

WJSC 6th Anniversary Special Issues (1): Hematopoietic stem cell transplantation**Allogeneic hematopoietic cell transplant for acute myeloid leukemia: Current state in 2013 and future directions**

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AML. Besides the conventional sibling and unrelated donor allografts, we review the available data and recent advances for alternative donor sources such as haploidentical grafts and umbilical cord blood. We also discuss conditioning regimens, including reduced intensity conditioning which has broadened the applicability of allo-HCT. Finally we explore recent advances and future possibilities and directions of allo-HCT in AML. Practical therapeutic recommendations have been made where possible based on available data and expert opinion.

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Key words: Acute myeloid leukemia; Allogeneic hematopoietic cell transplantation; Reduced intensity conditioning; Myeloablative conditioning; Haploidentical; Umbilical cord blood

Core tip: Acute myeloid leukemia (AML) represents a heterogeneous group of high-grade myeloid neoplasms of the elderly with variable outcomes. We discuss the role of allo-hematopoietic cell transplantation (HCT) in AML patients stratified by cytogenetic- and molecular-risk in first complete remission, as well as allo-HCT as an option in relapsed/refractory AML.

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Abstract

Acute myeloid leukemia (AML) represents a heterogeneous group of high-grade myeloid neoplasms of the elderly with variable outcomes. Though remission-induction is an important first step in the management of AML, additional treatment strategies are essential to ensure long-term disease-free survival. Recent pivotal advances in understanding the genetics and molecular biology of AML have allowed for a risk-adapted approach in its management based on relapse-risk. Allogeneic hematopoietic cell transplantation (allo-HCT) represents an effective therapeutic strategy in AML providing the possibility of cure with potent graft-versus-leukemia reactions, with a demonstrable survival advantage in younger patients with intermediate- or poor-risk cytogenetics. Herein we review the published data regarding the role of allo-HCT in adults with AML. We searched MEDLINE/PubMed and EMBASE/Ovid. In addition, we searched reference lists of relevant articles, conference proceedings and ongoing trial databases. We discuss the role of allo-HCT in AML patients stratified by cytogenetic- and molecular-risk in first complete remission, as well as allo-HCT as an option in relapsed/refractory

INTRODUCTION

Acute myeloid leukemia (AML) comprises a group of high-grade clonal neoplasms of the myeloid progenitor cells. With a median age of 66 years, AML is a disease

of the older age group with an annual incidence of 4.4 per 100000. It is estimated that approximately 15000 new cases of AML will be diagnosed in the United States in 2013^[1]. While the goal of initial therapy in AML is attaining complete remission (CR), without additional post-remission therapy disease relapse is inevitable in vast majority of the cases^[2]. In the past two decades little has changed in AML induction chemotherapy regimens, but our improved understanding of the disease biology in identifying high-risk groups with modern cytogenetics and molecular testing have led to better risk-stratification that facilitates customization of post-remission therapy based on the relapse-risk^[3-5]. While allogeneic hematopoietic cell transplantation (allo-HCT) has been long considered a potentially curative therapy for AML^[6], advances in human leukocyte antigen (HLA)-matching, supportive care, optimal pre-transplant conditioning and advent of alternative donor allografting have broadened the availability and improved transplant outcomes^[7]. Herein we review the role of allo-HCT in adults with AML in first complete remission (CR1), discuss the allograft options in advanced AML (beyond CR1), and review the current state of reduced-intensity and alternative donor allo-HCT in the management of AML.

PROGNOSTIC FACTORS IN AML

Traditionally used prognostic factors in AML include age, leukocyte count at diagnosis, performance status, extramedullary involvement, antecedent hematologic disorders and initial response to therapy. Cytogenetics by metaphase and interphase analysis are one of the most powerful prognostic factors in AML, providing us the ability to risk-stratify patients at diagnosis. Acute promyelocytic leukemia t(15;17) and core binding factor (CBF) leukemia t(8;21) and inv(16)/t(16;16) are favorable-risk AML, largely retaining their good prognosis even with additional cytogenetic abnormalities^[8-10]. Chromosomal abnormalities conferring poor outcomes include abnormalities of chromosome 3q (abn1 3q), deletions of 5q (-5q), monosomies of chromosome 5 or 7 (-5/-7), and complex karyotype. Large cooperative group studies have confirmed the impact of cytogenetics on survival rates, reporting 55%-65% and 5%-14% 5-year overall survival (OS) for patients with favorable- and poor-risk cytogenetics, respectively^[8,11,12]. Grimawade *et al.*^[10] reported outcomes in 5876 patients treated on Medical Research Council (MRC) trials and identified abn1 3q (excluding t(3;5)(q25;q34)), inv(3)(q21q26)/t(3;3)(q21;q26), add5q/-5q, -5, -7, add(7q)/-7q, t(6;11)(q27;q23), t(10;11)(p11;13;q23), other t(11q23) (excluding t(9;11)(p21;22;q23) and t(11;19)(q23;p13)), t(9;22)(q34;q11), -17, abn1(17p) and complex karyotype as poor risk cytogenetic aberrations. Presence of monosomal karyotype (defined as 2 or more autosomal monosomies or combination of 1 monosomy with structural abnormalities) is associated with very poor prognosis with 4-year OS < 5%^[13,14]. Similarly, the presence of subclones within the poor risk cytogenetic category (*i.e.*, clonal heterogeneity) may confer poorer

