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Risk Assessment before Allogeneic Hematopoietic Cell Transplantation for Older Adults with Acute Myeloid Leukemia

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SUMMARY

Acute myeloid leukemia (AML) most commonly affects patients older than 60 years. Outcomes of treatment of older AML patients have been poor. The advent of reduced-intensity conditioning (RIC) regimens made allogeneic hematopoietic cell transplantation (HCT) an available treatment option with curative intent for older AML patients. Because older patients are often excluded from clinical trials, little is known about the stratification of their risks before allogeneic HCT. While recent studies of RIC and allogeneic HCT have shown little impact of age on outcomes, other variables such as the recipient health status and the AML disease status and chromosomal aberrations have proven to be of prognostic significance. Here, we review recent studies of allogeneic HCT for older patients with AML with detailed evaluation of risk factors for relapse as well as non-relapse mortality. We have integrated the currently available information on transplant risks into a five-category risk-benefit system that could aid in the decision-making in this patient population.

Keywords

Acute myeloid leukemia; age; comorbidity; allogeneic hematopoietic cell transplantation; risk-assessment; Chromosome aberrations

INTRODUCTION

Acute myeloid leukemia (AML) is a disease of the elderly with a median age at diagnosis of 68 years. In 2006, an estimated 13,410 individuals (7,060 men, 6,350 women) in the United States (US) developed AML, while 8,990 individuals (5,020 men, 3,970 women) died from the disease. [1] While the average annual incidence of AML is approximately 3.43 per 100,000, the incidence increases progressively with age, to a peak of 55.1 per 100,000 at age 65. [2] Moreover, demographic changes in the US population suggest that patients 65 years old will constitute 20% at 2030 and they will experience a 77% increase in diagnoses of AML between years 2010 and 2030. [3] Thus, establishing criteria for outcome prediction among older AML patients is an important goal.

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Research on anti-leukemia therapy and improvements in supportive care in the past three decades has resulted in relative improvement in the outcomes of AML with 5-year survival of about 20%. [2] Nevertheless, the progress in treating older patients with AML has been very limited [4], with 5-year survival rates of only 5.3% and 1.6% for patients aged 65–74 and 75 years compared to 45.5% for those <45 years. [2] These results were recently confirmed by a retrospective assessment of data from 2444 older patients, who received induction chemotherapy on several protocols with a reported 5-years survival rate of 7%. [5] There are many presumed reasons for the poor outcomes among older AML patients. When compared with younger adults, AML in patients aged 60 years is more frequently associated with antecedent blood diseases, unfavorable cytogenetic abnormalities, expression of multi-drug resistance proteins such as P-glycoprotein, and hence poor response to chemotherapy. [6–8] In addition, older AML patients have relatively high day-30 non-relapse mortality (NRM), up to 25% [9] compared to younger patients (0–10%). [8] These results have limited the accrual of older AML patients to clinical trials exploring novel or higher intensity treatments.

Allogeneic HCT is a potentially curative treatment for many patients with AML. Historically, high-intensity conditioning regimens have been used with the dual aims of disease eradication and host immunosuppression for acceptance of the allografts [10,11]. More than a decade ago, reduced-intensity and truly nonmyeloablative conditioning regimens were introduced to reduce toxicities and mortality that can be associated with high-intensity conditioning [12–15]. The new regimens rely in part or entirely on graft-versus-leukemia effects for tumor eradication. Many phase II trials of RIC regimens have been published [reviewed in [16]]. These regimens allow older patients, those who failed preceding high-dose HCT, and those with comorbidities to undergo allogeneic HCT.

RIC regimens followed by allogeneic (HCT) have been hypothesized to reduce relapse rates of older AML patients; however, no information is available on the real rate of referral for this potentially curative procedure. Nor are standard selection criteria available to avoid denying the procedure to potentially eligible patients or offering it to those who might not tolerate it. Lack of prospective randomized studies and the suspicion of inherent selection bias have made the role of HCT in older AML patients elusive. Here, we review the impact of different risk factors, which may have opposing effects, in the decision-making for allogeneic HCT for older patients with AML. An emphasis on key questions that need to be addressed in future trials will be included.

PATIENT-SPECIFIC RISK FACTORS

Age

Until recently age alone had been the most-widely used measure of a patient's ability to tolerate a given conditioning regimen for allogeneic HCT. However, the prognostic role of age in the HCT setting has not been consistent. In the 1980s, when most of the patients received high-dose conditioning regimens and supportive care measures were less effective, patient age seemed to have an adverse impact on NRM and survival after HCT. [10,17] With the introduction of reduced intensity conditioning (RIC) regimens and improved supportive care, the adverse impact of age has been greatly brought into questions by three key studies.

The first study was a retrospective analysis of registry data from the European Group for Blood and Marrow Transplantation (EBMT) on a total of 1333 patients with myelodysplastic syndromes (MDS) or secondary AML. [18] Median age was 56 (range 50–74) years, among those 449 (34%) were older than 60 years. Grafts were either from HLA-identical siblings (n = 811) or unrelated donors (n = 522). Overall, the 4-year rate of survival was 31%. These estimates were 34% and 27% among patients of 50–60 years and those >60

years of age, respectively, [hazard ratio (HR)=0.87, P=0.23]. Similarly, estimates of NRM were 36% versus 39%, respectively, (HR=1.11; P=0.23). Multivariate analyses confirmed lack of any role of higher age on outcomes. Advanced diseases at HCT and poor-risk cytogenetics were the main determinants of poor survival.

The second study was also a retrospective analysis of registry data from the Center of International Blood and Marrow Transplantation Research (CIBMTR) on a total of 1080 patients including AML (n=545) in first remission and given RIC regimens prior to allogeneic HCT.[19] Among AML patients, 36% were >60 years of age, and 12% were >65 years old. Rates of 2-year survivals among AML patients aged 40–54, 55–59, 60–64, or 65 years were 44%, 50%, 34%, and 36%, respectively. Multivariate analyses showed no impact of chronological age on NRM, relapse, overall (OS), or disease-free survivals (DFS). In these models, unfavorable cytogenetics predicted higher risks for relapse and overall mortality, while Karnofsky performance status (KPS) scores of <80% were associated with higher overall mortality.

