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REVIEW ARTICLE

The evolving concept of indications for allogeneic hematopoietic cell transplantation during first complete remission of acute myeloid leukemia

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Abstract

The long-standing debate of whether patients with acute myeloid leukemia (AML) should proceed to allogeneic hematopoietic cell transplantation (HCT) during first complete remission (CR1) remains unsettled. Although allogeneic HCT during CR1 used to be recommended for those with intermediate or poor cytogenetics if they had a matched sibling donor, the concept of indications for allogeneic HCT during CR1 has been evolving by virtue of advances in understanding of the molecular pathogenesis of AML and innovations in transplantation practice attained over the last few decades. The incorporation of molecular profiles of leukemia has been shown to contribute to further refinements of risk classification that had previously relied mostly on cytogenetics, while the progress in transplantation procedures has made it possible to perform transplantations more safely even for patients without a matched sibling donor. These significant changes have underpinned the need to reappraise indications for allogeneic HCT during CR1 of AML. Improvements in clinical applications of genetic and measurable residual disease information as well as in transplantation technology are expected to further refine indications for allogeneic HCT during CR1, and thus promote an individualized approach for the treatment of AML.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is the most effective therapy for preventing relapse of acute myeloid leukemia (AML), which is the predominant cause of death for patients with the disease [1]. However, the efficacy of allogeneic HCT is compromised by high rates of morbidity and mortality related to the procedure. As a consequence, allogeneic HCT may be beneficial for some patients, but harmful for others, which makes it a matter of clinical concern whether allogeneic HCT should be recommended for AML patients who have attained first complete remission (CR1). This question has historically been examined in prospective studies that used biologic assignment according to donor availability, in which patients with a human leukocyte antigen (HLA)-identical sibling were assigned to undergo allogeneic HCT, while those without such a donor were assigned to chemotherapy with or without autologous HCT [2–11]. By integrating results obtained from such "donor vs no-donor" studies, a couple of meta-analysis studies published in the late 2000s showed that the beneficial effect of allogeneic HCT is greatest for patients with poor cytogenetics, also present for those with intermediate cytogenetics, but nonexistent for those with favorable cytogenetics [12, 13]. These results, however, do not seem to be directly applicable to current conditions for the following reasons. First, the practice of transplantation itself has evolved. With the advent of transplantation from alternative donors, donor versus no-donor studies have become less relevant today, because a considerable number of patients without a matched sibling donor may qualify for receiving allogeneic HCT from a matched unrelated donor, umbilical cord blood (UCB) or a haploidentical related donor [14, 15]. Second, our understanding of the molecular pathogenesis of AML has evolved. It is well recognized that the prognosis for patients in each cytogenetic risk group is still heterogeneous, and the incorporation of molecular profiles of leukemia has been shown to contribute to further

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refinements of risk classification that had previously relied mostly on cytogenetics [16, 17]. These significant changes attained over the last few decades have underpinned the need to reappraise indications for allogeneic HCT during CR1 of AML.

Basic principle

Because AML is a heterogenous disease consisting of subsets with distinct biological and prognostic features, a risk-adapted approach is a rational way for determining which patients should be selected for allogeneic HCT during CR1. The risk of relapse following chemotherapy and the risk of nonrelapse mortality (NRM) following allogeneic HCT represent the two most important factors to be taken into consideration. In 2012, experts provided, on behalf of the European LeukemiaNet (ELN), specific recommendations for indications for allogeneic HCT during CR1 of AML [18]. According to their recommendations, patients are classified into four relapse-risk groups primarily based on their genetic and cytogenetic profiles, and an acceptable post-transplant NRM rate is proposed for each of the groups (Table 1). This guide supports our clinical decision-making in daily practice.

