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Concise Review: The Role of Hematopoietic Stem Cell Transplantation in the Treatment of Acute Myeloid Leukemia

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative option for patients with acute myeloid leukemia (AML). Our understanding of the biology of leukemic stem cells has continued to improve over the last decade and risk stratification using cytogenetics and molecular markers have improved our ability to select patients who would benefit from allogeneic transplantation. Results of HSCT have also improved substantitally, extending the potential application of allogeneic transplant to more patients. This review discusses the theoretical aspects of transplant, analyzes clinical results, and provides recommendations for the use of HSCT in AML. Further study of the biology of leukemic stem cells and the role for HSCT is necessary to optimize outcomes in AML patients. STEM CELLS *2012;30:1581–1586*

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for many patients with acute myeloid leukemia (AML), the most common disorder for which it is used [1]. The curative effect of HSCT results from both the radiation and/or chemotherapy in the conditioning regimen and a graft-versus-leukemia (GVL) effect of the donor immune system [2, 3]. The safety and effectiveness [4] and the number of allogeneic transplants performed for AML have all increased substantially over the last decade. Despite this progress, wide variation remains in the application of HSCT in AML. Here, we review the basis for and the clinical application of HSCT in AML.

RATIONALE FOR ALLOGENEIC TRANSPLANTATION IN AML

Chemotherapy

Chemotherapy used to treat hematologic malignancies, including AML, is most effective in rapidly proliferating cells. Both normal and malignant stem cells, however, are quiescent, and in addition efficiently repair DNA, resist apoptosis, and excrete toxic drugs by ATP-binding transporters [5]. Induction chemotherapy, most commonly cytarabine for 7 days combined with an anthracycline for 3 days ("7 + 3"), achieves complete remission (CR) in 60%–80% of AML patients under the age of 60. Patients who achieve a CR, however, will invariably relapse without postremission therapy as a result of residual leukemic stem cells capable of engrafting and sustaining leukemia in immunodeficient mice [6]. Postremission therapy is required to eradicate this minimal residual disease. Three to four cycles of high-dose cytarabine is most commonly administered to nonelderly patients who achieve CR. Autologous transplantation, high-dose myeloablative chemotherapy followed by infusion of the patients' own previously procured and frozen hematopoietic cells, has been extensively used but does not prolong survival compared to standard chemotherapy [7]. Whole genome deep sequencing has validated hundreds of somatic mutations, discovered novel mutated genes, and provided insight into relapse after chemotherapy. Relapse commonly results from a subclone of the founding AML clone, which survives treatment and develops additional mutations associated with an increase in transversion, related to DNA damage by chemotherapy [8]. Thus the intensive chemotherapy used during induction and postremission contributes to the development of drug resistance. Cure rates remain understandably poor with this approach, and HSCT provides superior outcome in many circumstances.

HSCT

A single hematopoietic stem cell can restore the entire lymphohematopoietic system of a lethally irradiated syngeneic mouse [9]. Animals can be protected from lethal doses of total body irradiation (TBI) by infusion of syngeneic or allogeneic bone marrow [10, 11]. Thomas hypothesized that lethal doses of radiation and chemotherapy could destroy leukemic cells along with normal marrow and the immune system of patients with leukemia, and that infusion of marrow from histocompatible donors could be used to rescue them.

The major histocompatibility complex, human leukocyte antigen (HLA), genes are closely linked on chromosome 6 and inherited as haplotypes (siblings thus having one in four chance of being HLA-identical). The development of HLA-typing methods permitted Thomas and colleagues to perform HSCT from HLA-identical siblings in patients with endstage

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AML. In 1975, they reported that a small proportion of these patients were cured [12]. Shortly thereafter this group reported cure of 50% of patients who underwent HSCT in first remission [13]. The demonstration that patients who developed graft-versus-host disease (GVHD) had lower incidences of relapse [2] showed that the donor-derived immune system contributed to the eradication of AML. GVHD, caused by reaction of donor T-cells to recipient minor histocompatibility antigens, damages the skin, gastrointestinal tract, and liver and represents an important obstacle to successful transplantation. Donor T-cells reactive to recipient minor histocompatibility antigens also inhibit the growth of leukemic colonies and the development of AML in immunologically susceptible mice, [14] suggesting elimination of leukemic stem cells by alloreactivity. GVL and the sites of GVHD depend on the differential expression of the relevant minor histocompatibility antigens in each tissue. Significant GVHD can be prevented in most patients by the use of immunosuppressive agents for approximately 6 months.