The third study was an analysis of data from 372 patients, who were prospectively enrolled into 21 clinical trials of the Seattle Consortium collaborative group.[20] The analysis was specifically focused on patients aged ≥60 years, who received the Seattle-based nonmyeloablative regimen of 2 Gy total body irradiation alone or with fludarabine 90 mg/m². Overall, the cumulative incidence of NRM and the rate of relapse were 27% and 41%, respectively, leading to OS and DFS of 35% and 32%, respectively. Cumulative incidences of NRM were 27% versus 26% versus 31% (P=0.78) when stratified by age groups of 60–65, 65–70, or >70 years. At 5-years, 67% of living patients were entirely well while 33% continued on immunosuppressive medications for chronic GVHD with a median performance status of 90% for both cohorts. This study was unique in testing the impact of age after adjusting for the confounding effects of pre-transplant organ dysfunctions. In multivariate models, increasing age was not associated with any outcomes after HCT; while increasing burden of comorbidities and higher disease risks for relapse were strongly correlated with worse survivals. In a risk-stratification model, patients with low relapse risk and no comorbidities had 5-year rate of survival of 69% while those with the highest risks for relapse and highest burden of comorbidities had survival of 23%.

While these results suggest tolerance of older AML patients to reduced-intensity allogeneic HCT, it is not clear how to translate these results to the general population of older patients diagnosed with AML. Protocol criteria might have been selective for older patients, who had relatively better health status compared to the general population of older AML patients. Further, according to the CIBMTR, only 12% of patients treated with HCT between years 2004–2008 were >60 years old,[21] and in single center studies only a minority of AML patients who were seen in consultation for HCT ended up receiving it.[22] These observations highlight lack of standard criteria for referral of older AML patients to HCT and lack of information on the generalizability of this approach.

Comorbidities

Comorbidities are likely the main factors predisposing older patients with cancer to the morbidity and mortality associated with treatment. In a 'typical' geriatric series, individuals who are 65 years of age and older suffer on average from three different diseases [23]. Previous research has demonstrated that severity of a given comorbidity significantly alters the type of initial anti-cancer treatment.[24] Comorbidity has an independent impact from functional status and, therefore, provides additional prognostic information in older cancer patients [25]. Nevertheless, until 2004, there was almost no effort to evaluate the distribution of comorbidities among HCT recipients, to investigate their impacts on HCT outcomes, or to include them in designing clinical trials. Investigators from Fred Hutchinson Cancer

Research Center (FHCRC) have used a non-transplantation specific comorbidity index, namely the Charlson comorbidity index (CCI) to assess the effects of comorbidities on HCT outcomes. In multivariate analyses, the CCI scores proved to be the only independent predictor of NRM.

The CCI had shortcomings since it identified comorbidities in only 35% of all HCT patients and 12% of recipients of high-dose HCT [26]. Therefore, the same investigators developed a new HCT-CI suited specifically for recipients of allogeneic HCT. They used objective organ functions to redefine pulmonary, cardiac, hepatic, and renal comorbidities. The initial study included 1055 patients with different hematological diseases who were given allogeneic HCT after nonmyeloablative (n=249) or high-dose (n=761) conditioning. Two thirds of the patients were randomly assigned to a training set and one third to a validation set. Integer weights of comorbidities were calculated based on adjusted HRs from Cox proportional hazard models of 2-year NRM. The HCT-CI included 17 different types and grades of comorbidities that were assigned scores ranging from 1 to 3 with no upper limit for the summated score.[27] Scores were weighted for the impacts of regimen intensity and cancer types. In the validation set, HCT-CI scores of 0, 1–2, and 3 showed good discrimination of NRM (14%, 21%, and 41%) and survival (71%, 60%, and 34%), respectively. The HCT-CI scores showed higher discriminative power than the CCI scores both for NRM (c-statistic of 0.692 versus 0.546, $P < 0.001$) and survival (c-statistic of 0.661 versus 0.561, $P < 0.001$).

The same group then used the HCT-CI to stratify and compare outcomes of patients diagnosed with AML or MDS between nonmyeloablative (n=125) and high-dose conditioning regimens (n=452).[28] Multivariate analyses of risk factors among all patients showed that high HCT-CI scores and high disease risk were the most significant factors predicting NRM ($P < 0.0001$ and $P = 0.004$) and OS ($P < 0.0001$ and $P < 0.0001$), respectively. Patients could be stratified into four risk groups incorporating the impacts of both comorbidities and disease-risk. Recipient of nonmyeloablative compared to high-dose regimens who were in group I had comparable 2-year rates of OS of 70% versus 78%, respectively. These rates were 57% versus 50% for group II, 41% versus 45% for group III, and 29% versus 24% for group IV, respectively. In proportional hazard model adjusted for the pretransplantation differences, outcomes were not statistically significantly different among recipients of nonmyeloablative compared with high-dose conditioning, with the exception of lessened NRM (HR=0.50; $P = 0.05$) after nonmyeloablative conditioning in group IV only.

An inferior OS rate of 32% among patients with HCT-CI scores of 3 was confirmed in another study from United Kingdom and the Netherlands, where 128 patients with AML/MDS received alemtuzumab-based RIC followed by allogeneic HCT.[29] OS rates for patients with HCT-CI scores of 0 and 1–2 were 69% and 39%, respectively. In the multivariate analysis, both disease status at time of HCT and the HCT-CI scores had the strongest statistical association with risks for NRM and poor survivals. Investigators from EBMT showed that among AML patients in 1st complete remission (CR) given various RIC regimens, those with HCT-CI scores of 0, 1, 2, and 3 had 2-year cumulative incidences of NRM of 9%, 15%, 18%, and 31%, respectively.[30]

Based on these retrospective analyses, patients with low comorbidity scores were identified as candidates for prospective randomized trials comparing RIC versus high-dose conditioning regardless of disease-status in an ongoing clinical trial (BMT CTN 0901; NCT01339910). Patients with lower comorbidity burden but higher disease burden might benefit from enrolling in clinical trials investigating more intensified conditioning regimens. [31,32] Finally, patients with high HCT-CI scores could benefit from novel conditioning

regimens that target leukemia while sparing patients the lethal toxicities or by exploring novel maintenance drugs after RIC regimens.

Performance Status

Performance status scales are considered to provide a global estimate of the overall health of patients. KPS is one of these scales and it has been found to predict outcomes after RIC and HCT.[33] The KPS was originally developed to measure daily activities, self-care, and evidence of disease but it is not clear the extent to which this scale could capture comorbidities.[34] Previous reports using performance status as the sole measure of the patients' medical impairments have produced varying conclusions reporting correlations between KPS and both NRM and survivals,[35] NRM but not survival,[33] disease relapse and progression-free survival but not NRM,[36] or none of the outcomes.[37] Failure to account for comorbidities and/or absence of uniform guidelines to assess performance status may have been responsible for the variable results.

In a recent study, predictive factors for outcomes were analyzed among 339 patients with hematological diseases given nonmyeloablative conditioning and allogeneic HCT at five different academic institutions.[38] Weak Spearman rank correlations were noted between HCT-CI and KPS, indicating that each of these tools captured different levels of the patients' health status. In multivariate models, the HCT-CI had significantly greater independent predictive power for toxicities ($P=0.004$), non-relapse mortality ($P=0.0002$), and overall mortality ($P=0.0002$) compared to the KPS ($P=0.05$, 0.13 , and 0.05 , respectively). Patients with HCT-CI scores of 0–2 or 3 were further stratified based on KPS percentages of $>80\%$ versus 80% into 4 risk-groups with 2-year survivals of 68%, 58%, 41%, and 32%, respectively. Another study found KPS and comorbidity indices to independently predict NRM.[39] In summary, comorbidities and performance status should be assessed simultaneously before HCT. The use of both tools combined likely refines risk-stratification for HCT outcomes.