Table 1 The European LeukemiaNet Standardized Reporting System for risk stratification of acute myeloid leukemia based on cytogenetics and molecular testing¹

Risk category	Cytogenetic abnormalities	Molecular abnormalities
Favorable risk	t(15;17) inv(16)/t(16;16) ² t(8;21) ²	CN-AML with biallelic CEBPA mutation CN-AML with NPM1 mutated but FLT3-ITD negative
Intermediate risk	CN-AML t(9;11) All others abnormalities not classified as favorable or adverse risk	CN-AML with: NPM1 mutated/FLT3-ITD positive NPM1 wild type/FLT3-ITD negative t(8;21)/inv(16) with c-KIT mutation
Adverse risk	inv(3)/t(3;3) t(6;9) t(v;11)/MLL rearranged -5/-5q -7 Monosomal karyotype Abnormal 17p Complex cytogenetics	CN-AML with FLT3-ITD positive

¹Table modified from Mrózek *et al.*^[24]; ²The good prognosis of inv(16) and t(8;21) is maintained even with additional cytogenetic abnormalities. The presence of concomitant c-KIT mutation may increase relapse risk in t(8;21) and to lesser extent inv(16). CN-AML: Cytogenetically normal acute myeloid leukemia; CEBPA: CCAAT enhancer binding protein alpha; FLT3-ITD: FMS-like tyrosine kinase 3 gene-internal tandem duplication; MLL: Mixed lineage leukemia; NPM: Nucleophosmin.

outcomes^[15]. Recently, Middeke *et al.*^[16] found the presence of abn1(17p) and -5/-5q, within complex and monosomal karyotype AML characterized ultra high-risk disease.

Work done in the last decade has further enhanced our ability to stratify cytogenetically normal AML (CN-AML) based on presence of molecular aberrations into poor-risk [*e.g.*, FMS-like tyrosine kinase 3 gene-internal tandem duplication (*FLT3*-ITD), mixed-lineage leukemia gene-partial tandem duplication (*MLL*-PTD), overexpression of Wilms' tumor gene 1 (*WT1*), brain and acute leukemia, cytoplasmic gene (*BAALC*), ETS-related gene (*ERG*), *KIT*-gene and ecotropic viral integration site 1 gene (*EVII*)] and good-risk [nucleophosmin (*NPM1*), isocitrate dehydrogenase (IDH 1/2) and CCAAT enhancer binding protein alpha (*CEBPA*)] categories^[15,17-23]. Integrating conventional cytogenetics and the commonly utilized molecular testing markers (*FLT3*-ITD, *CEBPA* and *NPM1*), the European LeukemiaNet validated the effect of prognostic factors on remission rates, disease-free survival (DFS) and OS (Table 1)^[24,25]. The improved understanding of the molecular basis of AML and its ramifications on patient outcomes has important relevance in clinical decision making, heralding the era of "individualized" post-remission therapy (Figure 1).

