Allogeneic hematopoietic cell transplantation for adults with acute myeloid leukemia: myths, controversies, and unknowns

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Abstract

Progress in the last decade has improved the understanding of leukemia biology. Molecular markers in combinations with cytogenetics have improved the risk stratification of acute myeloid leukemia (AML) and informed decision-making. In parallel, several important advances in the transplant field, such as better supportive care, improved transplant technology, increased availability of alternative donors, and reduced intensity conditioning (RIC) have improved the safety as well as access of allogeneic hematopoietic cell transplantation (HCT) for a larger number of patients. In this review, the positioning of HCT in the management of patients with AML is evaluated in view of changing risk/benefit ratios associated with both conventional treatments and transplantation, and some of the controversies are addressed in light of emerging data. Increasing data show outcomes of alternative donor transplantation approaching HLA-identical sibling donors in high-risk AML supporting the inclusion of alternative donors in trials of prospective studies evaluating post remission strategies for high-risk AML. The use of RIC has expanded the eligibility of HCT to older patients with AML, and outcome data are encouraging. Continued study of HCT vs. alternative therapies is required to optimize patients’ outcomes in AML.
Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment option for patients with acute myeloid leukemia (AML). The curative effect of HCT in AML patients is contributed both by the chemotherapy and/or radiation in the preparative regimen, and more importantly by the immunological graft-versus-leukemia (GvL) effect\(^1\). Currently, AML is the most common indication for HCT. Data from Center for International Blood and Marrow Transplant Research (CIBMTR) indicate a sustained increase in number of AML allogeneic transplants in the last decade (Table 1). While transplant numbers from related donors have remained stable over the last decade; transplants from unrelated donors (URDs) are growing in numbers (Table 1). The growth of transplant activity is mainly in adults due to increased use of URDs, especially in first remission (CR1) (Table 1, Fig.1). CIBMTR data show that 47\% of CR1 allografts (all ages) in AML in 2008 were performed using URDs. Among URDs, umbilical cord blood (UCB) is becoming an important graft source in adults, and contributed to 11\% of adult transplants from URDs in 2008 (Table 1). Despite these trends, there remains wide variation in the application of HCT in AML patients, especially during CR1. The guidelines of various major organizations in Europe and the US on the use of HCT for AML patients are not consistent\(^2\).

Progress in the last two decades in understanding the disease biology of AML may guide further practice changes. Cytogenetics is the most robust prognostic marker for risk stratification of AML at the time of diagnosis as well as in selection of post-remission treatments\(^3\)\(^-\)\(^5\). Based on specific structural and numerical cytogenetic abnormalities, AML
patients are divided into favorable, intermediate or adverse risk groups. More recently, new molecular markers such as FMS-related tyrosine kinase 3–internal tandem duplication (FLT3-ITD), CCAAT/enhancer-binding protein-α (CEBPA), and the nucleophosmin-1 (NPM1) mutation have further refined the risk stratification, particularly in patients with cytogenetically normal AML (CN-AML). These cytogenetic and molecular markers have helped identify patients at different risk of relapse after achieving CR. In parallel, major advances have developed in the transplant field. Better supportive care, and selection of URD using high-resolution allele-level HLA-typing have improved the safety of transplantation. Increasing use of UCB, and application of reduced-intensity conditioning (RIC) regimens have increased the candidacy for HCT to include a wider group of patients, particularly older or ethnic minorities not well served by earlier HCT and donor search options.

In this review, we evaluate the positioning of HCT in the management of patients with AML in the light of changing risk/benefit ratios associated with both conventional chemotherapy and HCT, and address controversies highlighted by emerging data.

**HCT for Adult Patients With AML in CR1**

A number of studies have investigated the role of HLA-matched sibling donor (MSD) transplantation in patients with AML in CR1. The designs of these studies involve genetic assignment substituting for randomization based on the availability of a MSD. These studies were generally not powered to evaluate the outcome of HCT according to cytogenetic risks. Subgroup analyses of these studies based on cytogenetics included
small sample sizes. A recent systematic review and meta-analysis of prospective biologic assignment studies analyzed 3,638 patients with AML in CR1 by cytogenetic risk, and showed a significant survival advantage of HCT in comparison to non-allogeneic treatments for AML patients with intermediate and unfavorable cytogenetics, though not for good risk cytogenetics\(^7\). Recent progress in the understanding of leukemia biology has further refined prognostication of intermediate-risk group patients especially CN-AML, and identified sub-groups among those with favorable risk cytogenetics at higher risk of relapse. Current guidelines and new evidence for AML patients in CR1 based on leukemia biology raise new questions: 1. Should all patients with CN-AML with a suitable donor be referred for HCT in CR1?; 2. Is there a role of HCT for a sub-group of patients with good-risk cytogenetics in CR1?; 3. If a MSD is not available, is alternative donor HCT indicated in CR1?

**Should all patients with CN-AML be referred for HCT in CR1?**

CN-AML is a heterogeneous group comprising of approximately 40-50\% of AML patients <60 years, less common above 60, and currently categorized as intermediate-risk\(^3\)-\(^5\). Recently, several molecular alternations have helped to improve the individual risk assessment of CN-AML patients\(^8\). Several studies have shown prognostic significance for mutations in the NPM1, CEBPA and FLT3 genes alone or in combination in both younger and older adults with AML. Presence of FLT3-ITD mutation has been identified as a powerful indicator predicting more frequent and early relapse\(^9\)-\(^12\). The adverse impact in FLT3-ITD positive patients may be greater in those with a high level of the mutated allele\(^10\),\(^13\). The prognostic significance of FLT3-TKD
mutations remains controversial in view of conflicting data\textsuperscript{14-16}. NPM1 mutation (mNPM1) in the absence of FLT3-ITD mutation in CN-AML has been associated with lower cumulative incidence of relapse (CIR) resulting in better leukemia-free survival (LFS) and overall survival (OS)\textsuperscript{17-20}. The outcomes of AML with genotype “mNPM1 without FLT3-ITD” treated with conventional chemotherapy appear favorable and similar to patients with t(8;21) or inv (16)\textsuperscript{11,19}. CN-AML with mutations in CEBPA (mCEBPA) are associated with favorable prognosis\textsuperscript{11,21-24}. The role of molecular genetic alterations in AML has been recognized in the 2008 revised WHO classification, and AML with mNPM1 or mCEBPA have been incorporated in the WHO classification as provisional entities\textsuperscript{25}.

