HSCT from diagnosis (mo, IQR)	5.4 (4.2–7.9)		5.2 (4–7.7)		6(5–8.7)		
Year of SCT (after 2008)	274	59%	199	56.2%	75	68.2%	0.03

Abbreviations: HSCT, hematopoietic stem cell transplantation; CR, complete remission; AD, active disease; ELN, European LeukemiaNet; CBF, Core Binding Factor; CN, normal cytogenetics; PB, peripheral blood; BM, bone marrow; CB, cord blood; MRD, matched related donor; MUD, matched unrelated donor; MMD, mismatched donor; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; HCT-CI, Hematopoetic cell transplant-comorbidity index; NT, not tested.

* Intermediate-I included only FLT3-ITDmut patients since the number of patients with NPM1 and FLT3-ITD available were limited.

Table 3

Outcome estimates at 3-years by modified ELN in younger and older patients.

	Favorable	Intermediate-I	Intermediate-II	Adverse
Younger patients				
Relapse incidence	15.4%	36.5%	14.9%	39.8%
Leukemia-free survival	67.8%	53.4%	65.7%	44.6%
Overall survival	70.4%	57.6%	69.6%	52.9%
Older patients				
Relapse incidence	31.1%	28.5%	35.5%	49%
Leukemia-free survival	49.8%	50.7%	20.2%	23.8%
Overall survival	54.3%	55.3%	19.7%	37.6%

Abbreviations: ELN, European LeukemiaNet.

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Table 4

Multivariate regressions for transplant outcomes in younger patients.

	Relapse incidence*			Leukemia-free survival**			Overall survival**		
	HR	**95%CI**	**P**	**HR**	**95%CI**	**P**	**HR**	**95%CI**	**P**
Modified ELN									
IR-I vs. FR	2.7	1.2–6.1	0.01	1.8	0.97–3.5	0.06	1.4	0.7–2.9	0.3
IR-II vs. FR	0.99	0.4–2.2	0.9	1.2	0.7–2.1	0.5	1.1	0.6–2.0	0.7
Adverse vs. favorable	3.1	1.6–6.0	0.001	2.2	1.3–3.6	0.003	2.0	1.2–3.4	0.01
Age >=40 (yes vs. no)	1.8	1.1–2.9	0.02	1.5	1.001–2.1	0.049	1.6	1.1–2.4	0.03
AML-t (yes vs. no)				1.1	0.7–1.7	0.8	1.2	0.7–1.9	0.4
Donor									
MUD vs. MRD				1.2	0.8–1.7	0.3	1.2	0.8–1.8	0.3
MMD vs. MRD				1.4	0.9–2.2	0.2	1.6	1.004–2.6	0.048
HCT-CI									
1–2 vs. 0				1.1	0.7–1.8	0.6	1.3	0.7–2.1	0.7
3–4 vs. 0				1.4	0.9–2.3	0.2	1.9	1.1–3.2	0.02
>=5 vs. 0				1.4	0.9–2.3	0.2	1.7	1.02–3.0	0.04

Abbreviations: HR, hazard ratio; ELN, European LeukemiaNet; IR, intermediate risk; FR, favorable risk; AML-t; therapy-related AML; MUD, matched unrelated donor; MRD, matched related donor; MMD, mismatched related donor; HCT-CI, Hematopoietic cell transplant-comorbidity index.

* Only ELN classification and age at HSCT were forced into the model since they were the only variables with significance p<0.2 at univariate analyses.

** ELN classification, age at HSCT, AML-t, donor type and HCT-CI were forced into the model since they were the only variables with significance of p<0.2 at univariate analyses.

Table 5

Leukemia-free survival in younger adverse risk AML patients by −5/del5q, −7 and abnl(17p).

	N=109 (%)		Leukemia free survival	
		HR	95% CI	P
Absence of −5/del5q, abnl(17p) and −7	54 (49.5%)	1.00		
Absence of −5/del5q and abnl(17p) with presence of −7	13 (11.9%)	1.5	0.6–3.4	0.4
Presence of −5/del5q or abnl(17p) with absence of −7	24 (22%)	3.2	1.7–5.8	<0.001
Presence of −5/del5q or abnl(17p) with presence of −7	18 (16.5%)	2.7	1.3–5.5	0.006