Patient and physician Preferences

Patient wishes in regards to intensity and type of treatment may vary and should be incorporated systematically in the decision-making process. Physician perceptions of their respective patient chances of cure might be variable too, and hence might affect referral to transplant centers. A previous study on 436 newly diagnosed cancer patients showed that the impact of being diagnosed with a life-threatening illness may influence preferences to participate in the decision-making process.[40] Socio-demographic variables accounted for only 15% of variance in preferences, suggesting that these variables have limited role in making predictions about patients' decision-making style. Both patient and physician measures were recently validated among 43 older patients with advanced AML choosing between induction chemotherapy and non-intensive chemotherapy/best supportive care [41]. The study showed that patient and physician estimates of cure differed significantly and that regardless of treatment choice, patients reported not being offered treatment options. Most patients (68%) considered themselves to be a primary or equal decision maker with their physicians, whereas 66% of physicians identified themselves as the sole decision maker with or without input from patients. This small study highlighted the need for better and more effective communications during the critical time of decision-making for treatment of a new diagnosis of AML. Education materials including more recent publications in the field and targeting not only patients but also their respective physicians might reduce the magnitude of bias in treatment selection.

Socioeconomic Features

Socioeconomic status could impact choice of treatment, access to specialized care, and/or survival of cancer patients. Previously, a study done on patients from 4 states has shown that black patients were less likely to undergo HCT than white patients.[42] Two other studies assessed the impact of race on HCT outcomes. In the first study, among 2221 recipients of allogeneic HCT black race was associated with significantly higher risks for mortality compared to white race. This apparently was due to higher risks for acute GVHD and NRM among black compared to white race. While a matched-cohort analysis ruled out that the higher mortality among blacks could be due to socioeconomic differences, the authors acknowledged that their study might not have caught unidentified sociocultural differences that might influence medical care (for example there was no assessment of distance between residence and transplant center). Differences in GVHD risks might also have been due to unidentified genetic polymorphisms.[43]

Another study from CIBMTR including a large sample of 6207 recipients of unrelated donors showed, in Cox regression models, higher mortality rates among black patients; while NRM was higher among both black and hispanic patients compared to white patients. Across all racial groups, patients in the lowest quartile of median income had worse overall survival ($RR = 1.15$; $P = .005$) and higher risk of NRM ($RR = 1.21$; $P = .002$) than patients with higher incomes.[44] No statistically significant differences could be found between races in regards to socioeconomic status. Both studies did not report on the distribution of comorbidity among different races. One possibility could be more frequent comorbidities among the black race due to, in part, limited access to care. These questions need to be addressed in the future. Overall, race and socioeconomic status play significant roles in determining outcomes of allogeneic HCT.

Zip code of patient's primary residency has been used to estimate proximity to treatment centers. Among patients diagnosed with cancer, proximity to specialized clinical facilities has been shown to influence access to healthcare and outcomes.[45] Likewise, among allogeneic HCT recipients, driving time to transplant centers was found to independently impact survival. This effect was inversely related to the frequency of clinic visits to the transplantation center [46]. This is not surprising since allogeneic HCT is usually associated with serious complications such as graft-versus-host disease (GVHD) and infection particularly among older and medically infirm patients. Detection and management of these complications would require high level of promptness, a low threshold to intervene, and highly specialized experience.[47] Further studies are needed particularly testing the role of urban versus rural type of patients' primary residence on outcomes.

DISEASE-SPECIFIC RISK FACTORS

Disease Status, Chromosomal Aberrations, and Genetic Markers

The pre-transplant disease status and the types of cytogenetic abnormalities together constitute the most important predictive factor for allogeneic transplantation outcomes in AML.

Among recipients of conventional induction chemotherapy, cytogenetic analyses have allowed for discriminations of different categories of AML with widely different risks for relapse and survivals. Currently, there are three common cytogenetic prognostic/predictive categories (favorable, intermediate, and poor). While these cytogenetic risk groupings were initially developed from data concerning younger AML patients (age <60 years), the same grouping have been shown to apply to older patients as well. Table 1 shows the cytogenetic categories, their prevalence, and associated survival rates based on results from four

collaborative group studies focused on older patients receiving induction chemotherapy at diagnosis of AML.[48–51]

Various prospective studies have been implemented to assess the value of allogeneic HCT among younger patients with these cytogenetic categories of AML. Randomized controlled trials are the gold standard for the evaluation of treatment efficacy but have not been performed among AML patients so far. As the availability of a matched sibling donor is essentially a random process, the presence or absence of a donor was used as a surrogate for randomization. Five collaborative group trials have examined the role of allogeneic HCT in AML in first CR.[52–56] Patients with HLA-identical sibling donors were offered allogeneic transplantation (“genetic randomization”), while those without available donors were randomized between autologous HCT versus consolidation chemotherapy. Across all studies, relapse rates were lower following allogeneic HCT. A recent meta-analysis involving 6000 patients aged 40–60 years, who had AML in first CR assessed the role of “high-dose” conditioning plus allogeneic HCT from identical siblings.[57] In comparison to autologous HCT or intensive chemotherapy, allogeneic HCT conferred a lower HR of 0.8 for disease free survival across all cytogenetic risk groups ($p < 0.01$). Subset analyses, showed the benefit was limited to patients with either unfavorable (HR = 0.69) or intermediate (HR = 0.76), but not favorable-risk cytogenetics (HR = 1.06).

Similar studies have not been performed for older patients. When we discuss role of allogeneic HCT in older patients, we are limited to results from retrospective, mostly inadequately powered, studies. Investigators from the FHCRC analyzed outcomes of 274 patients with a median age of 60 years, who were treated with nonmyeloablative regimen followed by grafts from related or unrelated donors.[58] Overall, incidence of NRM at 5-years was 26% while rates of relapse and OS were 42% and 33%, respectively. Being in first or second CR resulted in comparable survival rates that were better than that among patients who were beyond second CR (rates were 37% and 34% versus 18%, respectively). Unfavorable-risk cytogenetics, as assessed per the Southwest Oncology Group (SWOG) criteria, had 2.7 folds higher risks for relapse compared to favorable- and intermediate-risk cytogenetics.