CONSOLIDATION WITH ALLOGENEIC HCT IN CR1

Remission induction reduces the leukemic burden

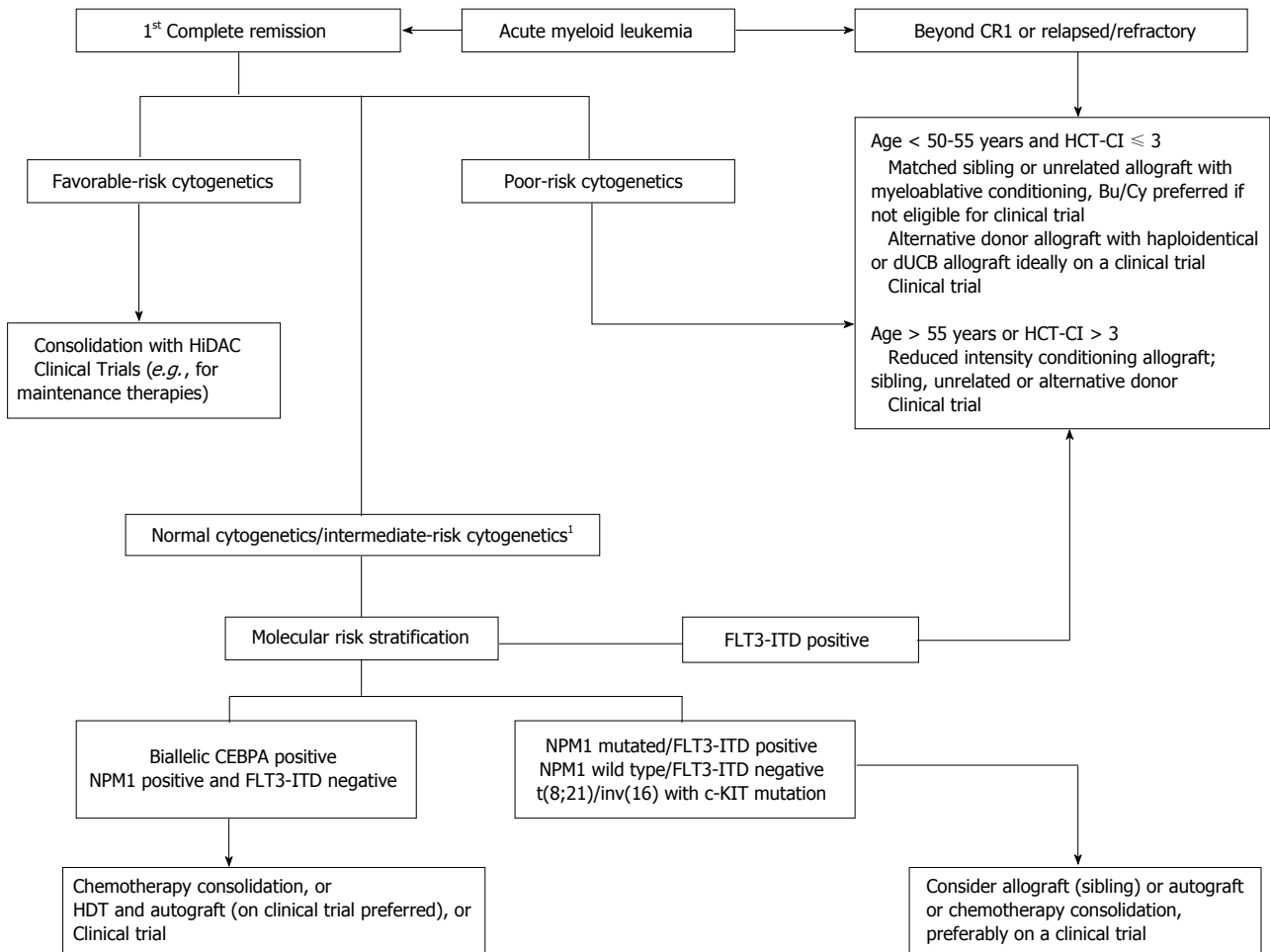


Figure 1 Clinically useful algorithm for optimal consolidation for acute myeloid leukemia patients based on cytogenetic and molecular genetic aberrations, based on available data and practice preference. Allogeneic HCT may be considered in medically fit AML patients with intermediate risk/normal cytogenetics in CR1. Bu/Cy: Busulfan/cyclophosphamide; CEBPA: CCAAT enhancer binding protein alpha; CR: Complete remission; dUCB: Double umbilical cord blood; FLT3-ITD: FMS-like tyrosine kinase 3 gene-internal tandem duplication; HCT-CI: Hematopoietic cell transplantation-comorbidity index; HDT: High dose therapy; HiDAC: High dose cytarabine; NPM: Nucleophosmin.

roughly from 1×10^{12} cells to approximately 1×10^9 cells, if the patient achieves a morphologic CR. Hence additional consolidative therapy is necessary to eradicate a sizeable leukemic clone in patients in morphologic CR to achieve long-term DFS. Generally using chemotherapy-based consolidation approaches alone, the relapse rates in intermediate- and poor-risk cytogenetic groups remain unacceptably high^[26] and represent an area where alternative consolidation approaches are warranted. Allogeneic HCT for patients in CR, not only provides a “tumor-free” graft, but more importantly the donor effector T-cells recognize and mount an effective immune response against the leukemia cells [*i.e.*, the graft-versus leukemia (GVL) effect], to provide patients with durable disease control. While the potent GVL effects of allogeneic HCT provide the most effective post-remission therapy for AML patients in CR1, the associated morbidity and mortality warrants careful selection of high-risk patients, likely to benefit the most from this approach, and sparing the toxicity in lower-risk cohorts.