A study from Germany analyzed the role of mutational status of NPM1, FLT3, CEBPA, along with MLL and NRAS in guiding post-remission therapy for CN-AML in CR\textsuperscript{11}. This study analyzed data of CN-AML patients treated in 4 prospective clinical trials. Treatment intention was similar in all 4 trials, and patients with a HLA-matched related donor (MRD) were assigned to undergo HCT in CR1; those without a donor were randomly assigned to receive high-dose cytarabine (HiDAC) consolidation or autologous transplant. HCT was performed in 82\% of assigned patients. Autologous transplant or consolidation therapy resulted in similar outcomes. An intention to treat analysis based on donor availability, showed significantly longer relapse-free survival (RFS) in the donor group (p=0.009). Data were further analyzed based on mutation status, and patients were further subdivided into two groups: patients with “mNPM1 without FLT3-ITD”, and patients with all other genotypes. Due to small numbers, patients with mCEBPA
were excluded. No differences in RFS was seen with or without a donor in the favorable genotype patients with mNPM1 without FLT3-ITD (p=0.71). Among the patients with CN-AML with genotypes other than “mNPM1 without FLT3-ITD”, superior RFS was observed in those with a donor. At present, there are no comparative data available on outcomes of HCT versus non-allogeneic treatments in CN-AML patients with “mCEBPA”. The outcome of “mCEBPA” patients is similar to “mNPM without FLT3-ITD”. Increasing data show that the better outcome of CEBPA mutations is restricted to patients with double mutation only. Therefore among the CN-AML, HCT in CR1 could be deferred in favorable genotype of “mCEBPA or mNPM1 without FLT3-ITD”. HCT should be considered in all other patients with CN-AML in CR1, at least up to age 60 years.

The definition of favorable genotype may be further refined with the identification of new mutations, though the favorable subtypes may remain uncommon. Recently identified isocitrate dehydrogenase enzyme isoform 1 mutations (mIDH1) and isoform 2 mutation (mIDH2) have been associated with a poor prognosis in AML. Of particular note, mIDH1 was seen among 21/86 patients with mNPM1. None of the 22 patients with mCEBPA had mIDH1. None of the patients with mNPM1 or mCEBPA had mIDH2. The authors suggested that favorable genotype among CN-AML patients should be modified to “mNPM1 or mCEBPA with neither FLT3-ITD nor mIDH1”. Other recently described mutations in the DNA methyltransferase gene DNMT3A are frequent in patients with intermediate-risk cytogenetics and associated with increased relapse risk and poor outcome. Of note, a significant benefit of HCT was observed in this small
series. Findings from these recent, but small studies need further validation before routine application. Evolving technologies such as microarray profiling\textsuperscript{31-33} and microRNA signatures\textsuperscript{34} have shown promise in improving the prognostic classification of AML; however these methodologies are not yet available for routine clinical use.

**Is there a role of HCT for patients with favorable risk cytogenetics in CR1?**

Patients with core binding factor (CBF) leukemia [i.e. t(8;21) or inv(16) or t(16;16)] or acute promyelocytic leukemia (APL) with t(15;17) are considered at relatively lower risk of relapse, and thus are considered to have favorable risk cytogenetics\textsuperscript{3-5}. The meta-analysis of prospective genetic randomization studies showed no benefit of HCT in patients with favorable risk cytogenetics in CR1\textsuperscript{7}. With ATRA or arsenic trioxide based treatments, the outcome of APL with t(15;17) has significantly improved. These treatment strategies lead to cure in most patients, and the expected relapse rate is usually 10-25\%\textsuperscript{35}. However, in CBF-AML, only 50\% of patients were alive at 5-years\textsuperscript{36}. Therefore, some of these patients may still have a high risk of relapse. The role of KIT mutations (mKIT) in CBF-AML has been investigated to identify a high-risk subset in the otherwise favorable CBF group\textsuperscript{37-40}. Two commonly identified KIT mutations [exon17 (mKIT 17), or exon 8 (mKIT 8)] in CBF-AML appear to have prognostic relevance; however the data from these studies are not consistent. Discrepant results may be related to small number of patients, and differences in the treatments.

Repetitive cycles of high-dose cytarabine (HiDAC) as post remission therapy is associated with favorable outcomes in patients with CBF-AML\textsuperscript{41,42}. A Cancer and
Leukemia Group B (CALGB) study investigated the role of mKIT in 61 adult patients with inv(16) and 49 patients with t(8;21) assigned to post remission therapy with HiDAC. In patients with inv (16), the 5-year relapse-risk was significantly higher in patients with mKIT (56% vs. 29%, p=0.05), and in particular mKIT17 (80% vs. 29%, p=0.002) in comparison to wtKIT. Similarly, in patients with t (8;21), the 5-year relapse-risk was significantly higher in those mKIT (70% vs. 36%, p=0.017). This relapse pattern is similar to that seen with patients with adverse cytogenetics. In view of these data, we may suggest that patients with “CBF-AML with mKIT” be considered for HCT in CR1.

It is noteworthy that at present, there are no available data to show the benefit of HCT in “CBF-AML with mKIT” although resistance to HiDAC or other consolidation strategies may not imply resistance to the allogeneic GvL effect. The high-risk of relapse in these patients merit the investigation of alternative treatment strategies including HCT or possibly molecular targeted therapies with tyrosine kinase inhibitors in future studies.