Outcomes following chemotherapy according to genetic and cytogenetic status

It is widely accepted that cytogenetic findings at diagnosis are closely associated with the biology of AML and have important prognostic implications for patients treated with conventional chemotherapy [4, 19, 20]. Despite the usefulness of cytogenetic risk stratification, however, patients in each cytogenetic risk group remain prognostically heterogeneous. Subsequent studies have shown that mutations in the *FLT3*, *NPM*1, and *CEBPA* genes are useful for stratifying patients with cytogenetically normal AML (CN-AML) into different prognostic subgroups [21–32]. In 2010, the ELN first proposed a risk stratification system for AML, by integrating genetic and cytogenetic profiles of leukemia (Table 2) [33]. The ELN 2010 system took into account the presence or absence of mutations in the *FLT3*, *NPM1*, *CEBPA* genes to classify patients with normal karyotype. In 2017, the ELN 2010 risk classification was updated in light of the enhanced understanding of prognostic significance of genetic profiles (Table 3) [17]. The ELN 2017 system eliminated the distinction between the intermediate-I and the intermediate-II categories, resulting in the reduction of the number of risk categories from four to three. Furthermore, the use of gene mutations for risk classification is no

Table 1 AML risk categories defined in the European LeukemiaNet AML Working Party consensus statement (see reference [18]).

Good	Intermediate	Poor	Very poor
• t(8;21) with WBC ≤ 20×10^3/μL • inv(16)/t(16;16) • Mutated *CEBPA* (biallelic) • Mutated *NPM1* (No *FLT3*-ITD mutation) • Early first CR and no MRD	• t(8;21) with WBC > 20×10^3/μL • Cytogenetically normal (or with loss of X and Y chromosomes) • WBC ≤ 100×10^3/μL and early first CR (after first cycle of chemotherapy)	• Otherwise good or intermediate, but no CR after first cycle of chemotherapy • Cytogenetically normal and WBC > 100×10^3/μL • Cytogenetically abnormal	• Monosomal karyotype • Abn3q26 • Enhanced *MECOM* expression

AML acute myeloid leukemia, *WBC* white blood cell, *CR* complete remission, *MRD* measurable residual disease.

Table 2 The 2010 European LeukemiaNet risk stratification by genetics and cytogenetics in AML (see reference [33]).

Favorable	Intermediate-I	Intermediate-II	Adverse
• 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 *CEBPA* (normal karyotype)	• Mutated *NPM1* and *FLT3*-ITD (normal karyotype) • Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) • Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)	• t(9;11)(p22;q23); *MLLT3- KMT2A* • Cytogenetic abnormalities not classified as favorable or adverse	• inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2-MECOM* • t(6;9)(p23;q34); *DEK-NUP214* • t(v;11)(v;q23); *KMT2A* rearranged • −5 or del(5q) • −7 • abn(17p) • Complex karyotype (3 or more)

AML acute myeloid leukemia.

Table 3 The 2017 European LeukemiaNet risk stratification by genetics and cytogenetics in AML (see reference [17]).

Favorable	Intermediate	Adverse
• t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or **with *FLT3*-ITD^{low}** • **Biallelic** mutated *CEBPA*	• Mutated *NPM1* and ***FLT3*-ITD^{high}** • Wild-type *NPM1* without *FLT3*-ITD or **with *FLT3*-ITD^{low}** • t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* • Cytogenetic abnormalities not classified as favorable or adverse	• t(6;9)(p23;q34.1); *DEK-NUP214* • t(v;11q23.3); *KMT2A* rearranged • t(9;22)(q34.1;q11.2); *BCR-ABL1* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2-MECOM* • −5 or del(5q) • −7 • −17/abn(17p) • Complex karyotype (3 or more) • **Monosomal karyotype** • **Wild-type *NPM1* and *FLT3*-ITD^{high}** • **Mutated *RUNX1*** • **Mutated *ASXL1*** • **Mutated *TP53***

The items in bold are changes from the European LeukemiaNet 2010 version.

AML acute myeloid leukemia.

longer restricted to patients with normal karyotype. Other major amendments include the consideration of only biallelic *CEBPA* mutations for the favorable-risk category, stratification of patients with internal tandem duplication (ITD) of the *FLT3* gene based on the allelic ratio, and the inclusion of *RUNX1*, *ASXL1*, and *TP53* mutations in the adverse-risk category. In addition, the ELN 2017 system has incorporated monosomal karyotype (MK) into the adverse-risk category. MK is defined as two or more autosomal monosomies or a single autosomal monosomy plus other structural abnormalities, and has recently been shown to be predictive of extremely poor prognosis [34–37].