Investigators from the Cooperative German Transplant Study Group analyzed outcomes of 113 patients given a regimen of fludarabine plus reduced-dose busulfan ($n=93$) or TBI of 4–8 Gy ($n=20$) followed by related or unrelated HCT grafts.[59] Rates of DFS were better (49%) among patients who were in morphologic remissions ($<5\%$ blasts in the marrow) compared to those with 5–20% blasts (24%) or $>20\%$ blasts (14%). Multivariate models confirmed the independent impact of pre-transplant disease status on DFS. DFS was also superior among patient who were in first CR (52%), compared to those who were in second CR (40%) or beyond ($<20\%$).

Another report included recipients of high dose and RIC regimens, who were diagnosed with AML or MDS.[60] RIC regimens included fludarabine and busulfan with addition of antithymocyte globulin for unrelated or HLA-mismatched grafts. Patients with active disease at HCT as defined by presence of chemo-refractory disease or who had $>10\%$ blasts in the marrow had a survival rate of 0% compared to 80% among those who were in CR. Multivariate analysis confirmed that active disease at HCT had the most significant association with increased relapse and mortality after HCT.

Another retrospective study compared outcomes among patients, who were 50–70 years old, given allogeneic HCT ($n = 152$) to those given chemotherapy only ($n = 884$).[61] Allogeneic HSCT in first CR was associated with a significantly lower 3-year rate of relapse (22% versus 62%; $P < 0.001$), which was not offset by the significantly higher cumulative

incidences of NRM (21% versus 3%; $P < 0.001$) resulting in better rates of OS (62% versus 51%; $P = 0.012$) and DFS (56% versus 29%; $P < 0.001$), respectively. Similar results were observed in a CIBMTR registry study focusing on AML patients aged 60–70 years compared recipients of between RIC allogeneic HCT ($n = 94$) to those receiving conventional chemotherapy under the CALGB studies.[62]

Monosomal karyotype abnormality

The presence of autosomal chromosome monosomies in AML is associated with poor prognosis. The monosomal karyotype (MK) entity is defined as the presence of 2 or more autosomal monosomies or combination of 1 monosomy with an additional structural abnormality. A recent retrospective study showed that the rate of 2-year survival was significantly decreased among patients with MK (7%) compared with those without this abnormality (22%; $P < .0001$). Among those with complex karyotype, patients with MK(+) versus those with MK(–) had survival rates of 8% versus 28%, $P = 0.03$. [63] Investigators from FHCRC retrospectively analyzed 432 patients treated with allogeneic HCT, of whom 14% were MK(+). The 4-year rates of OS were 25% for MK(+) AML and 56% for MK(–) AML ($HR = 2.29$, $P < .0001$). The presence of complex karyotype among patients with MK(+) was associated with a significantly worse outcome compared with those with noncomplex karyotype ($HR = 2.70$, $P = .03$). [64]

While the prognosis of MK(+) patients after HCT appears to be remains worse compared to those with MK(–), HCT seems to improve the overall outcome of MK(+) patients when compared to conventional chemotherapy, especially among patients without a complex karyotype. However, patients with MK(+) and age of > 60 years had a 1-year rate of OS of 6%, stressing the need for novel interventions in these patients.

New molecular markers

The intermediate-risk cytogenetic category is the most heterogeneous group in AML, because it includes both normal karyotype without gross structural abnormalities and those with structural changes that are considered neither poor-risk or favorable. The role of HLA-identical sibling HCT among patients in first CR with intermediate-risk cytogenetics remains controversial. Molecular profiling is increasing the ability to identify mutations at the molecular level that are undetectable with standard cytogenetic analyses. These genetic abnormalities could segregate the nearly 50% of patients with normal cytogenetics into less favorable (partial tandem duplications of MLL gene, FMS-like tyrosine kinase 3 (*FLT3*) internal tandem duplications [*FLT3*-ITD], and high expression of BAALC) or more favorable risk (nucleophosmin [*NPM1*] or CEBP- α transcription factor gene point mutation) groups.

Analysis of 4 trials assigning patients with normal cytogenetics and an HLA-matched sibling donor to allogeneic transplantation showed that patients whose leukemia was *NPM1* without *FLT3*-ITD had no improvement in LFS with transplantation versus no transplantation, whereas patients with other combinations more than doubled their 4-year LFS with allogeneic-HCT (47% versus 23%). [65] An analysis of 94 patients with acute myeloid leukemia and normal karyotype after first relapse showed that the presence of a *FLT3*-ITD abnormality was associated with a significantly lower rate of second complete remission. The 6-year survival rate of patients with versus without this abnormality was 15% versus 56%. These differences persisted among the group of patients who received allogeneic HCT as salvage treatment for relapse. [66] Further studies are needed to address the role of these markers among older AML patients treated with allogeneic HCT.

Gene expression profiling is the examination of multiple expressed genes and/or proteins that may provide information about classification and prognostication of individual cancers. The measurement of the expression of thousands of genes was made possible by the development of microarray methodology. GEP represents the “molecular signature” of an individual patient’s tumor and by revealing molecular differences between individual patient’s diseases better selection of treatment should theoretically be possible. In AML, several investigators have identified prognostically important subgroups of patients. [67,68] This is of particular possible benefit for the large group (50%–70%) of AML patients with normal or risk-indeterminate karyotypes. GEP was analyzed in a group of 170 older patients with AML using an unsupervised approach (no knowledge of prior class definitions) that allowed for detection of fundamental groups of patients sharing similar expression signatures.[69] Investigators were able to classify patients into 6 groups, each with clusters of specific genes. These groups were statistically significantly variable in rates of CR ($P = 0.023$), persistent disease ($P < 0.001$), and DFS ($P = 0.023$). Cluster A mainly included NPM1 mutations (78%) and normal karyotypes (75%) and it was associated with the highest 5-year rates of OS (25%) and DFS (27%). Cluster B was dominated by multidrug resistant gene expression (ABCG2, MDR1) and was associated with the highest rate of persistent disease (77%). The lowest rates of OS were seen among patients in clusters B and C (5% and 6%, respectively). Cluster D had the lowest prevalence of NPM1 mutations and the highest prevalence of karyotypic abnormalities with 5-year OS of 18%. Cluster E has the smallest group of patients (11%) and had OS rate of 15%. Finally, cluster F was characterized by predominance of monocytic leukemias (97%) and high representation of NPM1 mutations (61%). The value of these studies in allogeneic HCT outcome prediction remains to be investigated.