Clinical Application of HSCT

Specific patient and disease-related factors differentially influence outcome following treatment with chemotherapy or HSCT. While older age has been widely used to exclude patients from transplantation, assessment of comorbid conditions as measured by the hematopoietic cell transplantation-specific comorbidity index may help estimate risk of treatment-related mortality following HSCT [15–17]. In the presence of significant comorbidities, the danger of transplantation is far greater than postremission chemotherapy and may exclude patients from HSCT. The most powerful factor determining the biologic behavior and risk of relapse is the specific genetic abnormalities in the leukemic cells. Transplantation lowers relapse rates compared to chemotherapy, most dramatically in patients with highest relapse risk.

Allotransplantation in First CR

The best results of HSCT in AML, as demonstrated by Thomas and colleagues, occur in patients in first CR. The role of allogeneic HSCT in AML in CR1 was initially examined by "genetic randomization," that is, comparing results in patients who have an HLA-identical sibling donor and undergo transplantation to those without a donor, randomized to postremission chemotherapy or autologous transplantation. Such studies generally demonstrated similar survival rates, with the significantly lower relapse rate of transplantation offset by its higher incidence of nonrelapse mortality. Such studies were flawed by the failure to prospectively analyze risk of relapse based on cytogenetics and the inclusion (based on intention-to treat analysis) in the transplant arm of many patients who did not undergo transplantation [18]. Meta-analysis of prospective biologic assignment studies analyzed more than 3,500 patients with AML in CR1 by cytogenetic risk and demonstrated a significant survival advantage of HSCT for AML patients with intermediate and unfavorable, but not good risk, cytogenetics [19]. Thus, a significant majority of patients with AML and an HLA-identical sibling donor, in the absence of significant comorbidities, appear to benefit when HSCT is performed in first CR. Risk of relapse, based on cytogenetics, is used to determine postremission therapy. It is important to realize, however, that limited prospective randomized data exist regarding the value of allogeneic HSCT within cytogenetic risk groups, emphasizing the need for well-designed therapeutic trials.

Favorable Cytogenetics

Patients with t (8;21), inv (16), or t (16;16), the core binding factor (CBF) leukemias, or with acute promyelocytic leukemia with t (15;17) are at modest risk of relapse, fare well with postremission high-dose cytarabine (HiDAC), and do not benefit from HSCT in CR1 [19]. Approximately 50% of patients with CBF-AML treated with HiDAC are alive at 5 years [20]. Transplantation should be reserved for patients in whom remission is not attained or who relapse.

Patients with CBF-AML who carry the KIT mutation (mKIT), however, have a much greater risk of relapse [21]. HSCT in CR1 should be considered in patients with CBF-AML with mKIT.

Adverse Cytogenetics

Patients less than 60 with adverse cytogenetics, for example, deletions of chromosomes 5 or 7, del(5q); abnormalities of 3q, or complex abnormalities, have poor outcomes when treated with conventional induction and postremission chemotherapy, with 5-year survival in less than 15%. More than twofold improvement is achieved in these patients with allogeneic transplantation [19, 22, 23]. Patients with monosomal karyotype, defined by $\geq$2 autosomal monosomies or a single monosomy with additional structural abnormalities, have a particularly poor 5-year survival of $<$4%. In one large study, only those who had undergone HSCT were long-term survivors [24]. The Seattle group reported 4-year survival of 25% in these patients who undergo HSCT [25]. Thus while unfavorable cytogenetics adversely influence relapse rates after HSCT, the impact on relapse and survival is less dramatic than following postremission chemotherapy.

