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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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A B S T R A C T

We evaluated the prognostic significance of a modified European LeukemiaNet (ELN) classification for patients with acute myelogenous 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 4 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, patients with normal cytogenetic were classified by *FLT3-ITD* mutational status: favorable risk if *FLT3-ITDwild* and intermediate-I if *FLT3-ITDmut*. The best outcomes occurred in the ELN favorable and intermediate-II groups in younger AML patients 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; leukemia-free survival at 3 years was 67.8% versus 49.8% in favorable, 53.4% versus 50.7% in intermediate-I, 65.7% versus 20.2% in intermediate-II, and 44.6% versus 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 leukemia-free survival rates 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 a selection of patients for post-transplant strategies to improve outcomes.

INTRODUCTION

Achieving cure in acute myelogenous leukemia (AML) depends on successful induction therapy to achieve a complete remission (CR) and subsequent postremission 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 CR (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 progression-free survival exceeds that achieved with conventional chemotherapy. Based on prospective and

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retrospective studies as well as meta-analyses, patients with intermediate or high-risk cytogenetics have been considered candidates for hematopoietic transplantation, whereas 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 that impact prognosis [3]. 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 into 4 distinct genetic risk groups [3]. At least 2 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 [4,5]. Adults younger than age 60 with favorable, intermediate-I, intermediate-II, and high-risk AML have 3-year progression-free survival rates 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 with chemotherapy [6].

The outcomes for patients in ELN risk categories and the impact of age on the transplant outcome in each ELN category have not been determined for HSCT. In the present analyses, we investigated 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 M.D. Anderson Cancer Center between January 1, 2001 and June 30, 2014. Disease status at HSCT was defined in accordance with previously published criteria [7]. Patients with incomplete hematopoietic recovery were not included in the analyses. The evaluation of comorbidities and assignments of scores were done using the consistent definitions for coding the 17 components of the hematopoietic cell transplant-comorbidity index (HCT-CI) [8].

Cytogenetic and Molecular Analyses and Grouping of Patients

Complete cytogenetic information was available in 452 of 464 patients (97.4%). Assessable patients with diagnostic cytogenetic abnormalities were evaluated for the presence of specific chromosomal abnormalities and complex karyotype (CK) defined as ≥3 cytogenetic aberrations. Core binding factor (CBF) abnormalities included t(8;21), inv(16)/t(16;16) and high-risk chromosomal abnormalities included 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 using the ELN classification as published in 2010 [3]: favorable, intermediate-I, intermediate-II, and adverse risk (Table 1). Of 174 patients with normal cytogenetics (CN), *FLT3-ITD* mutation was assessable in 145 patients (83.3%), *NPM1* in 77 patients (44.3%), and *CEBPα* in 46 patients (26.4%). Seventy-five CN patients (43.1%) with both *FLT3-ITD* and *NPM1* mutations were assessable. Therefore, we modified the ELN classification, and prognostic classification of CN patients was determined only by the presence of *FLT3-ITD* mutation. Patients with CN were classified as favorable risk if they had *FLT3-ITDwild* and intermediate-I if *FLT3-ITDmut*.

HSCT Characteristics

Patients with peripheral blood, bone marrow, and cord blood as the hematopoietic stem cell source were included. Among peripheral blood or bone marrow recipients, 211 (45.5%) had matched related donors (MRDs) and 176 (37.9%) matched unrelated donors (MUDs). Five patients (1.1%) had mismatched related donors, and 27 patients (5.8%) had 1-antigen mismatched unrelated donors. Twenty patients (4.3%) received a haploidentical graft. Because of small sample sizes, recipients of mismatched related donors, mismatched unrelated donors, haploidentical donors, and cord blood units were analyzed together as mismatched donors (MMDs).

Table 1
Standardized Reporting for Correlation of Cytogenetic and Molecular Genetic Data in AML 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 *CEBPα* (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

The impact of conditioning regimens on outcomes was analyzed by their dose intensity, using Center for International Blood and Marrow Transplant Research criteria [9]. Tacrolimus and methotrexate were used as graft-versus-host disease prophylaxis in most patients (n = 368, 84.4%).

Statistical Analysis and End Point Definitions

Outcomes analyzed were 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 [10] or the Fine and Gray method [11] for competing hazards was used for multivariate regression. Variables were included in the multivariate model if they were conceptually important or if they approached ($P < .2$) 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 at 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 to 59). This patient population comprised 354 adults (76.3%) aged less than 60 years and 110 adults (23.7%) 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 assessable 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. The distribution of modified ELN classification among younger and older patients was similar ($P = .09$).

In the subgroup of 75 CN patients with both *FLT3-ITD* and *NPM1* mutations, 9 could be categorized as favorable by ELN because they had *NPM1mut* and *FLT3-ITDwild*. The remaining 66 of 75 patients were intermediate-I by ELN: 27 had *NPM1wild* and *FLT3-ITDwild*, 33 *NPM1mut* and *FLT3-ITDmut*, and 6 had *NPM1wild* and *FLT3-ITDmut*. The modification of ELN led to 27 patients (36%) with *NPM1wild* and *FLT3-ITDwild* 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%) had t(6;9), 26 (17.9%) t(v;11)(v;q23), 59 (40.7%) had −5/del5q, 46