TRANSPLANT-RELATED RISK FACTORS

Conditioning Regimens

High-dose regimens are usually not offered to older patients because of the perception that they could cause major organ toxicities in patients older than 60 years. Other conditioning regimen options include first, nonmyeloablative regimens, which cause minimal cytopenia, and little early toxicity, but are immunosuppressive to the extent that they achieve full engraftment when followed by granulocyte-colony stimulating factor mobilized peripheral blood mononuclear cells.[70] These regimens include fludarabine/cyclophosphamide combination,[71] total lymphoid radiation and ATG combination,[72] and 2 Gy TBI-based regimens.[73] Second options include RIC regimens that cause cytopenia, which may be prolonged, and do require stem cell support. It is possible that autologous recovery would eventually occur, although pancytopenia would be of such duration to cause significant morbidity and mortality. RIC regimens differ from high-dose regimens because the dose of alkylating agents or TBI is reduced by at least 30%. These regimens commonly combine fludarabine with an alkylating agent, melphalan[74], busulfan[75], thiotepa[76] or fludarabine in combination of TBI with >5 Gy[77] To date, no prospective studies have been performed to compare the efficacy of these different reduced-intensity regimens among each other.

The feasibility of RIC allogeneic HCT was addressed in one relatively small study from the MD Anderson Cancer Center, which included all untreated AML patients aged ≥ 50 years. Ninety-nine (38%) of a total of 259 enrolled patients achieved CR.[22] Of the 99 patients, 53 were seen by the transplant service for a consult. The reasons for not referring the remaining 46 were unclear in almost half ($n=21$). Among the 53 patients referred to HCT, suitable HLA-matched donors were found for 26 patients and 14 patients actually underwent HCT. The authors attempted to find one or more chemotherapy pair-mates for each patient who underwent transplantation based on cytogenetic risks, age, and lead time bias. There

was a >99% probability that the outcome after RIC was superior to that seen in patients not transplanted. Clearly, this study suffered from small sample size of the patients who received HCT and did not examine the role of comorbidities in the decision not to transplant. Recently, investigators from FHCRC retrospectively reviewed the frequency of RIC allogeneic HCT between 2008 and 2011 in patients with AML in 1st CR.[78] They found that 68% of patients who achieved CR after induction chemotherapy received allogeneic HCT at a median of 5.1 months (range, 1.2–20 months) from their CR1 date. In regression models, increasing age ($P=0.54$) and unfavorable cytogenetics ($P=0.18$) did not influence the frequency of HCT while poor performance status ($P=0.005$) and early relapse ($P<0.001$) did. This more recent study suggests that HCT can be performed in CR1 in the majority of high-risk AML patients in whom it is currently recommended. Prospective studies focusing on older AML patients are needed to assess the extent to which these results can be generalized. NCT00766779 is an on-going Phase III clinical trial of older patients with AML, who achieve CR after 1–2 induction chemotherapy regimens, with a randomization between allogeneic HCT and consolidation chemotherapy.

A database registry study retrospectively examined the outcomes following RIC allogeneic ($n=361$) compared to high-dose autologous HCT ($n=1369$) in patients ≥ 50 years of age, who had de novo AML and were treated between 1997–2003.[79] Recipients of allogeneic HCT had a lower risk for relapse [relative risk (RR) of 0.77, $P=0.013$] and better chances for DFS (RR 1.22, $P=0.02$) and OS (RR 1.32, $P=0.005$) compared to recipients of autologous HCT. Interestingly, no survival benefit could be observed among patients who were in first CR since the fewer relapses were counterbalanced by significantly increased NRM when comparing RIC allogeneic to autologous HCT.

Patients with high-risk AML might have poor response to induction chemotherapy or develop serious infections that preclude them from proceeding to allogeneic HCT. In order to address these problems, several investigators explored the use of “up-front” allogeneic HCT for patients with high-risk or secondary AML.[80,81] In a recent study, 30 untreated patients (20 high-risk MDS and 10 secondary AML) were given first-line therapy with fludarabine, 30 mg/m², amsacrine, 100 mg/m², and Ara-C, 2 g/m², daily for 4 days followed after 2–3 days with high-dose melphalan alone or melphalan and thiotepe and HCT from related ($n=13$) or unrelated ($n=17$) donors.[81] GVHD prophylaxis comprised if antithymocyte globulin, tacrolimus, and mycophenolate mofetil (MMF). CR could be achieved in all patients except 1 due to primary graft failure. Rates of OS, DFS, and NRM at 2-years were 70%, 63%, and 30%, respectively.. Another approach to increase frequency of older patients who survive initial therapy and proceed to HCT is to use novel, non-intensive treatment options to reduce AML disease bulk and bridge patients to HCT. The hypomethylating agent decitabine was used in 15 patients (median age of 69 years) with MDS ($n=10$) or AML ($n=5$) as a first-line treatment. All patients proceeded to reduced-intensity conditioning comprising fludarabine, carmustine, and melphalan followed by allogeneic HCT (4 related and 11 unrelated donors). Among the 15 patients, 1 had graft rejection, 4 died from relapse, 4 died with non-relapse causes, and 6 are alive and in CR.[82] Results from these two approaches are encouraging but require validation at other centers and with larger number of AML patients.

Donor Type

Based on historical data from allogeneic HCT in younger patients with AML, HLA-identical siblings have been the most preferred donor type due to less risks of acute GVHD and NRM hence better survival compared to other donor types. However, the chance of a patient's sibling to be HLA genotypically identical is only 25%. HLA-matched unrelated donor grafts constitute a reasonable alternative to sibling donor grafts. A study from Seattle compared 184 recipients of unrelated to 221 of related grafts. All patients received the

nonmyeloablative preparative regimen of 2 Gy of TBI with (78%) or without (22%) fludarabine, along with posttransplantation MMF and cyclosporine (CSP). In multivariate analyses adjusted for other covariates, the two groups of patients had no statistically significant differences in NRM (HR = 0.98), relapse (HR = 1.04), and OS (HR = 0.99).[83] However, the same group of investigators has reported in an updated analysis statistically significant higher risks for GVHD-associated NRM with unrelated grafts.[84] Investigators from Dana Farber Cancer Institute suggested that the increased minor HLA disparity in unrelated compared to related donors could enhance the GVL activity. They retrospectively compared recipients of HLA-matched unrelated (n=246) to related donors (n=187). All patients received fludarabine and intravenous busulfan conditioning regimen. While the cumulative incidence of NRM at 2-years were comparable between the two groups (8% versus 6%), 2-year relapse rate was lower (52%) after unrelated HCT compared to related HCT (65%, $p=0.005$) resulting in better DFS (39.5% versus 29%, $p=0.01$) but not OS. Multivariate analyses confirmed the advantage of unrelated grafts in lessening risks for relapse (HR = 0.67), $p=0.002$.[85] Clearly, the role of unrelated grafts in allogeneic HCT compared to sibling grafts could be better demonstrated in randomized clinical trials. So far, such trials have not been implemented mainly due to ethical concerns.

The chances of finding even suitably phenotypically matched unrelated donors range from 60% among Caucasians to <20% for ethnic minorities.[86] Moreover, identifying a suitably matched unrelated donor might sometimes consume 2–3 months, which might not be feasible for some patients with potentially high risk for progression or relapse.