**Is there a role of Alternative donor transplantation in CR1?**

Most AML patients with adverse cytogenetics relapse within a year, and likelihood of subsequent CR is very low. Meta-analysis of prospective biologic assignment studies comparing the role of HCT to non-HCT treatments for patients with adverse cytogenetics in CR1 have shown a strong survival advantage for HCT during CR1. Most patients in these studies received HCT using MSD, and comparisons of URD HCT to non-allogeneic treatments are limited. A recent study from CIBMTR compared the outcomes of URD and MSD transplants in patients with AML in CR1 with unfavorable cytogenetics. This study showed similar LFS and OS of HLA-well matched URD (no known disparity
at HLA-A, B, C or DRB1) in comparison to MSD, whereas outcomes were not as good for HLA-partially matched URD (disparity at one locus). Prospective comparisons of MSD and URD for high risk AML patients in CR1 on a limited number of patients show equivalent outcomes\(^{46,47}\). Therefore, if a MSD is not available, an HLA-well matched URD is appropriate for patients with AML with adverse cytogenetics in CR1.

There are only scanty data on comparisons of MRD and URD transplantation in intermediate-risk AML in CR1. A study from Seattle compared 85 patients with URD vs. 135 patients undergoing MRD transplantation in CR1\(^ {49}\). In the intermediate risk group, 58 and 83 patients underwent HCT using URD and MRD, respectively. Majority of patients in intermediate-risk had normal karyotype. While these sample sizes are modest, the outcomes of URD and MRD appear similar. Among the patients with normal karyotype, those with FLT3-ITD mutations are at a higher risk of relapse. At present, no comparative data are available on outcomes of MSD and URD in AML patients with FLT3-ITD mutations. The high-risk of relapse in these patients merit the use of HCT using either related or URD HCT and further investigation of novel molecular targeted therapies. A high-risk of early relapse and lengthy time for volunteer URD searches confound the use of URD HCT in CR1 in high-risk AML patients. Therefore, donor searches for such patients should be initiated early, during the initial induction.

An important, but as yet incompletely addressed question is the utility of UCB-HCT for patients with high-risk AML in CR1. Previous registry studies have compared the outcomes of unrelated UCB with unrelated bone marrow (URD-BM) grafts in adults with
acute leukemia. A study from the EBMT showed similar outcomes among the two cohorts, whereas the study from CIBMTR showed lower TRM, treatment failure, and overall mortality among the recipients of HLA-matched BM grafts; and similar outcomes for patients receiving mismatched UCB transplants and mismatched URD-BM grafts. A recent study from CIBMTR compared outcomes of UCB (n=165) with URD-PB (n=888), URD-BM (n=472) in patients with acute leukemia. The majority of patients receiving UCB graft were 4/6 antigen match (70%). The LFS in patients after 4-6/6 matched UCB-HCT were comparable with that after 8/8 or 7/8 allele matched URD-PB or URD-BM recipients; however the TRM was higher after UCB-HCT. A recently published study from Minnesota and Seattle demonstrated similar outcomes in double unit UCB and matched URD compared to MSD after myeloablative HCT in hematologic malignancies. As these studies analyzed impact of graft source in patients with mixture of different disease status in acute leukemia or hematologic malignancies, results are hard to interpret for AML in CR1. A recent study from the Japan evaluated the disease specific comparison of unrelated UCB recipients and HLA-allele matched URD-BM recipients in 484 adult patients with AML (173, CB; and 311, BM). In this study, 180 AML patients underwent transplant in CR1 (50, CB; and 130, BM). Multivariate analysis showed inferior survival of patients in CR1 receiving UCB-HCT vs. URD-BM [RR 2.92 (95% CI 1.38-6.18), p=0.005]. The inferior survival with UCB-HCT in these patients was associated with higher TRM in UCB group. Contrary to the commonly held belief that GvL effect after URD or mismatched donor is more potent in comparison to MSD; the studies comparing different donor sources show that the relapse rate was not decreased after well matched URD or mismatched URD/UCB-HCT.
Should haplo-identical transplantation (haplo-HCT) be a suitable option for high-risk AML in CR1? There are very limited data available on use of haplo-HCT in patients with AML in CR1. A recent study from the EBMT analyzed the outcomes of haplo-HCT in patients with acute leukemia in remission\textsuperscript{56}. This study included 86 patients with AML in remission (25 in CR1). The 2-year cumulative incidence of TRM, relapse, and probability of LFS was 36\%, 16\%, and 48\%, respectively in CR1 patients. The effect of donor graft sources in AML from various studies are summarized in Table 2\textsuperscript{46,48,49,54,57-59}. These data are intriguing, but insufficient to guide decisions about URD, UCB or haplo-HCT, particularly in centers with little experience with either UCB or haplo-HCT where complications of graft failure or slower immune recovery need extra attention, even if GvHD is less common. However, their rapid availability offers an important clinical advantage for patients in whom donor search was delayed or cohorts of higher risk where remission duration may be brief. Current data suggest that these options be used only in the absence of a timely available URD. No data exist on the comparison of UCB and haplo-HCT to non-allogeneic treatments in AML in CR1 at present; emerging data support the inclusion of UCB, haplo-HCT in addition to volunteer URD in prospective studies evaluating post remission strategies for high-risk AML in CR1.

**Relapsed AML**

The treatment of AML in first relapse is associated with unsatisfactory results and survival is usually poor. There are no prospective studies evaluating the outcome of HCT in comparison to conventional chemotherapy in patients with relapsed AML. All reported
data are retrospective in nature and have the limitations of treatment heterogeneity and selection bias. However, a prospective study in this area is logistically difficult and unlikely to be performed. HCT is often used in this setting, despite only limited evidence about its outcome.