The clinical utility of the ELN 2017 system has been validated in a large cohort of patients enrolled on two successive trials conducted by the German AML Cooperative Group (AMLCG), in which the ELN 2017 system proved to show a better discrimination of risk groups than the ELN 2010 system [38]. The incorporation of additional genetic information in the ELN 2017 system has contributed to the identification of more patients falling under the favorable- and adverse-risk categories. The usefulness of the ELN 2017 system has been confirmed by other studies, although some controversies remain, for example, regarding the prognostic significance of the allelic ratio of *FLT3*-ITD [39–42].

More detailed assessments of genetic profiles may further refine the ELN 2017 risk classification. Investigators in the Cancer and Leukemia Group B (CALGB) have shown that *NPM1*/ *WT1* co-mutations, *DNMT3A* mutations, *ZRSR2* mutations, and mutated *NPM1* with *FLT3*-ITD high allelic ratio represent an adverse prognosis [43], which suggests that an inclusion of additional gene mutations may identify more patients with poor prognosis.

Outcomes following allogeneic HCT according to genetic and cytogenetic status

Cytogenetics can also predict outcomes after allogeneic HCT [44, 45]. Several studies have evaluated whether and to what extent post-transplant outcomes differ according to specific mutation status [46–49]. A study conducted by the Center for International Blood and Marrow Transplantation Research compared patients with or without *FLT3* mutations who underwent allogeneic HCT during CR1 or second CR (CR2) [47]. For this study, data on the type of mutations, that is, ITD or tyrosine kinase domain mutations, were not available, and thus they were combined to form a *FLT3*-mutated group. Patients with *FLT3*-mutated AML showed a higher risk of post-transplant relapse, but there was no difference in NRM, relapse-free survival (RFS), or overall survival (OS) on the basis of the presence or absence of the *FLT3* mutations.

The European Society for Blood and Marrow Transplantation (EBMT) study analyzed the effect of combinations of the *NPM1* mutation and *FLT3*-ITD status on outcomes after allogeneic HCT for CN-AML [46]. In this study, molecularly defined subgroups were found to have different prognoses, with the best outcomes for the mutated *NPM1* group without *FLT3*-ITD. Patients with wild-type *NPM1* without *FLT3*-ITD had similarly favorable results, whereas outcomes were inferior for those with *FLT3*-ITD. More recently, the EBMT has proposed a prognostic model based on cytogenetics and *FLT3*-ITD for patients undergoing allogeneic HCT during CR1 [48]. This study showed that the presence of *FLT3*-ITD was significantly associated with worse outcomes only for the intermediate cytogenetic risk group.

Investigators at Leipzig University examined the prognostic impact of the ELN 2017 system in a cohort of

patients treated with allogeneic HCT at their single center [49]. The study results showed that the ELN 2017 classification made it possible to differentiate patients into three groups with significantly distinct prognoses.

Risk of nonrelapse mortality following allogeneic HCT

Post-transplant NRM is another important factor when deciding indications for allogeneic HCT during CR1. Despite availability of several predicting systems for NRM after allogeneic HCT [50–56], the establishment of an accurate prediction model remains a challenge because the risk of NRM is multifactorial and can therefore vary according to disease and disease status. In response to this situation, we recently developed a comprehensive system to provide more accurate predictions of NRM during their CR1 for AML patients having undergone allogeneic HCT [57]. After assigning 2344 patients to a training set or a validation set, we first identified and scored five parameters—age, sex, performance status (PS), HCT-specific comorbidity index (HCT-CI), and donor type—on the basis of their effect on NRM in the training set. The new scoring system which was named the "NRM-J index", used the sum of the assigned scores to stratify patients into four distinct risk groups, 0–3 points, 4 points, 5 points, and 6 or more points (Table 4). The application of the NRM-J index to patients in the validation set resulted in a clear differentiation of NRM, with expected 2-year rates of 11%, 16%, 27%, and 33%, respectively. The discriminative capability of the NRM-J index was found to be better than that of the EBMT score [50] or the HCT-CI [51]. The NRM-J index was developed based on data of patients with AML undergoing allogeneic HCT during first CR, which makes it more specific to this patient population. When combined with the ELN recommendations shown in Table 1 [18], the NRM-J index is expected to be able to provide practical guidance for indications for allogeneic HCT during CR1.

Table 4 The NRM-J index (see reference [57]).