Intermediate Risk Cytogenetics

Approximately 45% of all AML patients have no detectable cytogenetic abnormalities (CN, normal cytogenetics) or changes not categorized as favorable or adverse. They have an intermediate risk of relapse and 30%–35% survival at 5 years following postremission chemotherapy. A large prospective trial in which 80% of patients "randomized" to transplantation actually underwent the procedure demonstrated superior leukemia-free survival with allogeneic HSCT for the intermediate as well as the poor-risk group [22]. The identification of molecular mutations with prognostic impact has further improved selection of therapy in CN-AML. The FMS-related tyrosine kinase 3-internal tandem duplication (FLT3-ITD) constitutively activates this tyrosine kinase receptor. It occurs in 30% of AML patients and confers a high relapse risk, [26] which escalates with increasing mutant/wild-type ratios and with longer ITD mutations [27]. Homozygous FLT-3 ITD evolves by segmental uniparenteral disomy after an initial heterozygous mutation [27].

Nucleophosmin 1 (NPM1) mutations occur in approximately half of adult CN-AML patients and are associated with favorable survival. Patients with NPM1 mutations without FLT3-ITD enjoy a good prognosis with chemotherapy, similar to CBF-AML [28]. Mutations in CCAAT/enhancer-binding protein alpha (CEBPA) are also associated with a favorable prognosis [29]. Analysis of 872 adult CN-AML patients younger than 60 entered on four therapeutic trials demonstrated significant benefit of HSCT from an HLA-matched related donor in patients with FLT3-ITD regardless of other mutations or wild-type NPM1 and CEBPA without FLT-3 ITD, but no benefit for transplantation in those with mutated NPM1 or CEBPA in the absence of FLT3-ITD [29]. Mutational status of these genes and their interactions can be used to guide selection of therapy.

Somatic mutations of isocitrate dehydrogenase enzyme isoform 1 (IDH1) and isoform 2 (IDH2) [30] and the DNA methyltransferase gene DNMT3A [31] in CN-AML have been associated with adverse outcomes depending on their association with other mutations. The validation and identification by deep sequencing of hundreds of somatic mutations in AML [8] suggest that better genetic definition will further refine selection of patients for HSCT. Integrated mutational profiling evaluating molecular mutations and their interactions highlights that the effect of certain mutations depends on the presence of other mutations. For example, the favorable effect of NPM1 mutations now appears limited to patients with IDH mutations, and these patients benefit from more intensive induction chemotherapy [32]. With greater numbers of prognostic markers identified, integrated approaches based on both clinical and molecular markers and their interactions have been proposed to help better predict outcomes for patients and identify those who will benefit from more intensive therapies [33].

Therapy-Related AML

Therapy-related AML (t-AML), which constitutes an increasing proportion of AML, is associated with a substantially higher incidence of adverse cytogenetic abnormalities than de novo AML, accounting in part, but not completely, for its poorer prognosis.

Cytogenetics is predictive for t-AML, as for de novo disease [34]. Conventional chemotherapy is rarely curative in t-AML lacking favorable karyotype, but when results are adjusted for disease status and cytogenetics, results of transplantation in patients with t-AML appear similar to those for de novo disease [35, 36]. Cytogenetics, molecular testing, and previous treatment can be used to develop guidelines for selecting postremission therapy (Table 1).

Table 1. Categorization by cytogenetics, molecular markers, and prior to treatment for determining postremission therapy

	Recommended postremission treatment, considering other prognostic factors (i.e., donor availability, comorbidities, and performance status)
Modest risk of relapse	
APL t(15;17)	Chemotherapy with ATRA/ arsenic-based treatment
CBF-AML inv16; t(16;16); t(8/21)	Chemotherapy
CN-AML	
mNPM1 without FLT3-ITD	Chemotherapy
mCEBPA	Chemotherapy
High risk of relapse	
Abnormal karyotype (complex cytogenetics, monosomy 5, 7, del 5q, t(6;9), t(9;22), abnormal 3q 3q, 9q, 11q, 20q, 21q, 17p)	Allogeneic HSCT
CBF-AML with mKIT	Allogeneic HSCT
CN-AML	
FLT3-ITD	Allogeneic HSCT
Wild-type FLT3, NPM1, and CEBPA	Allogeneic HSCT
Therapy-related AML	
with t(8;21)	Chemotherapy
with inv16	Chemotherapy
t-APL	Chemotherapy with ATRA/ arsenic-based chemotherapy
Other karyotypes	Allogeneic HSCT