One study from Europe evaluated the outcomes of 667 AML patients in first relapse among 1540 newly diagnosed non-M3 AML patients (age 15-60 years) entered into 3 consecutive cooperative group trials\textsuperscript{60}. This study identified 4 prognostic factors in multivariate analysis: relapse-free interval from CR1, cytogenetics at diagnosis, age at first relapse, and autologous or HCT prior to first relapse. Based on these factors, a weighted prognostic score was proposed to identify three risk groups: favorable, intermediate, and poor risk. For patients able to achieve CR2, comparison of chemotherapy versus HCT among these 3 groups showed superior 5-year survival in patients undergoing HCT [favorable, 88\% vs. 33\%; intermediate, 48\% vs. 31\%; poor, 26\% vs. 6\%]. Achievement of CR2 and application of salvage HCT are crucial for improving the prognosis of these patients\textsuperscript{60,61}. Survival of patients in first relapse undergoing salvage HCT was significantly better for those who achieved CR2 compared to those not in remission at HCT (3 year survival 59\% vs. 21\%)\textsuperscript{61}. Little data on comparison of UCB-HCT/ haplo-HCT vs. chemotherapy in this setting are reported.

Given the poor prognosis associated with chemotherapy alone, UCB or haplo-HCT for patients in CR2 may be valuable, particularly in light of their rapid availability.
**HCT in patients with AML not in remission**

The utility of HCT for patients with AML with active disease remains controversial. Several studies have reported the outcomes of HCT in patients with acute leukemia not in remission at the time of transplant with variable outcomes\(^{62-68}\). Small sample sizes, mixture of patients with AML, ALL and CML blast crisis, and publication bias confound interpretation of data.

A recent CIBMTR study evaluated the outcome of 1673 patients with AML not in remission at the time of HCT\(^{69}\). Survival at 3- and 5-years was 19% and 17%, respectively. In the multivariate analysis, five adverse patient-, disease- and transplant-related factors were identified: first CR duration <6 months, circulating blasts, donor other than MSD, performance score <90%, and adverse risk cytogenetics. The 3-year survival of patients with none of these risk factors was 42%, and those with 1, 2 or ≥3 risk factors was 28%, 15% and 6%, respectively. These results provide important guidance in identifying groups where the transplant procedure has reasonable chances of success, as well as identifying patients for whom transplant procedure is likely to be futile. This study included only patients treated with myeloablative conditioning. The role of RIC in patients with active acute leukemia is unclear. Some investigators have suggested that RIC may be an option\(^{67,70,71}\), while others have reported futility of this procedure in such patients\(^{72}\).

For patients with refractory AML (primary induction failure (no CR after 2 cycles of therapy), relapse following a CR1 <6 months, second or higher relapse, or resistant
elapsed disease, success in achieving CR with any further salvage therapy is very low (10-15% at best). Further chemotherapy extends the risks of opportunistic, often fungal infection and organ toxicities, any of which can increase TRM of future HCT. A sequential approach of use of salvage chemotherapy for reduction of leukemia burden followed by RIC was reported from Germany71. This approach led to encouraging 3-year LFS and OS of 30% and 32% in patients with refractory AML, yet still reflects substantial patient selection.

Relapse is the major cause of failure in AML patients not in remission at HCT, and novel strategies to improve the efficacy of conditioning such as addition of targeted radiation73, intensity modulated radiation therapy74, or post HCT strategies such as azacytidine, prophylactic DLI, adoptive transfer of natural killer cells, leukemia specific T cells or leukemia vaccines aimed at promoting a more potent or durable GvL effect require study71,75-77.

Guidelines for the indications of HCT in AML from various donor sources are summarized in Table 3. With in the framework of these guidelines, each patient should be carefully evaluated for the risk posed by disease itself vs. risk from the transplant procedure taking in considerations factors such as age, performance status, comorbidities, and donor-recipient matching. Decisions may further be guided by the likely ability to achieve CR2 in case of relapse.
Therapy-related AML

With the expanding pool of cancer survivors, therapy-related AML (t-AML) is increasingly encountered, and constitute approximately 10-20% of newly diagnosed patients with AML. Conventional chemotherapy is not curative, and HCT is a potential treatment for patients with t-AML. However, the best t-AML candidates for HCT are not well defined. There are no prospective data defining the value of HCT in patients with t-AML to guide treatment decisions.

Outcomes of HCT in patients with t-AML are inferior to published data on de novo AML. This is due in part to a high number of t-AML patients with poor leukemia biology including unfavorable cytogenetics, prior t-MDS, and active disease at the time of HCT. However in some reports, when adjusted for disease status and cytogenetics, there was no difference in outcomes of t-AML and de novo AML. The results of t-MDS/AML from three major registry studies from the French Society of Bone Marrow Transplantation, EBMT and CIBMTR are summarized in Table 3. Several common conclusions can be drawn from these studies. HCT yields encouraging outcomes in younger patients in remission with MSD, well matched URD (8/8) or partially matched URD (7/8). Poor risk cytogenetics has a significant adverse impact on relapse. Based on 4 prognostic factors for survival (age >35 years, poor risk cytogenetics, AML not in remission or advanced MDS, and donors other than MSD, well matched or partially matched URD), the CIBMTR study proposed a prognostic scoring system for t-AML undergoing HCT. Five year survival of patients with score 0, 1, 2, 3 and 4 was 50%, 26%, 21%, 10%, and 4%, respectively. This scoring system may be particularly useful to
guide selection of subset of patients likely to benefit from HCT and suggest investigational or palliative approaches for those lacking the favorable features.