SIBLING DONOR ALLOGENEIC HCT IN CR1

Prospective single institution studies comparing allo-HCT with consolidation chemotherapy (CC) in the 1980s and early 1990s showed lower relapse rates and improved DFS with allo-HCT for AML patients in CR1, but none conclusively demonstrated an OS advantage^[27,28]. Subsequently, six cooperative group trials (Table 2) have examined the role of allo-HCT in AML in CR1^[28-33]. Those with HLA-matched siblings were offered allo-HCT (“genetic randomization”) while the others were randomized to autologous transplantation or CC on an intention-to-treat analysis. In the European Organization for Research and Treatment of Cancer (EORTC)-Gruppo Italiano Malattie Ematologiche Maligne Ddell’Adulto (GIMEMA) trial^[29], superior 4 year DFS was noted with allo-HCT (55%) and autologous HCT (48%) compared to CC (30%). However, no OS improvement was seen with either transplant modality^[34]. In the Groupe Ouest-

Table 2 Cooperative group trial of allogeneic hematopoietic cell transplantation for acute myeloid leukemia in first complete remission

Cooperative group	Relapse rate			Disease free survival			Overall survival		
	Allo	Auto	CC	Allo	Auto	CC	Allo	Auto	CC
EORTC/GIMEMA AML-8	24% ¹	41%	57%	55% ¹	48% ¹	30%	59%	56%	46%
GOELAM	37%	45%	55%	49%	48%	43%	55%	52%	58%
ECOG/CALGB/SWOG	29% ¹	48%	61%	43%	34%	34%	46%	43%	52% ¹
EORTC/GIMEMA AML-10	30% ¹	52%	-	52% ¹	42%	-	58%	50%	-
UK MRC AML-10 ^{2,3}	36% ¹	52%	-	50% ¹	42%	-	55%	42%	-
HOVON-SAKK ³	32% ¹	59%	-	48% ¹	37%	-	54%	46%	-

¹Represents statistically significant and favorable outcome with the treatment modality; ²The 4-year relapse rate, disease free survival and overall survival shown in all studies, except the UK-MRC AML-10 which reported 7-year outcomes; ³All studies designed to compare outcomes between allograft *vs* autograft *vs* consolidation chemotherapy except the UK MRC AML-10 and HOVON-SAKK trial which did not differentiate between autograft and chemotherapy. Allo: Allogeneic transplantation; auto: Autologous transplantation; CC: Consolidation chemotherapy.

Est Leucémies Aigues Myeloblastiques study, the relapse rates following allo-HCT were unusually high (37% at 4 years) and likely explain the lack of therapeutic benefit with allografting in this study^[30]. The MRC reported improved DFS but not OS in the MRC AML-10 patients randomized to allo-HCT^[31]. Similarly the US intergroup trial showed that the higher treatment related mortality (TRM) in patients randomized to allo-HCT arm negated the benefits of lower relapse rates in this group, resulting in no net OS advantage with transplantation in CR1 over chemotherapy alone^[28]. Although provocative, the data from these cooperative group trials failed to provide any concrete guideline for selecting the optimal post-remission strategy for individual patients with a matched sibling donor available in CR1.

Impact of cytogenetic and molecular markers on allo-HCT in CR1

Integrating information regarding cytogenetic-risk categories in the outcome analysis of aforementioned cooperative group trials was the next logical step. Reanalysis of the EORTC/GIMEMA AML-10 trial by cytogenetic-risk stratification showed superior DFS (43% *vs* 18%) and OS (50% *vs* 29%) with allo-HCT compared to autografting in patients with poor-risk cytogenetics^[32]. However allo-HCT did not benefit patients with good-risk [t(8;21), inv(16)] or intermediate-risk (normal or -Y) cytogenetics. Similar cytogenetic-risk stratification of the US intergroup trial showed a 5-year OS of 44%, 13% and 15% with allo-HCT, autologous-HCT and CC respectively, in patients with poor-risk cytogenetics^[12]. No improvement in OS was observed in patients with good or intermediate-risk disease. Unlike the prior studies, the Dutch-Belgian Haemato-Oncology Co-operative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) trial demonstrated superior DFS with allo-HCT for both intermediate and poor cytogenetic-risk patients^[33]. It may be noted that risk stratification in the HOVON-SAKK trial included additional variables. Patients with intermediate-risk cytogenetics requiring two induction cycles to achieve CR1 were classified as poor-risk, only t(8;21) AML patients with a white blood cell count of < 20 × 10⁹/L were considered favorable and patients with

unknown cytogenetics (*n* = 89) were considered intermediate-risk group. Two separate meta-analyses conducted by the HOVON-SAKK group and Koreth *et al*^[35] have confirmed survival benefit with allo-HCT in patients with intermediate- and poor-risk cytogenetics in CR1. Allogeneic HCT in CR1 also appears to improved DFS and OS in AML with monosomal karyotype, compared to other consolidation strategies.