Abbreviations: APL, Acute promyelocytic leukemia; ATRA, all-trans-retinoic acid; CBF-AML, core binding factor acute myeloid leukemia; CN-AML, normal cytogenetics-acute myeloid leukemia; FLT3-ITD, FMS-related tyrosine kinase 3-internal tandem duplication; HSCT, hematopoietic stem cell transplant; mCEBPA, mutation in CCAAT/enhancer-binding protein alpha; mNPM1, mutated nucleophosphim 1; t-APL, therapy-related acute promyelocytic leukemia

HSCT for Refractory and Relapsed AML

HSCT is the only curative option for AML patients who fail to achieve CR following induction and those who relapse after achieving CR, but results are substantially poorer.

Survival at 3 years was 19% for 1,673 patients with AML not in remission at the time of HSCT [37]. CR1 duration <6 months, presence of circulating blasts, having a donor other than a matched sibling, performance status <90%, and adverse cytogenetics were associated with poor outcome. Survival of patients with none of these risk factors was 42%, and with more than three risk factors was 6%, identifying patients in whom HSCT is likely to be futile and those in whom it should be contemplated.

In patients who achieve CR, but in whom transplantation is not performed, a plan should be formulated in anticipation of potential relapse, including HLA typing of the patient and siblings. Approximately 30% of patients in whom transplantation can be performed in early relapse, at a time when the marrow shows <30% blasts, achieve sustained leukemia-free survival, [38] similar to that for patients in second CR. Patients who relapse and receive chemotherapy, but fail to achieve second CR, have dismal outcomes following HSCT [39].

Graft Source

Donor hematopoietic cells were originally obtained by bone marrow harvest. Since hematopoietic stem cells continuously detach from marrow and enter the circulation, peripheral blood is a convenient alternate source and has been increasingly used over the last decade. Peripheral blood transplantation grew in popularity because of ease for the donor and physician, reliability in achievement of high CD34+ cell doses, and faster hematopoietic and immune recovery. More than two-thirds of allotransplants are now performed using peripheral blood [40]. CD34+ cells are obtained through pheresis of peripheral blood mobilized with granulocyte colony stimulating factor. Peripheral blood contains higher T-cell numbers; however, a recent randomized trial using unrelated donors (URDs) found no differences in survival, acute GVHD, or relapse, but a higher incidence of chronic GVHD and a requirement for immunosuppressive treatment further out from transplant in those receiving peripheral blood [41]. These results suggest that for patients with URDs, bone marrow may be the preferred source of hematopoietic cells. In contrast, a large study using HLA-identical related donors demonstrated significantly better leukemia-free survival, although not overall survival, for mobilized peripheral blood cells and no difference in the incidence of chronic GVHD or duration of immunosuppression [42].

Alternative Donors

Only approximately 30% of patients have an HLA-identical sibling donor. Matched URDs, umbilical cord blood (UCB), or haploidentical donors can be used in patients lacking sibling donors.

Unrelated Adult Donors

The use of DNA typing to identify HLA alleles and the most closely matched donor has led to better results and more widespread use of URD. In AML patients with unfavorable cytogenetics in CR1, well-matched URD and sibling