Cytogenetic classification is an independent prognostic parameter in patients with t-AML\textsuperscript{84}. However when comparable cytogenetic groups were evaluated, the survival of t-AML with favorable cytogenetics was inferior to those with de novo AML. Among the CBF-AML, the outcome of t(8;21) in t-AML appears inferior when compared to de novo AML\textsuperscript{84,85}, while the outcomes appear similar for the rare patients with inv(16)\textsuperscript{84}. The outcome of t-APL does not appear different from de novo-APL when treated with an ATRA containing regimen\textsuperscript{86}. For t-AML, should patients with rare CBF leukemia or CN-AML with favorable molecular profile be referred for HCT in CR1? Currently, there are no data to determine the prognostic impact of “mNPM without FLT3-ITD” or “mCEBPA” in the small subset of t-AML patients in comparison to de novo AML patients.

Given the poor prognosis of t-AML with conventional chemotherapy, HCT should be considered during CR1 for all patients in the transplant age group with suitable donors. HCT can be deferred for t-APL, and possibly inv(16) in CR1, but even these data are limited.

Similar to t-AML, AML evolving from preceding myelodysplastic syndrome or myeloproliferative disorder is recognized as high risk and as such, is not curable with conventional chemotherapy. HCT has promise, but no prospective data directly addresses this topic.
HCT in older patients with AML

Conventional chemotherapy options are not curative in a majority of AML patients ≥60 years. High peri-transplantation mortality with myeloablative transplant was assumed to be a major barrier resulting in only limited application of HCT in older patients. The introduction of RIC has enabled to overcome the barrier of early TRM, and several studies have shown the feasibility and reasonable outcomes with RIC in older patients with AML ≥60 years using related and URDs. It appears that the likelihood of older patients being referred for HCT is very low in comparison to younger patients. Hesitancy of treating physicians, uncertainty regarding outcomes of HCT, lack of comparative data on the outcomes of HCT vs. non-transplant treatments in older patients, and insurance coverage are some of the barriers contributing to underutilization of HCT in older patients.

A recent study from CIBMTR evaluated the impact of age in 545 patients with AML in CR1 with age ≥40 years undergoing RIC (40-54 years, 201; 55-59 years, 149; 60-64 years, 132; ≥65 years, 63). In this study, 2-year LFS and OS in all age groups were similar and no impact of age was observed. Two single centre studies showed no impact of age on post transplant outcomes in patients ≥60 years treated with RIC. Another multicenter study from the Seattle consortium, the outcomes of 274 patients with AML treated with a non-myeloablative conditioning included 135 patients with AML ≥60 years and no impact of age was observed. An important observation was that MSD and well matched URD transplants led to similar survival. In view of the above data, HCT can be considered in patients up to the age 70 years. Very few HCT patients older than 70
years have been reported. Therefore, suitably fit patients between the age 60-70 years should be informed about the option of HCT, and donor searches should be initiated promptly after diagnosis to allow this option if a CR is achieved.

Most of the comparisons of allogeneic versus non-allogeneic treatments in AML are reported in younger patients up to the age 60 years; and at present there are no prospective comparisons of allogeneic versus conventional treatments in older patients. Preliminary results of a retrospective case-controlled study from the CIBMTR and CALGB comparing the outcomes of RIC transplantation (n=100) with conventional chemotherapy (n=96) in patients ≥60 years with AML were recently reported97. To avoid selection bias for the HCT arm, only patients remaining in CR1 for at least 4 months treated on CALGB trials were included in the chemotherapy arm. The 3-year LFS from CR1 for HCT patients was 32% compared to 15% for chemotherapy-treated patients (P=0.006). Although relapse-risk in HCT arm was significantly lower (32% vs. 81%, p<0.001); TRM was significantly higher (22% vs. 3%, p<0.001) resulting in marginal difference in OS (HCT, 37% vs. chemotherapy, 25%;p=0.08). These data indicate the importance of ongoing efforts to improve the results of HCT with a focus to decrease TRM as well as novel strategies to decrease the relapse risk in non-allogeneic treatments. Continued efforts should be made to recruit these patients in to prospective studies comparing HCT vs. non-allogeneic treatments.
Intensity of conditioning chemotherapy – myeloablative versus reduced?

The preferred intensity of conditioning therapy for AML patients remains a subject of debate. In the last decade, a plethora of RIC regimens have been developed. The spectrum of intensity of RIC regimens vary from minimal to moderately intense. To facilitate comparisons of intensity of conditioning regimens, CIBMTR has developed guidelines to define these regimens, and based on the expected duration of cytopenia and on the requirement for stem cell support, these regimens are defined as (1) myeloablative conditioning (MAC), (2) RIC, and (3) nonmyeloablative (NMA) conditioning.

Various studies comparing the outcomes of RIC/NMA conditioning with MAC in AML patients are summarized in table 4. Results of these retrospective studies are limited by significant differences in patient populations and the analysis may be influenced by selection bias. Patients expected to have a high risk of relapse may be selected for MAC; and patients with advanced age and/or comorbidities may more often be selected for RIC/NMA regimens. Missing data on co-morbidities and details of the decision-making process for RIC/NMA are other major limitations. Importantly, all studies have reported similar LFS and OS in patients undergoing MAC and RIC, respectively. Some have reported decreased TRM with RIC in comparison to MAC, while others have reported similar TRM. A comparison of NMA vs. RIC vs. MAC regimens showed similar outcomes of RIC and MAC, whereas outcomes were inferior for NMA due to increased relapse. A comparison of RIC vs. NMA in patients with AML/MDS suggested better outcomes with RIC. Relapse rates between MAC and RIC appear similar in patients with leukemia in CR at the time of...
HCT\textsuperscript{72,99,105}; dose intensity appears particularly important for patients with leukemia not in remission at the time of HCT\textsuperscript{70,72}. Importantly, none of the studies so far has shown superiority of RIC/NMA to MAC in AML. Therefore, RIC/NMA should only be offered to the patients considered ineligible for MAC. At present, the indications of RIC/NMA are not consistent. Tools such as HCT-specific comorbidity index (HCT-CI)\textsuperscript{108}, pre-transplant assessment of mortality (PAM) score\textsuperscript{109}, and understanding of interaction of comorbidities, performance status, with age may aid in developing objective criteria for candidacy for RIC/NMA. The best regimen for RIC/NMA is not known, but available data support the use of RIC over NMA regimens for AML.