Risk factor	Score
Age, years	
16–49	0
50–59	1
≥60	2
Sex	
Male	0
Female	1
Performance status	
0	0
1	1
≥2	2
HCT-CI	
0–2	0
≥3	1
Donor type	
Related bone marrow	0
Related peripheral blood	2
Unrelated bone marrow	1
Umbilical cord blood	3

On the basis of the sum of assigned points, patients were classified into low-risk (≤3 points), intermediate risk (4 points), high-risk (5 points), and very high-risk groups (≥6 points).

NRM nonrelapse mortality, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index.

Studies comparing transplant versus non-transplant strategy for genetically distinct populations

Several studies have evaluated the efficacy of allogeneic HCT in comparison to that of chemotherapy with or without autologous HCT for patients with distinct genetic features [58–64]. However, the number of patients in any given genetic subgroup is generally small, which precludes a firm conclusion regarding the utility of allogeneic HCT, even from the results of an analysis of a large cohort. Therefore, most of such studies comparing allogeneic HCT with non-transplant therapy were post-hoc analyses based on pooled data of multiple prospective studies [58, 59, 62–64].

Schlenk et al. analyzed patients with CN-AML who entered one of four trials conducted by the German–Austrian Acute Myeloid Leukemia Study Group (AMLSG), in which only patients with a matched related donor were assigned to undergo allogeneic HCT [58]. Within the favorable subgroup of patients with mutant *NPM1* without *FLT3*-ITD, donor availability did not make any difference in terms of RFS. For those with mutant *CEBPA*, a donor vs no-donor analysis could not be done because of limited sample size. For the remaining patients with non-favorable risk, the donor group showed better RFS than the no-donor group.

Röllig et al., on behalf of the Study Alliance Leukemia (SAL), evaluated outcomes for cytogenetically intermediate-risk patients with mutant *NPM1* enrolled in their AML 2003 trial [60]. Patients in the donor group showed significantly better RFS than those in the no-donor group. However, OS of the donor and no-donor groups did not differ, primarily because of high rates of CR2 attainment after relapse and of proceeding to allogeneic HCT from an alternative donor for patients in the no-donor group. The SAL investigators also reported results of a donor versus no-donor analysis for patients with intermediate cytogenetics who had no

FLT3-ITD, *NPM1*-, or biallelic *CEBPA* mutations who were enrolled on two prospective trials [63]. This study showed that RFS was significantly better for patients in the donor group than the no-donor group, but the difference in OS again did not reach statistical significance. Investigators from the Dutch–Belgian Hemato-Oncology Cooperative Group and Swiss Group for Clinical Cancer Research (HOVON/SAKK) evaluated the efficacy of allogeneic HCT for AML with MK, by using data of patients who participated in their three consecutive phase 3 trials [59]. For these studies, poor-risk patients were assigned to allogeneic HCT if a matched sibling or unrelated donor could be identified. They used allogeneic HCT as a time-dependent covariate, and showed a significant advantage of allogeneic HCT in terms of reduction of relapse and improvement of survival. The beneficial effect of allogeneic HCT for AML with MK was also reported by a joint study conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA), in which OS was shown to be better for patients with an HLA-identical related donor based on a donor versus no-donor analysis [64].

Measurable residual disease

Measurable residual disease (MRD) during and after treatment detected by flow cytometry, quantitative PCR, or next-generation sequencing (NGS) has emerged as a novel indicator for response to therapy. Achievement of MRD negativity has been shown in many studies of AML patients to be a powerful prognostic factor [65–74].

Freeman et al. attempted to determine the prognostic impact of MRD measured by multiparameter flow cytometry (MFC) after one course of induction therapy in a cohort of patients enrolled and treated in the National Cancer Research Institute (NCRI) AML17 trial [71]. The prognosis of patients who achieved CR could be clearly differentiated by the presence or absence of MRD, with OS for patients with MRD-positive CR resembling that for patients with partial remission rather than that for patients with MRD-negative CR.

Balsat et al. assessed post-induction *NPM1*-mutated MRD for patients enrolled in the Acute Leukemia French Association (ALFA) 0702 trial to determine whether *NPM*1 MRD can be used as a predictive factor for benefits from allogeneic HCT [70]. After induction therapy, patients who did not achieve a 4-log reduction in *NPM1* MRD in the peripheral blood had a higher incidence of relapse and a shorter OS. Outcomes were significantly improved by the use of allogeneic HCT for patients with a less than 4-log reduction in *NPM1* MRD, but this benefit was not observed for those with a more than 4-log reduction.