Umbilical cord blood (UCB) has the advantage of immediate availability, not to mention absence of any risk to donors and a greater tolerance to HLA disparity with lessened risks of acute GVHD but comparable efficacy of graft-versus-leukemia effects when compared to unrelated donors.[87] The negative impact of HLA mismatch on hematopoietic recovery and survival was shown to be partially overcome by increasing the infused UCB cell dose.[88] Transfusing a relatively high cell dose has become an important element of UCB HCT. Current approaches to achieve this goal include the infusion of two partially mismatched units or the infusion of an ex vivo expanded unit together with an unmanipulated unit. The use of RIC regimens has allowed even further reduction in risks of mortality, by reducing NRM, allowing offering UCB HCT to older patients with AML. A recent study reported the use of low dose TBI conditioning prior to double UCB HCT in treatment of 30 patients, among whom 16 had AML, 11 in first CR and 5 in second CR. Median age was 60 (range 24–73) years. NRM and OS rates at 1-year were 29% and 37.5% for AML patients.[89] Another report using fludarabine/cyclophosphamide conditioning had similar results with NRM of 26% and OS of 45% at 3-years.[90] Other approaches and future advances in UCB transplantation are reviewed in[91].

Another donor type for patients lacking HLA-matched donors is HLA-haploidentical family donors, typically from a parent, sibling or child. The large majority of patients have such a donor available. Success of haploidentical transplants has been dependent on eliminating the severe and often fatal hyperacute GVHD as well as the potent immunologic graft rejection caused by the profound HLA-disparity. One approach is to use T-cell depleted grafts to ameliorate these reactions, resulting in encouraging rates of engraftment and disease control with acceptable rates of GVHD[92]. Recently, investigators at John Hopkins Medical School have used nonmyeloablative conditioning with 2 Gy TBI and fludarabine, 150 mg/m², in addition to cyclophosphamide administered before and after HLA-haploidentical related HCT to facilitate engraftment and delete alloreactive donor T-cell clones presumably involved in GVHD. Sixty-eight patients with advanced hematological malignancies were studied. While NRM was relatively low at 1-year (15%), the rate of relapse was 50% at 1-year resulting in OS and DFS rates of 45% and 32%, respectively. In general patients with

myeloid malignancies had worse DFS compared to those with lymphoid malignancies.[93] Other approaches and future advances in HLA-haploidentical transplantation are reviewed in[94].

HLA-mismatched donors represent another alternative for donor grafts. In one study, the use of 2 Gy TBI-based nonmyeloablative conditioning regimen followed by related (n = 5) or unrelated donor grafts (n = 54) with 1 antigen +/- 1 allele HLA class I mismatch or 2 HLA class I allele mismatches resulted in 2-year OS of 29%.[95] The main limitation of this approach has been the relatively high incidence of grades II-IV acute GVHD (69%) resulting in a NRM incidence of 47% at 2-years. Cyclosporine and mycophenolate mofetil were used for GVHD prophylaxis in this study. Current approaches are testing alternate GVHD prophylaxis regimens to maximize the benefit from these mismatched transplants. A large study from CIBMTR assessed the association between HLA matching and outcome in unrelated-donor HCT. Overall, 1933 unrelated-donor recipients were included in the study, among those 946 (49%) were diagnosed with AML, 811 (42%) were aged ≥ 50 years, and 673 (35%) received RIC regimens. All patients had high-resolution typing for HLA-A, -B, -C, -DRB1, -DQA1, and -DQB1.[96] When outcomes were compared between HLA-matched and HLA-mismatched pairs, after adjusting for patient and transplant characteristics, 8/8 matching for HLA-A, -B, -C, and -DRB1 alleles was associated with better survival at 1 year compared with 7/8 HLA-matched pairs (56% vs. 47%). HLA-C antigen mismatches (n = 189) were statistically significantly associated with lower leukemia-free survival (relative risk [RR] = 1.36; $p=0.001$), and increased risk for mortality (RR = 1.41; $p=0.0005$), NRM (RR = 1.61; $p=0.0002$), and grade III-IV acute GVHD (RR = 1.98; $p<0.0001$). HLA-B antigen or allele mismatching was associated with an increased risk for acute GVHD grade III-IV. No statistically significant differences in outcome could be detected for HLA-C allele (n = 61), HLA-A antigen/allele (n = 136), HLA-DRB1 allele (n = 39), or HLA-DQ antigen/allele (n = 114) mismatches compared with 8/8 HLA-matched pairs. HLA mismatch was not associated with relapse or chronic GVHD. Clearly, the study had the limitation of small sample size for some of the mismatch groups and the study was not dedicated to older AML recipients of RIC regimens. Future studies are still needed to ensure that the impacts of these matches are reproducible in the older population given RIC regimens.

Donor Age

The increasing trends of allogeneic HCT among older patients resulted in an increase in the median age of sibling donors raising concerns of donor safety, among donors with significant comorbidities, and the quality and quantity of mobilized peripheral blood stem cells and hence transplant outcomes. Studies focusing on young recipients of high-dose conditioning have suggested an association between advanced donor age and risks of acute and chronic GVHD[97] and risks of poor survivals.[98] These results were not reproduced among older patients given RIC regimens. In 125 recipients (median age was 55 years) of nonmyeloablative conditioning and allogeneic HCT, multiple linear regression analysis showed that advanced donor age was only associated with lower day +28 donor T-cell chimerism ($p=0.02$).[99] There were no impacts of donor age on relapse or survival. Another study found an adverse impact of advanced donor age on counts of naïve CD4 T cells on days 180–365 after HCT.[100] A recent study found in multivariate models that older donor age by decade was associated with lower risk of NRM (HR = 0.64, $p=0.013$) and improved OS (HR = 0.76, $p=0.045$).[101] Another study asked the question whether an older HLA-matched donor confer an inferior outcome compared to an available younger allele-level 8/8 HLA-matched unrelated donor.[102] This was a CIBMTR study analyzing outcomes of leukemia/ lymphoma patients aged ≥ 50 years comparing recipients of older related (n=1,415) versus younger unrelated donors (n=757). Overall, recipients of younger

unrelated grafts had higher risks of acute GVHD grade 2–4 (HR 1.63; $P<0.001$) and chronic GVHD (HR 1.48; $P<0.0001$) compared to those of older related grafts.

Results from these studies suggest a possible adverse impact of older related donor age on immunological recovery but without significant impact on other outcomes. Grafts from older HLA-identical siblings should still be preferred to those from younger HLA-matched unrelated donors

GLOBAL PROGNOSTIC MODELS

The previously described risk factors have been used individually in regression models to tease out the most important ones for decision-making for a uniform group of patients. Hence, investigators can choose the most suitable factors for their analyses or clinical trial assessments based on the transplant setting being tested.