Current data on application of RIC/NMA regimens in AML lack prospective comparison of allogeneic versus non-allogeneic treatments. A retrospective study evaluated RIC HCT in comparison to chemotherapy in 95 patients with high-risk AML in CR\textsuperscript{110}. Using an intention to treat approach, a “donor” versus “no donor” comparison showed better LFS in the donor group (54\% versus 30\%, p=0.01). These encouraging results further need prospective validation including from studies presently in progress.

**Relapse after HCT**

Relapse is one of most common cause of failure of HCT for AML, and is associated with very poor prognosis\textsuperscript{111}. The preferred management of relapse after HCT is not known. Conventional treatment options include supportive care, chemotherapy, second HCT using the same or alternative donor, DLI, and cytokines. Substantial selection bias confounds interpretation of the reported literature.
Second HCT after failure of first HCT has limited efficacy in patients with AML\textsuperscript{112-116}. Available literature suggests that duration of remission after first HCT is the most important prognostic factor\textsuperscript{114-116}. A reasonable outcome can be expected in selected patients, whose duration of remission after first HCT is $\geq$1-year, and who achieve CR prior to a second HCT\textsuperscript{114-116}. DLI has limited efficacy in patients with AML. Two prospective studies have evaluated the strategy of reduction of disease burden with chemotherapy, and followed by GCSF-primed DLI in patients with advanced myeloid malignancies\textsuperscript{117,118}. This strategy was beneficial to those who were able to achieve CR. Patients with remission lasting $>6$ months had a higher likelihood of response. The efficacy of DLI was retrospectively studied by EBMT including 399 patients in first relapse after HCT for AML who received DLI\textsuperscript{(n=171)}, or not \textsuperscript{(n=228)}\textsuperscript{119}. Clinical benefit of DLI was seen only in a minority particularly with those with a lower tumor burden at relapse ($<35\%$ BM blasts), female sex, favorable cytogenetics, and remission prior to DLI.

Therefore, a second allogeneic treatment can be considered in selected patients, whose duration of remission after first HCT is $>6$ months. Decision-making and the selection of second HCT vs. DLI should be individualized based upon donor availability and achievement of remission prior to DLI or second HCT. Recently, low dose azacytidine has been reported to be of benefit in patients relapsing after HCT in small series, and this strategy may be useful tool for disease debulking as an alternative to chemotherapy prior...
to DLI/second HCT\textsuperscript{75}. More research is needed to understand the biology of relapse to develop novel interventions for this difficult problem.

**Summary**

The trend of growth of numbers of HCT in adult patients with AML can be expected to continue based on acceptance and availability of URD and UCB donor. The highly specialized nature and resource intensity of HCT will lead to major challenges for manpower and resources. Little data are available for the reliable estimates of the number of transplants for AML and the total number of AML patients for whom transplantation is appropriate. With the expansion of donor registries, and availability of UCB grafts a suitable donor can potentially be found for nearly all patients with AML\textsuperscript{46}. However, there appears a great discrepancy in the number of newly diagnosed AML patients in the transplant age group, and the number of cases reported to the CIBMTR. Volunteer URD searches limit timely availability of graft as patients with acute leukemia may relapse while waiting for transplant\textsuperscript{120}. In addition, while race and ethnicity may limit URD availability, significant barriers such as age, gender, socio-economic status, donor registry and center funding plus insurance restrictions, and other unknown barriers for access to HCT still exist\textsuperscript{121}. Addressing these challenges will be required to harness the full potential of HCT for patients with AML.
Acknowledgement

We acknowledge assistance from the CIBMTR for the data on trends in AML HCT.

Author contributions

V.G. prepared the initial draft of manuscript; D.W. and M.T. provided further knowledge, insights, and helped in critical review; all authors approved the final version of the manuscript.

Conflict of interest disclosure

The authors declare no potential conflict of interest relevant to this article.
References


41. Byrd JC, Dodge RK, Carroll A, et al. Patients with t(8;21)(q22;q22) and acute myeloid leukemia have superior failure-free and overall survival when repetitive cycles of high-dose cytarabine are administered. *J Clin Oncol.* 1999;17(12):3767-3775.


104. Aoudjhane M, Labopin M, Gorin NC, et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling


Table 1. Trends in AML allogeneic transplant activity – Cases registered with Center for International Blood and Marrow Transplant Research (CIBMTR)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>No of centers reporting to CIBMTR</strong></td>
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<td>171</td>
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<td><strong>AML patients undergoing AlloHCT (all ages)</strong></td>
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<td><em><em>Adult</em> AML AlloHCT patients using vURD</em>*</td>
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</tr>
</tbody>
</table>

*Adult defined as ≥ 18 years; CIBMTR, Center for International Blood and Marrow Transplant Research; AlloHCT, allogeneic hematopoietic cell transplantation; RD, related donor; vURD, voluntary unrelated donor; UCB, umbilical cord blood; CR, complete remission;
Table 2. Comparative outcomes of various donor sources for HCT in AML