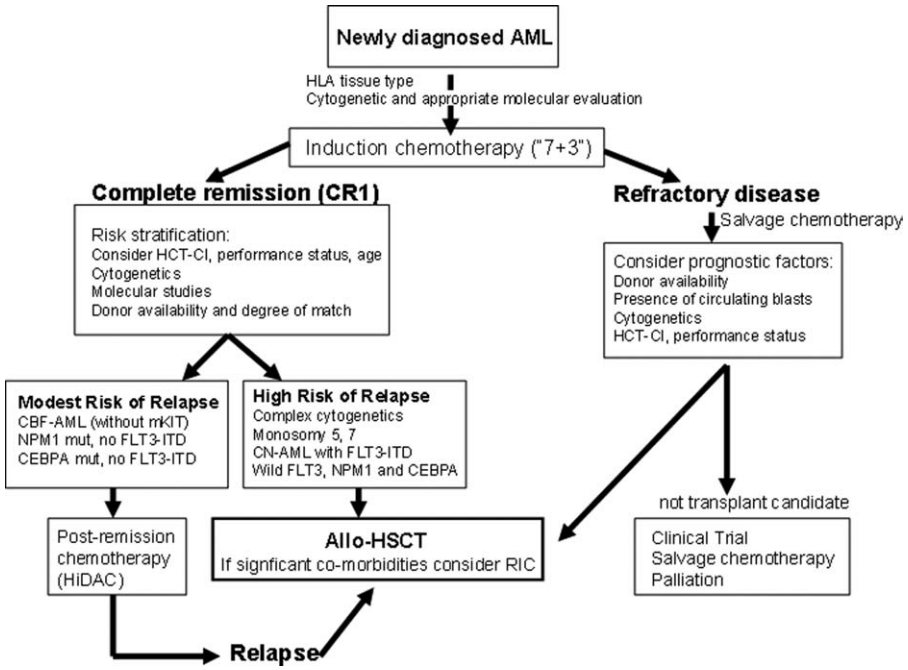

Figure 1. General approach to treatment of adults with AML. Abbreviations: AML, acute myeloid leukemia; CBF-AML, core binding factor-acute myeloid leukemia; CEBPA, CCAAT/enhancer-binding protein alpha; CN-AML, normal cytogenetics- acute myeloid leukemia; CR, complete remission; FLT3-ITD, FMS-related tyrosine kinase 3-internal tandem duplication; HCT-CI, hematopoietic cell transplantation comorbidity index; HiDAC, high-dose cytarabine; HLA, human leukocyte antigen; mKIT, KIT mutation; NPM1, nucleophosmin 1; RIC, reduced intensity conditioning.

transplants have similar survival, whereas outcomes are not as good for partially matched URD [43]. Similar survival rates for 8/8 matched unrelated and sibling donors were also demonstrated among more than 2,000 AML patients at various disease stages [44]. These data support the use of an 8/8 matched URD when an HLA-identical sibling is not available. A single HLA mismatch is a significant risk factor for the development of GVHD and is associated with higher mortality and decreased survival [45]. If a well-matched URD is unavailable, UCB transplantation should be considered.

UCB Donor

UCB is rich in hematopoietic stem cells, but limited in volume, and can be collected and frozen immediately after birth. While cord blood requires less stringent HLA matching and mismatched cord blood transplants cause less GVHD, results are better with fewer mismatches and with larger numbers of CD34+ cells. Minority populations, underrepresented in adult registries, particularly benefit from the lower matching stringency. Frozen cord blood is more rapidly accessible and is commonly transplanted in children instead of cells from unrelated adult donors. In adults with AML, it is often used when an 8/8 matched URD cannot be identified in a timely manner. Data from the CIBMTR demonstrate similar outcomes in recipients of 4–6/6 HLA-matched UCB compared with one antigen mismatched URD, [46] with lower rates of GVHD, confirming UCB as an acceptable alternative to one antigen mismatched URD and is preferred when the cell dose is high and the HLA match is close. Long-term survival in patients with UCB appears comparable to those receiving URD transplants; however, nonrelapse mortality is higher, [47] due to slower engraftment and more frequent infection. The use of two separate cord donations in cases where CD34+ cell numbers of individual units is insufficient has improved engraftment and overall results [48].

Haploidentical Donors

High rates of graft rejection, GVHD, and poor immune reconstitution have historically limited the use of haploidentical donors. Technical advances have improved results with ex vivo T-cell depletion and illustrated the role of natural killer (NK) cell alloreactivity. NK cells express activating and inhibitory immunoglobulin-like receptors which interact with HLA class I epitopes and induce inhibitory or activating signals to determine NK cell cytolytic activity; alloreactivity improves engraftment, reduces GVHD, and reduces relapse rates in AML [49]. Favorable results have been reported using unmanipulated haploidentical mobilized peripheral blood cells after nonmyeloablative conditioning and cyclophosphamide (Cy) after transplantation to reduce rejection rates and GVHD, but relapse rates appear high [50]. Improved results would extend the use of allotransplantation because most patients have a haploidentical sibling, parent, or child and donors can be selected to optimize NK cell reactivity.