Recognition of the prognostic value of additional molecular markers is facilitating further risk stratification of the heterogeneous group of patients with CN-AML. The German-Austrian Acute Myeloid Leukemia Study Group showed that transplantation might have an important role in a molecular subset of patients with CN-AML. Patients with normal cytogenetics were randomized based on availability of an HLA-identical sibling donor for allo-HCT in CR1 *vs* chemotherapy alone. No benefit of allogeneic transplantation was seen in patients whose leukemia was *NPM1* mutated without *FLT3*-ITD. Conversely, patients with the *FLT3*-ITD mutation or the genotype consisting of wild-type *NPM1* and *CEBPA* without *FLT3*-ITD, benefited from an allogeneic transplant performed during CR1^[36]. In double mutant *CEBPA* allo-HCT or autografting in CR1 improved DFS without impacting OS compared to CC^[37].

Matched sibling allo-HCT in medically fit AML patients, with poor- and intermediate-risk (at least in the *FLT3*-ITD+ or *NPM1*-/*CEBPA*-/*FLT3*-ITD- subgroups) cytogenetics, who are able to achieve CR1 should be considered a standard option.

UNRELATED DONOR ALLOGENEIC HCT IN CR1

The strength of evidence presented above supports allo-HCT from a sibling donor in intermediate-/poor-risk AML in CR1. Unfortunately only approximately 25%-30% of AML patients have an HLA-identical sibling. No randomized trials have looked at unrelated donor (URD) allo-HCT for AML in CR1. Yakoub-Agha *et al*^[38] reported similar outcomes with respect to acute graft-versus-host disease (GVHD), TRM, and OS in patients with standard-

risk hematologic malignancies who received HLA-A, -B, -C, -DRB1, and -DQ (10/10) allele-matched allografts from either sibling or unrelated donors. Although randomized, prospective trials of URD transplantation for AML in CR1 are lacking, a number of retrospective studies provide evidence in support of the approach. Sierra *et al*^[39] reported outcomes of URD transplantation in 161 AML patients at various stages of disease including 16 patients with poor-cytogenetic risk AML in CR1 with a 5-year DFS of 50%. The corresponding DFS for those undergoing allo-HCT in CR2, relapse, or primary induction failure were 28%, 7%, and 19%, respectively. Bashir *et al*^[40] reported a 3-year OS and TRM of 78% and 15% respectively in a cohort of 44 patients (59% poor risk cytogenetics) who underwent URD allo-HCT in CR1. In a Center for International Blood and Marrow Transplant Registry (CIBMTR) analysis of 476 patients undergoing URD allo-HCT; adjusted 3-year OS, and DFS, in CR1 were 44%, and 43% respectively^[41]. Interestingly, Tallman *et al*^[42] found no difference in survival by cytogenetic-risk stratification for AML patients undergoing URD allo-HCT in CR1. However, the reported 5-year DFS of 30% in cytogenetically poor-risk AML likely represents a better outcome than with other non-HCT treatment strategies^[43]. The presence of complex cytogenetics (> 3), however likely represent a high- risk group with poorer outcomes even with allo-HCT in CR^[44].

European Group for Blood and Marrow Transplantation (EBMT) recently reported outcomes of 206 CN-AML patients in CR1 undergoing HLA-identical sibling or matched URD allo-HCT with reference to their *FLT3-ITD* status (present: $n = 120$, 58%; absent: $n = 86$, 42%)^[45]. *FLT3-ITD*-positive patients, compared with *FLT3-ITD*-negative patients had higher 2-year relapse incidence (30% *vs* 16%, $P = 0.006$) and lower DFS (58% *vs* 71%, $P = 0.04$). More importantly, more than half of the patients harboring this mutation who received matched sibling or URD allo-HCT were alive and leukemia free at 2 years. URD allo-HCT in CR1 however may be associated with a higher TRM as noted in a registry study that reported trends of outcomes over the last two decades, underlining the need to carefully select patients for URD allo-HCT. For poor-risk cytogenetics and *FLT3-ITD*+ CN AML patients in CR1 lacking an HLA-matched sibling donor, it is certainly reasonable to consider matched URD allo-HCT.

OPTIMAL CONDITIONING REGIMENS

Myeloablative conditioning regimens (MAC) utilizing chemotherapy and/or total body irradiation (TBI) have been the basis of most of the studies discussed thus far. The two most commonly utilized MAC regimens are busulfan/cyclophosphamide (Bu/Cy) and cyclophosphamide/TBI (CY/TBI). Although prior studies showed inferior DFS and OS with Bu/Cy conditioning^[46,47], a large meta-analysis did not show any difference between the two regimens with regards to survival and relapse^[48]. It has been widely noted that the erratic bioavailability

of oral busulfan was the likely cause inferior outcomes. Recent EBMT data comparing intravenous Bu/Cy to CY/TBI in AML found increased incidence of GVHD with TBI conditioning, and a trend towards improved TRM with Bu/Cy but no difference in DFS at 2-year^[49]. A larger CIBMTR analysis clearly showed better DFS (RR = 0.70, 95%CI: 0.55-0.88, $P = 0.003$) and OS (RR = 0.68, 95%CI: 0.52-0.88, $P = 0.003$) in AML patients receiving IV, but not oral busulfan compared to TBI^[50]. Similar observations (lower TRM with Bu/Cy and better OS compared to TBI-based regimens) were made in a prospective cohort study of CIBMTR^[50,51]. Collectively these data suggest that in the era of pharmacokinetically driven adjustment of intravenous busulfan dosing, in younger (< 50-55 year) AML patients Bu/Cy should be considered the preferred MAC regimen for allo-HCT.