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size &amp; Patient population</th>
<th>Disease status</th>
<th>Main Comparison</th>
<th>LFS and OS</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hegenbert et al, 200657, Multicenter, Seattle Consortium</td>
<td>122, age 17-74, using NMA conditioning only</td>
<td>CR1 (n=51), CR2 (n=39), advanced (n=32)</td>
<td>MRD (n=58) vs. MUD (n=64)</td>
<td>No difference between MRD and MUD</td>
<td>Disease status at HCT and cytogenetics most important factors for LFS and OS</td>
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<tr>
<td>Moore et al, 200758, Multicenter, Australasian Registry</td>
<td>210, age 16-59, using MAC only</td>
<td>CR1 (n=36), &gt;CR1/others (n=174)</td>
<td>MSD (n=105) vs. URD (n=105)</td>
<td>No difference between MSD and URD</td>
<td>Matched Case controlled study</td>
</tr>
<tr>
<td>Schetelig et al, 200859, Multicenter, Germany</td>
<td>368, age 50-73 years, both MAC and RIC</td>
<td>CR1 (n=136), advanced (n=228), others (n=4)</td>
<td>MSD (n=168) vs. M/MRD (n=12) vs. MUD (n=51) vs. possibly MUD (n=68) vs. partially MUD (n=45) vs. poorly MUD (n=24)</td>
<td>No difference between different donor types</td>
<td>Advanced disease at HCT, secondary AML, and high risk cytogenetics associated with poor outcomes</td>
</tr>
<tr>
<td>Atsuta et al, 200954, Multicenter, JMDP/JCBB N</td>
<td>484, age 16-69 years, using MAC only</td>
<td>CR1 (n=180), Others (n=304)</td>
<td>MUD (n=311) vs. UCB-HCT (n=173)</td>
<td>Inferior outcomes in UCB-HCT due to increased TRM</td>
<td>No difference in risk of relapse</td>
</tr>
<tr>
<td>Walter et al, 201049, Single Center, Seattle</td>
<td>220, age 18-69 years, using MAC only</td>
<td>CR1 Intermediate cytogenetics (n=141), high risk cytogenetics (n=60), others (n=19)</td>
<td>MRD (n=135) vs. 10/10 MUD (n=62) vs. 9/10 URD (n=23)</td>
<td>No difference between MRD vs. 10/10 MUD vs. 9/10 URD</td>
<td>Unfavorable cytogenetics and high HCT-CI score associated with worse outcomes</td>
</tr>
<tr>
<td>Gupta et al, 201048, Multicenter, CIBMTR</td>
<td>584, Age &lt;1-74, Both MAC and RIC</td>
<td>AML in CR1 with adverse cytogenetics</td>
<td>MSD (n=226) vs. well-matched URD (n=254) vs. Partially matched URD (n=104)</td>
<td>Similar between MSD and well matched URD, inferior for partially matched URD</td>
<td>Lower risk of relapse in patients with chronic GvHD</td>
</tr>
<tr>
<td>Schlenk et al, 201046, Multicenter, Germany and Austria</td>
<td>162 Age 19-61 Both MAC and RIC</td>
<td>High risk AML in CR1, patients refractory to induction therapy</td>
<td>MRD (n=62) vs. MUD (n=89) vs. CB/HaploHCT (n=11)</td>
<td>Similar between MSD and MUD</td>
<td>Prospective study, also compared with patients who could</td>
</tr>
</tbody>
</table>
not get transplant, benefit of HCT seen in comparison to non-HCT patients in landmark analysis

LFS, leukemia-free survival; OS, overall survival; NMA, non-myeloablative, RIC, reduced intensity conditioning; MAC, myeloablative conditioning; CR1, first complete remission; CR2, second complete remission; MRD, matched related donor; MSD, matched sibling donor; URD, unrelated donor; MUD, matched unrelated donor; M/MRD, mismatched related donor; UCB, umbilical cord blood; HaploHCT, haplo-identical cell transplantation; HCT, hematopoietic cell transplantation; JMDP, Japanese Marrow Donor Program; JCCBN, Japanese cord blood bank network; TRM, transplant related mortality; HCT-CI, hematopoietic cell transplantation comorbidity index; CIBMTR, center for international blood and Marrow transplant research; GvHD, graft versus host disease;
Table 3. Guidelines for indications for HCT in adult patients with AML

<table>
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<tr>
<th></th>
<th>MSD</th>
<th>MUD</th>
<th>UCB</th>
<th>Haplo-identical</th>
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<td><strong>First Remission</strong></td>
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<td>Favorable cytogenetics</td>
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<td>APL</td>
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<td>CBF-AML*</td>
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<td>with mKIT</td>
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<tr>
<td>without mKIT</td>
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<td>CN-AML*</td>
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<td>Uncertain</td>
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<td>“mNPM1 without FLT3ITD”</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<td>“mCEBPA”**</td>
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<td>Others than above</td>
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<td>Intermediate risk with abnormal cytogenetics</td>
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<td>Not in remission****</td>
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<td>Yes</td>
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</table>

Uncertain implies insufficient published data for a recommendation

MSD, matched sibling donor; MUD, matched unrelated donor; UCB, umbilical cord blood; APL, acute promyelocytic leukemia; CBF, core binding factor [t(8;21) or Inv(16)]; mKIT, KIT mutations; CN-AML, cytogenetically normal AML; mNPM1, mutated NPM1; mCEBPA, mutated CEBPA;
* If the data on molecular markers not available
**Increasing data show that the beneficial effect may be restricted only to patients with double mutations
***Only at experienced centres and in the absence of a timely available MUD.
**** Carefully selected patients with good performance status and low disease burden; CIBMTR risk score may aid the patient selection
Table 4: Multicenter studies evaluating prognostic risk factors in patients with therapy-related MDS/AML (t-MDS/AML) undergoing HCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Adverse prognostic factors for Survival</th>
<th>Other Factors</th>
<th>Other Comments</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Age</td>
<td>Cytogenetics</td>
<td>Disease status</td>
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<td>Yakoub-Agha et al, JCO, 2000&lt;sup&gt;81&lt;/sup&gt; (The French Society of BMT)</td>
<td>70</td>
<td>t-MDS=31 t-AML=39</td>
<td>&gt;37 years</td>
<td>not evaluated</td>
</tr>
<tr>
<td>Kroger et al, Haematologica, 2009&lt;sup&gt;80&lt;/sup&gt; (EBMT)</td>
<td>461</td>
<td>t-AML=264 t-MDS=168</td>
<td>&gt;40 years</td>
<td>abnormal cytogenetics</td>
</tr>
<tr>
<td>Litzow et al, Blood, 2010&lt;sup&gt;79&lt;/sup&gt; (CIBMTR)</td>
<td>868</td>
<td>t-AML=545 t-MDS=323</td>
<td>&gt;35 years</td>
<td>poor risk cytogenetics*</td>
</tr>
</tbody>
</table>