Conditioning Regimens

The optimal conditioning regimen for specific situations remains a subject of debate due to limited prospective data. Studies comparing myeloablative conditioning regimens with TBI and Cy with busulfan and Cy have not generally demonstrated significantly different outcomes [51]. The availability of an i.v. form of busulfan and the ability to measure busulfan levels and adjust subsequent doses would make a new prospective study relevant to present circumstances.

Over the last decade, a multitude of reduced intensity and nonmyeloablative regimens have been developed. The range of intensity of regimens varies from minimal to intense and is defined on the basis of the expected duration of cytopenias and the requirement for hematopoietic stem cell support.

Evidence of immunologic eradication of leukemic cells by the donor immune system led to development of reduced intensity preparative regimens in patients who, because of older

age, and/or comorbidities, were at high-risk for transplant-related morbidity and mortality. Based on a canine model, Storb used low doses of TBI and immunosuppressive drugs to facilitate engraftment and prevent GVHD. The addition of fludarabine reduced the rejection rate, and was associated with mild toxicity including limited neutropenia and thrombocytopenia, [52] but, this nonmyeloablative regimen is associated with high relapse rates in patients with advanced acute leukemia. Reduced doses of busulfan or melphalan compared to those used in standard myeloablative regimens have been used with better antileukemic efficacy than nonmyeloablative regimens and less toxicity than myeloablative regimens.

More than 5,000 patients undergoing transplants for AML and myelodysplastic syndrome achieved 5-year survival rates of 34%, 33%, and 26% for myeloablative, reduced-intensity, and nonablative transplants, respectively [53]. Nonablative conditioning was associated with more relapse and inferior survival compared to both other groups.

The majority of studies comparing outcomes of reduced intensity and nonmyeloablative conditioning with myeloablative regimens have been retrospective and are limited by selection bias and differing patient populations. None of the studies have shown superiority of reduced intensity to myleoablative transplants in AML.

Older Patients

The median age of patients with AML exceeds 65 years. Results of treatment with chemotherapy alone in older patients who lack favorable cytogenetics are dismal, but older patients have traditionally been excluded from HSCT. It is now clear, though, that age alone should not be used to exclude patients from undergoing transplantation, even with a myeloablative regimen [54]. Comorbidities and performance status outweigh age in predicting how well intensive preparative regimens will be tolerated. A 2-year survival rate of 68% was attained for selected older (aged 55–76, median 58) patients in first CR given myeloablative doses of busulfan and fludarabine [55]. Results in more advanced older patients were similar to those achieved in younger patients. A retrospective comparison of patients 60–70 years undergoing reduced-intensity transplantation and standard chemotherapy demonstrated significantly lower risk of relapse and longer leukemia-free survival, despite higher risk of nonrelapse mortality, among the transplanted patients [56]. Allogeneic transplantation is an established standard of care for older patients with AML [57].

Conclusions

The difficulty of curing AML was emphasized in a recent study of patients who relapsed after haploidentical transplantation. In five patients' mutant leukemic cells, the HLA haplotype that differed from the donor was lost at relapse due to acquired uniparental disomy of chromosome 6p [58]. T-cells from the donor that recognized and killed the original leukemic cells could no longer recognize and/or kill the mutant leukemic cells.

Nevertheless, results of HSCT in AML have improved substantially, and progress using alternative donors and reduced intensity regimens has extended the potential application of allotransplantation to most patients. An approach to the use of HSCT in AML is provided in Figure 1. Improved integrative methods to assess the risk of transplantation and the risk of relapse guides selection of patients for transplant in first remission, where it is most effective. The application of available techniques to measure minimal residual disease will further refine selection. Despite the progress, transplant-related mortality due to GVHD and relapse remain as huge obstacles, which require basic study and better understanding. Patients with AML should be encouraged to enroll in prospective clinical trials to further improve our understanding of the biology of acute leukemia and further assess the role and value of allogeneic transplantation.

Disclosure of Potential Conflicts of Interest

Neither author has potential conflicts of interest to disclose.

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