Jongen-Lavrencic et al. from the HOVON/SAKK group analyzed samples of bone marrow or peripheral blood before and after induction therapy by using NGS, and demonstrated that the detection of persistent mutations during CR, except for those associated with clonal hematopoiesis, are predictive of higher relapse and worse OS [72]. They also showed that NGS and MFC each had independent and additive prognostic value with respect to relapse and survival.

The GIMEMA investigators conducted a prospective study to test a treatment approach risk-adapted according to genetic and cytogenetic profiles at diagnosis and post-consolidation MRD status as defined by MFC [74]. Patients with favorable and poor risk were assigned to autologous and allogeneic HCT, respectively, regardless of MRD status, and those with intermediate risk were assigned to autologous if MRD was negative, and to allogeneic HCT if MRD was positive. This study showed similar RFS for patients with intermediate risk with or without MRD, and their RFS was almost identical to that for patients with favorable risk. These results suggest that, for patients with intermediate risk, allogeneic HCT may be able to override poor prognosis associated with positive MRD, and also that it may be possible to avoid allogeneic HCT if MRD is negative.

Although MRD response has been shown to be predictive of better outcomes [65–74], there is a significant heterogeneity across studies depending on the patient population, regimen used, MRD method and target, timing of MRD assessment, and threshold to define adequate response [75]. To focus the knowledge incorporating the findings of various studies on the clinical utility of MRD and generalize this knowledge for use in clinical practice, the priority needs be placed on attainment of standardization of the measuring procedure.

Future considerations

The last few decades have witnessed significant improvements in risk estimation for relapse by taking profiles of selected genes into account. However, some uncertainties remain regarding genetic risk in AML. First, elucidation of the genetic landscape of AML is still a work in progress, and novel genetic mutations of clinical significance are sure to be identified hereafter. Second, specific combinations of mutations may have an impact [76]. Third, a risk classification may be subject to the effect of treatments given to the patients analyzed. Accordingly, genetic mutations considered as adverse or favorable for patients treated with standard chemotherapy may lose their prognostic capability for patients treated with hypomethylating agents [77, 78] or venetoclax-based regimens

[79, 80], and the addition of targeted agents, such as *FLT3*, *IDH1*, and *IDH2* inhibitors to standard chemotherapy may cause changes in genetic risk classification [81, 82]. Because of the limited number of patients with a given type of genetic mutation, intergroup collaborations are required to develop and upgrade an accurate genetic risk classification system.

Another aspect to be taken into account is that indications for allogeneic HCT cannot be determined by genetic risk alone. The prognosis for patients in a genetically adverse-risk category is worse not only when they are treated with chemotherapy but also when they are treated with allogeneic HCT. What matters is whether there is a net benefit for the patients when they do or do not proceed to allogeneic HCT during CR1. This highlights the importance of comprehensive assessments by considering not only genetic and cytogenetic profiles but also age, comorbidities, PS and other factors. One major challenge would be the development of algorithms that combine pre-treatment risk factors and longitudinal MRD data to guide individualized treatments. In recent years, a knowledge bank that integrates clinical, genetic, cytogenetic, and therapeutic variables has been developed to estimate individualized survival. The French group evaluated use of the knowledge bank approach to act as a guide for decisions as to whether to proceed to allogeneic HCT during first CR by using data for patients enrolled in their ALFA 0702 trial [83]. The knowledge bank approach proved to not only result in more accurate survival prediction than the ELN 2017 system, but also better identified patients who might benefit from allogeneic HCT or chemotherapy alone.

Conclusions

The long-standing debate of whether AML patients in CR1 should proceed to allogeneic HCT remains unsettled. Although allogeneic HCT during CR1 used to be recommended only for those with intermediate or poor cytogenetics if they had a matched sibling donor [12, 13], the concept of indications for allogeneic HCT during CR1 has been evolving by virtue of advances in understanding of the molecular pathogenesis of AML and innovations in transplantation practice attained over the last few decades. Improvements in clinical applications of genetic and MRD information as well as in transplantation technology can be expected to further refine indications for allogeneic HCT during CR1 and promote an individualized approach for the treatment of AML.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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