The use MAC is limited to medically fit, younger AML patients. The observed lower TRM rates using the so-called non-myeloablative (NMA) or reduced-intensity conditioning (RIC) regimens have broadened the applicability of allo-HCT to elderly patients or younger patients with comorbidities. Unlike MAC regimens; the NMA/RIC allo-HCT relies more heavily on the GVL effects to eradicate disease in the recipient. The decision to use NMA or RIC regimens for AML patients undergoing allo-HCT is not always clearly delineated, and significant variations exist in the selection criteria used by transplant centers across the globe. Sorror *et al*^[52] evaluated the impact of a priori medical comorbidities on transplant outcomes by using the HCT-Comorbidity Index (HCT-CI), and reported significantly higher TRM rates and inferior OS in patients with an HCT-CI score of ≥ 3 . While not validated in prospective clinical trials, it is increasingly becoming common practice to offer RIC allo-HCT to AML patients of advanced age (generally > 50-55 years), and/or HCT-CI > 3 (regardless of age), or with a prior history of autologous transplantation or less optimal performance status^[53,54].

The acute leukemia working party of the EBMT compared transplantation outcomes for 315 RIC and 407 MAC recipients^[55]. While the incidence of grade II-IV acute GVHD (22% *vs* 31%) and 2-year TRM (18% *vs* 36%) significantly favored the RIC group, more patients with RIC allograft experienced disease relapse compared to MAC regimens (41% *vs* 24%). The DFS and OS did not differ between the two groups. Another report noted grade II-IV acute GVHD rates and 2-year relapse rates of 40% and 39% respectively in 122 AML patients who received a RIC regimen with 2-year DFS of 44%^[56]. A Spanish prospective, multicenter trial of patients with poor-risk AML/myelodysplastic syndrome reported 4-year DFS and OS rates of 43% and 45% with RIC and showed that development of chronic GVHD was strongly associated with reduced risk of relapse and improved OS and DFS, providing proof of concept for clinically relevant GVL effects with RIC allotransplantation^[57].

RIC in AML has generally shown lower TRM with comparable OS and DFS to MAC regimens, but follow up is relatively short thus limiting conclusions. The ongoing

ing prospective randomized BMT-CTN 0901 clinical trial (NCT01339910) comparing RIC regimens against MAC in AML/myelodysplastic syndrome will hopefully clarify the optimal conditioning intensity in AML. The advent of RIC allo-HCT has indeed extended the feasibility and applicability of allogeneic transplantation to include those with advanced age and multiple co-morbidities, thus offering them possibly a better chance for long term DFS.

ALTERNATIVE DONOR TRANSPLANTATION

Umbilical cord blood transplantation

For those high-risk patients who do not have an HLA-identical sibling or unrelated donor available, alternative donor sources may be necessary. Umbilical cord blood transplantation (UCBT) is an attractive alternative donor option due to its rapid and easy availability^[58-62]. UCBT is associated with lower GVHD rates for the degree of HLA-disparity. In a direct comparison of outcomes in adults with hematological malignancies, Laughlin *et al*^[61] reported no difference in TRM or relapse rates between UCBT and mismatched URD bone marrow transplantation, although outcomes were inferior to matched bone marrow allografts. Similarly, Rocha *et al*^[59] in a study that included patients with acute leukemia who received UCB or matched URD marrow ($n = 582$) grafts showed no difference in TRM, relapse rate, DFS, and OS between the two groups.

The low cell dose available from individual cord blood units has been the major limitation against the widespread use of UCBT in adults with AML or other hematologic malignancies. However work done by the group in University of Minnesota has firmly established the feasibility of combining two cord blood units, in the so-called double UCBT (dUCBT), to overcome dose limitation of a single cord unit for adult patients^[63]. A large multicenter collaborative effort comparing dUCBT, matched-sibling allo-HCT, matched URD allo-HCT and mismatched URD allo-HCT showed similar 5-year DFS with all 4 modalities. dUCBT was associated with lower relapse rates but higher TRM^[64]. The preliminary results of Societe Française De Greffe De Moelle Osseuse Et Therapie Cellulaire and Eurocord's multicenter phase II trial for UCBT in patients with AML were presented in abstract form^[65]. At 1 year the rates of OS, DFS, relapse and TRM for the 65 AML patients on the study were 60%, 52%, 30% and 18%, respectively. The wider acceptance of UCBT has markedly extended the application of allogeneic transplantation, particularly to minority populations who are underrepresented in current volunteer donor databases.