Global prognostic models are designed under a different concept with the intent of being applicable to any transplant situation. One of the earliest models is the EBMT risk score, which was originally developed among patients diagnosed with chronic myeloid leukemia, the most common indication for an allogeneic HCT prior to the availability of tyrosine kinase inhibitors.[103] The model included patient age, disease stage, donor type, time from diagnosis to HCT, and donor/recipient gender combinations as variables acquiring scores in an additive way with a range of 0–7 total score. The EBMT risk score was tested for prediction of outcomes of HCT among other hematological malignancies in a group of 56,505 patients with a median age of 33 (range 0.5–77) years, who were treated between 1980–2005.[104] Patients diagnosed with AML were a large sample of 16,113 patients. It is not clear how many older AML patients were included in this study but 5661 were older than 40 years. Overall, the risk score predicted outcomes well with survival rates ranging between 75% for those with score 0 to 25% for those with the highest scores, 6–7. Similarly, incidences of NRM ranged between 11% and 45%, respectively. No outcomes percentages were provided per disease categories. The predictive power of the model was tested by computing the receiver operating characteristics area under the curve using Harell's *c*-statistics. The EBMT risk score among AML patients had a *c*-statistic estimate of 0.630 indicating only moderate degree of predictive power since for example, the previously described HCT-CI, as a single risk factor summarizing burden of comorbidities, had *c*-statistic estimates of 0.661.[27]

Another model is the pre-transplantation Assessment of Mortality (PAM) score that incorporated 8 variables: patient age, donor type, disease risk, conditioning regimen, forced expiratory volume in one second (FEV1), carbon monoxide diffusion capacity, serum creatinine level, and serum alanine aminotransferase concentration with a possible total score of up to 50-points.[105] Similar to the EBMT score, since the PAM had a mix of patient-, disease-, and transplant-specific factors it was meant to estimate probabilities of survival not NRM. Validation cohorts for this index were chosen from the same sample used to design the model, and these incorporated the three cohorts with the most common diagnoses, CML ($n=1017$), AML ($n=667$), and MDS ($n=407$). Among patients with AML, the lowest category had no patients while HRs increased in categories 3 and 4 compared to category 2. The *c*-statistic for prediction of survival among AML patients was 0.72. Lack of an independent validation cohort and absence of any follow up studies assessing the external validity of the PAM have limited its usage.

EXPERT COMMENTARY

We have described in Table 2 the most important criteria that define patients for whom allogeneic HCT might not be indicated either due to lack of evidence for survival benefit

compared to non-transplant treatments (category 1) or due to unacceptable mortality risks that predict survival chances <5% at 1-year (category 5). Patients under category 5 could be considered for allogeneic HCT if under a clinical trial with conditioning and GVHD prophylaxis regimens that are adapted to one or more of the associated higher-risk features.

The table also includes three other categories (categories 2–4) for risk-benefit ratio assessments before HCT: good-, intermediate-, and poor-risk categories. Patients under the good risk category could expect 5-years survival rates of 70% or more. Patients under the intermediate and poor-risk categories would experience less favorable survival compared to the good-risk category. Patients from these higher-risk categories could benefit from enrollment into clinical trials exploring novel, less toxic AML-targeted therapeutic additions to conditioning regimens to improve disease control without significant increase in NRM. Poor-risk category patients might also benefit from interventions aimed at improving their physical performance and/or ameliorating their comorbidities during the peri-transplant period (days –20 to day +80).

Clearly, age per se has no determinant effect on HCT outcomes with the exception that the maximum age range for RIC and allogeneic HCT reported in clinical trials was 75 years. Therefore, we limited our risk stratification criteria to this age range. Patients aged >75 years who are interested in allogeneic HCT have to be informed of the lack of literature on HCT in this age group and should be treated under a clinical trial. If transplant is considered in that higher age range, the presence of good criteria under all other risk-factors becomes a necessity.

Other than age, patient-risk factors, particularly comorbidities greatly impact the risks for NRM while disease-risk factors, particularly disease status and cytogenetics, greatly impact the risks for relapse and relapse-related mortality. Transplant-risk factors seem to contribute equally to both outcomes. Advances in transplantation outcome research tend to improve but at the same time complicate the decision-making process. Ten years ago, disease status, cytogenetics, and type of donor were the main factors determining the path to allogeneic HCT. In the current era, enough evidence has become available to show that comorbidity burden, socioeconomic status, specific gene profile, and the degree of HLA-allele matching play similarly important roles in determining chances of survival. Lack of increasing mortality risks with increasing age in studies targeting older populations does not mean that allogeneic HCT for the older population carries the same risk of that for patients in their 20s. As indicated earlier, older populations are the ones with the highest risks for having more comorbidities, limited social support, limited physical performance, complex and adverse cytogenetics, and lack of healthy living identical sibling donors. Since our statistical models nowadays tend to adjust for all these adverse variables, older patients' outcomes,[106]not surprisingly, do not seem statistically different from those of younger patients. A term “biologically older versus younger patients” might need to be used in future studies to differentiate between those of the same age group but have impaired versus normal health status, respectively. The advances in knowledge and level of sensitivity of risk-assessment is expected to benefit those older patients with good-risk features, by allowing them the chance of a potentially curative treatment, as well as those with poor-risk features, by avoiding a possibly traumatizing treatment approach with futile results.

FIVE-YEAR VIEW

Further advances in individualizing treatment interventions based on risks are expected in the next five years. Whole genome sequencing and additional genetic analyses are expected to refine the search for molecular biomarkers for AML. DNA polymorphism studies are expected to further improve our prognostication for transplant related toxicities and hence

mortality.[107] Similar advances are expected in detecting patient-donor differences for non-HLA genetic variations within the major histocompatibility complex by using single nucleotide polymorphism discovery analysis and validation to select the donor with the least possible risk for causing acute GVHD.[106] Micro-RNAs (MiRs) are small non-coding RNAs (~22 nt) that negatively regulate gene expression. MiRs expression profiles could further insight our understanding of mechanisms of disease prognosis and further risk-stratify the heterogeneous group of patients with normal cytogenetics.[108]

The field will probably witness trials of novel RIC regimens incorporating agents like clofarabine or treosulfan that might confer better AML disease control, awaiting the effects of GVL, while not causing major organ toxicities. It would be imperative to design a national multi-center phase III study that randomize older patient, within given acceptable risk category (Table 2), to two of the most popular RIC regimens. A follow-up study could then randomize the most successful RIC regimen to conventional chemotherapy with quality of life in addition to survival as study end points. The use of novel biomarkers for early prediction of acute GVHD and testing of new immunosuppressive medications (sirolimus or co-stimulatory blockade-based) might help in reducing the risks of acute GVHD and its associated mortality.