CR, complete remission; HCT, allogeneic hematopoietic cell transplantation; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; EBMT, European group of Blood and Marrow Transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; MSD, matched sibling donor; URD, unrelated donor; *, defined according to SWOG/ECOG classification for AML patients and IPSS classification for MDS patients;
Table 5. Comparisons of Myeloablative and reduced intensity or nonmyeloablative conditioning in adult patients with AML

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Sample size</th>
<th>LFS</th>
<th>OS</th>
<th>Other Comments</th>
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<tr>
<td>Aoudjhane et al, 2005104;</td>
<td>AML, &gt;50 years, MSD only</td>
<td>722</td>
<td>Similar</td>
<td>Similar</td>
<td>Decreased aGvHD, cGvHD, and TRM, but increased relapse with RIC</td>
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<td>Multicenter, EBMT</td>
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<td>RIC=315</td>
<td>MAC=407</td>
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<td>Alyea et al, 200670;</td>
<td>AML/MDS, 21-70 years, MRD and URD donors</td>
<td>136 (AML, 82)</td>
<td>Similar</td>
<td>Similar</td>
<td>Decreased TRM, and increased relapse with RIC</td>
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<td>Single Center, Boston</td>
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<td>RIC=39</td>
<td>MAC=97</td>
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<tr>
<td>Scott et al, 2006102;</td>
<td>MDS/sAML with previous MDS, 40-72 years, MRD and URD</td>
<td>150 (AML, 55)</td>
<td>Similar</td>
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<td>No difference in relapse/TRM</td>
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<td>Single Center, Seattle</td>
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<td>NMA=38</td>
<td>MAC=112</td>
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<tr>
<td>Shimoni et al, 200672;</td>
<td>AML/MDS, 17-70 years, MRD and URD</td>
<td>112 (AML, 56)</td>
<td>Similar</td>
<td>Similar</td>
<td>Similar outcomes for patients in remission at HCT, inferior outcomes of patients with active disease treated with RIC</td>
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<tr>
<td>Single Center Tel-Hashomer</td>
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<td>RIC=67</td>
<td>MAC=45</td>
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<td>Flynn et al, 2007103;</td>
<td>AML/MDS, 19-69 years, MRD and URD (included UCB grafts)</td>
<td>219 (AML, 160)</td>
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<td>Similar TRM, but increase in relapse with RIC</td>
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<td>RIC=32</td>
<td>MAC=187</td>
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<td>Ringden et al, 2009101;</td>
<td>AML, 16-76 years, URD transplants only</td>
<td>1555</td>
<td>Similar</td>
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<td>Reduced NRM in ≥50 years, and increased relapse in patients &lt;50 years with RIC</td>
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<td>EBMT Multicenter</td>
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<tr>
<td>Lim et al, 2010106; EBMT,</td>
<td>MDS/sAML with previous MDS, ≥50 years, MRD and URD</td>
<td>1333 (AML, 334)</td>
<td>Not reported</td>
<td>Similar</td>
<td>Increased relapse, and decreased TRM with RIC</td>
</tr>
<tr>
<td>Multicenter</td>
<td></td>
<td>RIC=833</td>
<td>MAC=500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khabori et al, 201099;</td>
<td>AML/MDS, 40-60 years, MRD and URD transplants</td>
<td>101 (AML, 77)</td>
<td>Similar</td>
<td>Similar</td>
<td>Poor outcome in patients with high risk disease biology due to higher relapse rate</td>
</tr>
<tr>
<td>Single Center, Toronto</td>
<td></td>
<td>RIC=39</td>
<td>MAC=62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luger et al, CIBMTR105</td>
<td>AML/MDS, 18-70 years, RIC/NMA=1448,</td>
<td>5179</td>
<td>Similar</td>
<td>Similar</td>
<td>Late TRM negated any advantage</td>
</tr>
<tr>
<td>Multicenter</td>
<td>MRD and URD</td>
<td>MAC=3731</td>
<td>MAC vs. RIC, inferior for NMA</td>
<td>MAC vs. RIC, More relapse with NMA</td>
<td>offered by RIC or NMA</td>
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</tbody>
</table>

MAC, myeloablative conditioning; NMA, non-myeloablative, RIC, reduced intensity conditioning; LFS, leukemia-free survival; OS, overall survival; EBMT, European Group for Blood and Marrow Transplantation; MRD, matched related donor; URD, unrelated donor; MUD, matched unrelated donor; UCB, umbilical cord blood; TRM, transplant related mortality; sAML, secondary AML; NRM, non-relapse mortality; HCT, hematopoietic cell transplantation; CIBMTR, center for international blood and Marrow transplant research; GvHD, graft versus host disease;
Figure Legends

Figure 1. Trends in allogeneic hematopoietic cell transplantation (HCT) activity in adult AML patients (≥18 years) using unrelated donors according to disease status at HCT—cases registered with CIBMTR from 1998-2008 1a. CR1, CR2, CR3 and not in remission 1b. CR1
Fig 1a. Adult AML patients (≥18 years) undergoing unrelated HCT and registered with CIBMTR from 1998-2008.
Fig 1b. Adult AML patients (≥18 years) undergoing unrelated HCT in CR1 and registered with CIBMTR from 1998-2008

- Cord Blood
- Peripheral Blood Stem Cells
- Bone Marrow

Number of Transplants

Year of Transplant

Allogeneic hematopoietic cell transplantation for adults with acute myeloid leukemia: myths, controversies, and unknowns

Vikas Gupta, Martin S. Tallman and Daniel J. Weisdorf