Haploidentical transplantation

Almost all AML patients without an HLA-identical donor will find a haploidentical related (parents, sibling or children) donor. Enthusiasm for this modality was subdued early on due to the increased risks of GVHD, TRM, graft

rejection and opportunistic infections. However, renewed interest in haploidentical transplants has been noted with T-cell depleted as well as unmanipulated allografts with novel strategies for GVHD prevention^[66,67]. The Perugia group reported DFS of 30%-45% in AML with rigorous *ex-vivo* T-cell depletion and intense myeloablative conditioning^[68-70]. Although such transplantation has been demonstrated as feasible, it is associated with slow immune reconstitution and high rates of TRM, in smaller centers.

Recently, an alternative approach to haploidentical allo-HCT was developed with the addition of post-transplant cyclophosphamide to prevent GVHD and graft rejection in the setting of a marrow allograft after reduced intensity conditioning^[71,72]. This approach has demonstrated promising results, including acceptable rates of TRM and severe GVHD in single- and multi-institution studies. Variations including myeloablative conditioning and use of peripheral blood grafts with post transplant cyclophosphamide treatment are being studied in prospective trials^[73]. Limited retrospective data suggest comparable outcomes of matched sibling HCT, URD all-HCT and haploidentical transplantation utilizing post-transplant cyclophosphamide administration, in patients with hematological malignancies^[74]. Bone Marrow Transplantation-Clinical Trials Network's (BMT-CTN) two parallel multicenter phase II trials (BMT-CTN 0603 and BMT-CTN 0604) showed comparable 1-year OS and progression-free survival with RIC dUCBT (54% and 46%, respectively) and haploidentical bone marrow transplantation (62% and 48%, respectively) in hematological malignancies^[75]. These trials have paved the way for the ongoing BMT-CTN 1101 trial (NCT01745913) randomizing patients with hematological malignancies to either haploidentical transplantation or dUCBT. This study will hopefully guide us further in choosing the optimal alternative donor source.

Continued research is needed to better define preferred conditioning regimens, methods and degree of T-cell depletion, reduce high relapse rates with haploidentical transplantation and improved delayed immune-reconstitution inherent to all alternative donor HCT. Recently, allelic polymorphism in donor natural killer-cell immunoglobulin like receptor (*KIR*) gene has been shown to impact allograft outcome and may play important role in donor selection, including alternative sources^[76]. In centers with available expertise, alternative donor allo-HCT for carefully selected high- or intermediate-risk AML patients in CR, or those beyond CR1 is reasonable, however enrollment of such patients on any available protocols is preferred.

ALLOGENEIC-HCT FOR AML BEYOND CR1

Second complete remission (CR2)

Relapsed AML patients, who are able to achieve a second CR (CR2), typically do not enjoyed sustained responses

with chemotherapy alone. A retrospective matched-pair analysis that compared the outcomes of autologous HCT versus HLA-identical sibling allo-HCT in AML CR2 ($n = 288$) showed that while allograft recipients had higher TRM it was offset by a much lower relapse rate leading to better OS (39% *vs* 30%) at 4-years^[77]. Burnett *et al*^[78] reported outcomes of 1271 patients aged 16-49 years who entered the MRC AML10, AML12, and AML15 trials and did not receive a transplant in CR1 and then subsequently relapsed. Fifty-five percent of patients who relapsed entered CR2. Sixty-seven percent of remitters received an allotransplant that delivered superior OS compared with patients who did not receive a HCT (42% *vs* 16%). A more-stringent assessment of a transplant by using delayed-entry (Mantel-Byar) analysis confirmed the benefit of transplant overall and within intermediate- and poor-risk groups but not the favorable-risk subgroup. Allo-HCT is the preferred option for most medically fit patients with AML in CR2, including carefully planned alternative donor allografts. For those unable to undergo an allograft (due to comorbidities, personal preference, *etc.*) are best treated in the context of a clinical trial when available.

Beyond CR2

Allogeneic HCT offers the best prospect of long term DFS for patients with relapsed/refractory AML beyond CR2^[79,80]. Sierra *et al*^[39] reported 5-year DFS of 50%, 28%, 27% and 7% with allo-HCT in CR1, CR2, beyond CR2 and in untreated relapse respectively. The corresponding relapse rates were 19%, 23%, 25% and 44%, respectively. A history of prior autologous transplantation adversely affects the success of a subsequent allo-HCT^[79].