The benefit of allogeneic HCT in curing AML could be maximized by using multiparametric flow cytometry to sensitively detect minimal residual disease[109] before and after allogeneic HCT. Patients with minimal residual disease before HCT could benefit from the addition of radiolabeled monoclonal antibody to CD45 to the nonmyeloablative regimen to enhance disease control,[31] while those with MRD after HCT could be candidates for trials investigating post-HCT AML targeted therapy using, for example, tyrosine kinase inhibitor of FLT3 or vaccination against leukemia-specific antigens.[110] Graft engineering is another approach attracting interest with great potential to improve HCT outcome. Suicide genes can be used to modify GVHD reactions in vivo by inserting a specific marker gene, for example the herpes simplex virus thymidine kinase gene that can be used to selectively deplete activated T cells, using ganciclovir, should GVHD occur. [111,112] DLI engineering by inserting tumor specific receptors (either chimeric T cell receptor or antibody receptors) and vaccine-based approaches to enhance graft-versus-leukemia effect are other potentially interesting approaches to improve post-transplant control of malignancy.(Reviewed in [113])

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KEY ISSUES

- Acute myeloid leukemia is a disease of the older population with a median age at diagnosis of 68 years. Unfortunately, the outcomes of older AML patients remain poor.
- Chronological age, per se, between 60 and 75 years does not seem to be a barrier to reduced-intensity conditioning and allogeneic HCT. However, the criteria for selection of older patients with AML to be eligible for allogeneic HCT have not been well studied.
- Health status measures particularly comorbidity indices such as the HCT-CI, and performance status scales independently and strongly impact risks for NRM after allogeneic HCT. Both measures should be assessed before HCT for stratification of risks for NRM.
- Patient and physician preferences and their perceptions of chances for cure might bias selection for HCT candidacy. These factors together with race and socioeconomic features should be more appropriately addressed in future studies.
- First or second CR at time of HCT and having more favorable cytogenetic abnormalities signifies better outcomes after allogeneic HCT for older AML patients.
- Novel chromosomal abnormalities or genetic markers should be incorporated in future clinical trials to further improve risk-benefit ratio assessments before allogeneic HCT.
- RIC regimens followed by allogeneic HCT resulted in better survivals among older patient when compared, mostly retrospectively, to either autologous HCT or conventional chemotherapy.
- Grafts from HLA-identical siblings continue to be associated with the most favorable outcomes after allogeneic HCT. Acceptable outcomes have been reported using alternative donor grafts.

Table 1

Cytogenetic classifications per four different collaborative group studies

Classification	AMLSG[51] (N = 361)			CALGB[49] (N=635)			HOVON[50] (n=293)			MRC[48] (n = 1065)		
	Features	Prevalence %	3-year Survival %	Features	Prevalence %	5- Survival %	Features	Prevalence %	3-years Survival %	Features	Prevalence %	5-years Survival %
Favorable (low-risk)	t(15;17), inv(16)	7	38	t(8;21), inv(16), t(16;16)	5	19.4	t(8;21), inv(16), del(16), t(16;16)	2	60	t(15;17), t(8;21), inv(16)	7	34
Intermediate (standard-risk)	Normal, t(8;21), 11q abnormalities, +8 and +11 within noncomplex karyotype	58	18	Others	75	7.5	Normal, -Y, del(7q)	67	30	Others	79	13
Unfavorable (high-risk)	Others	35	5	Complex "rare aberrations"	20	0	Others	31	5	Complex	14	2

AMLSG indicates The German and Austrian Acute Myeloid Leukemia Study Group; CALGB, Cancer and Leukemia Group B; HOVON, the Dutch-Belgian Hemato-Oncology Cooperative Group; MRC, the United Kingdom medical research council; and NA, not available.

Table 2

Risk-benefit ratio system for eligibility, ineligibility, and risk-categorization of allogeneic hematopoietic cell transplantation (HCT) as a treatment option for older patients with acute myeloid leukemia

Category 1: Too good for early HCT

- 1 First CR; Plus either:
 - a. inv(16), t(16;16) or t(8;21) together with c-kit⁻
 - b. Normal cytogenetics together with NPM⁺ Flt3⁻ or CEBPA gene mutation

Category 2: Good-risk transplant candidates

- 1 Age <76 years
- 2 HCT-CI scores of 0
- 3 KPS scores of 90–100%
- 4 Favorable socioeconomic factors: high income and education levels and good social support.
- 5 First CR; Plus
 - a. Normal cytogenetics together with NPM⁻ Flt3⁺ or without CEBPA gene mutation
- 6 Second CR; Plus
 - a. inv(16), t(16;16) or t(8;21)
 - b. Normal cytogenetics together with NPM⁺ Flt3⁻ or CEBPA gene mutation
- 7 Reduced-intensity conditioning regimens
- 8 HLA-identical sibling donor

Category 3: Intermediate-risk transplant candidates

- 1 Age <76 years
- 2 HCT-CI scores of 1–2
- 3 KPS scores of 80–85%
- 4 Intermediate-risk socioeconomic factors: moderate income, education levels, and social support.
- 5 First CR; Plus
 - a. Adverse cytogenetics
- 6 Second or higher CR; Plus
 - a. Normal cytogenetics together with NPM⁻ Flt3⁺ or without CEBPA gene mutation
- 7 Nonmyeloablative or reduced-intensity conditioning regimens
- 8 HLA-8/8 allele matched or single antigen or allele mismatched unrelated donor

Category 4: High-risk transplant candidates

- 1 Age <76 years
- 2 HCT-CI scores of 3–7
- 3 KPS scores of 60–70%
- 4 Poor-risk socioeconomic factors: low income, education levels, and social support.
- 5 Not in CR
- 6 Unfavorable or complex cytogenetics
- 7 Monosomal karyotype
- 8 Short duration between first CR and relapse
- 9 Reduced-intensity conditioning regimens

- 10 No available HLA-matched related or unrelated donors: UCB, single antigen HLA-mismatched, or HLA-haploidentical donor is available.

Category 5: Not transplant candidates*

- 1 Age >75 years
- 2 HCT-CI scores of 8 and/or major organ dysfunction (decompensated liver cirrhosis, decompensated heart failure with low survival probabilities, active severe infection, or pulmonary function tests <40% normal), or another malignancy or major illness with limited survival chances.
- 3 KPS scores of 50%
- 4 Extremely poor-risk socioeconomic factors: no income or very limited education, no social support.
- 5 Behavioral issues: lack of compliance in past medical history, persistent or frequent use of drugs after diagnosis with cancer, and anger or high-risk behaviors with medical teams
- 6 Rapidly progressive or refractory disease after induction failure
- 7 Complex cytogenetics plus monosomal karyotype
- 8 Lack of a suitable donor.

* Unless patients are offered transplant within a clinical trial adapted to the higher-risk features.