The first relapse of AML poses a management dilemma regarding whether to proceed directly with allo-HCT or to administer salvage chemotherapy to attain remission. Retrospective data indicate 3-year DFS rates of approximately 30% for patients transplanted in untreated first relapse^[81,82]. Salvage chemotherapy generally induces subsequent CR in approximately 30% of relapsed AML patients^[83]. Considering that only 35%-45% of these patients may achieve long-term DFS with allo-HCT (approximately 15% of all relapsing patients), theoretically allografting in untreated relapse may cure more patients than additional chemotherapy. However, in clinical practice the logistics of HLA-typing, identifying and evaluating potential donors, and stem cell collection generally necessitate administration of chemotherapy for disease control before transplantation. Moreover, relapse/refractory patients may not be prime candidates for myeloablative conditioning regimes that are likely required for optimal disease control to facilitate graft-versus-leukemia effect. This fact also highlights the importance of initiating the donor search in AML patients at the time of diagnosis^[84,85].

Primary refractory AML

Allo-HCT likely represents the only curative option for patients with primary refractory AML^[83]. Retrospec-

tive analyses have shown long-term survival in a subset of patients receiving allo-HCT for primary refractory AML^[86-89]. Despite the relatively high TRM (30%-50%), the reported 3-year OS and DFS of approximately 20%-30% are encouraging for this otherwise poor prognosis group. CIBMTR reported outcomes of 1673 AML patients undergoing allo-HCT with refractory/active disease^[90]. Five adverse pre-transplantation variables significantly influenced survival: first CR duration < 6 mo, circulating blasts, non-HLA-identical sibling donor, Karnofsky score < 90, and poor-risk cytogenetics. Patients who had 0 adverse factors had 42% OS at 3 years, whereas OS was 6% for a score ≥ 3 . These important results highlight that allo-HCT can salvage a highly select subgroup of AML patients, who are not able to achieve a CR before transplantation. Based on promising phase I / II data, the use of novel clofarabine and busulfan conditioning is being explored in this population (NCT01457885)^[91].

FUTURE DIRECTIONS

Great strides have been made in the field of AML and allo-HCT resulting in a steady increase in the number of allogeneic transplantation done for AML. Risk stratification of AML based on conventional cytogenetics and now molecular profiling has been instrumental in identifying higher-risk groups who may benefit from early allo-HCT. Studies looking at whole-genome and whole-exome sequencing have been reported^[92] and this information will be vital not only in prognostication but is likely to lead to discovery of novel therapeutic targets. The cytogenetic and molecular signature of AML has become expansive and its clinical application ought to be carefully interpreted. The identification of higher-risk cytogenetic groups, novel molecular stratifications incorporating coinciding aberrations and the presence of clonal heterogeneity in poor-risk AML may allow us to better predict relapse risk, recommend allo-HCT and other strategies to improve disease control and survival in an individualized fashion. The presence of minimal residual disease (MRD) is another area of active interest that may help identify those subsets of AML with the highest risk of early relapse and thus may benefit from early interventions such as allo-HCT. This may be especially important in good-risk and intermediate-risk group AML^[93]. Similarly evidence of persistent MRD post allo-HCT is a marker of poor outcomes. Such AML patients with evidence of MRD post allografting could be enrolled in trials designed to eradicate persistent low level disease (*e.g.*, by rapid taper of immune suppression, planned/escalated donor-lymphocyte infusions, low-dose chemotherapies, or novel targeted agents, *etc.*).

Allogeneic HCT itself has indeed undergone tremendous advancement in the last 2 decades. High-resolution allele level HLA-typing, improvements in supportive care, use of alternative donor allograft and RIC has widely broadened the use of allo-HCT in AML. The newest concept of adoptive cellular therapy is the so-

called “microtransplantation” where HLA-mismatched peripheral blood stem cells are infused into the recipient after consolidative chemotherapy with cytarabine, the hypothesis being that the alloreactive HLA-mismatched cells would not engraft, but during their transitory period will destroy AML clone without causing GVHD^[94]. Concerted efforts are needed to devise strategies to prevent relapse post allo-HCT using novel maintenance or consolidation strategies (*e.g.*, FLT3 inhibitors post allo-HCT in FLT3⁺ patients, hypomethylating agent administration to eradicate minimal residual disease). Rigorous research efforts in the development of novel preparative regimens able to provide better early disease control and limiting TRM are need. In this regard total marrow irradiation programs and/or immune-radioisotope-based conditioning appear promising. Additional avenues include using propylene glycol free melphalan (to limited renal toxicity), and pharmacokinetically dose busulfan (to limited organ damage, and prevent underdosing) as safer conditioning drugs. Immunological strategies to modulate patient or donor’s immune system, so that they mount response against tumor specific antigens are ongoing. Various antigens (Wilms Tumor gene, NOTCH, PR1, *etc.*) are being tested to develop vaccine to achieve a lasting immune response in the setting of relapsed leukemia or MRD after transplant. Newer mobilization regimens (*e.g.*, plerixafor for sibling donor mobilization) and more effective methods to prevent GVHD^[95-101] as well as increased availability of alternative-donor approaches, are ongoing and will add to our ability to cure patients with AML in the coming years.

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