Hematopoietic Stem Cell Transplantation in Adults with Acute Myeloid Leukemia

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ABSTRACT
Hematopoietic stem cell transplantation (HSCT) is an integral part of the treatment of many patients with acute myeloid leukemia (AML). Despite extensive study, the appropriate role and timing of allogeneic and autologous transplantation in AML are poorly defined. This review critically analyzes the extensive literature, focusing on the recent advances, and provides practical recommendations for the use of HSCT in AML.

KEY WORDS
Acute myeloid leukemia • Hematopoietic stem cell transplantation • Bone marrow transplantation • Reduced intensity • Acute leukemia • Graft-versus-leukemia effect

INTRODUCTION
Acute myeloid leukemia (AML) is currently the most common indication for allogeneic hematopoietic stem cell transplantation (HSCT), and also accounts for a large proportion of autologous HSCT [1]. Despite numerous studies, the use and timing of allogeneic and autologous transplantation in AML vary widely, and many important questions remain unresolved. At the same time, modifications of supportive care and preparative regimens continue to improve results and extend the application of HSCT in AML. We review here the theory of HSCT in AML, critically analyze the vast literature on its use, and make recommendations for clinical practice.

THEORETIC BASIS FOR ALLOGENEIC TRANSPLANTATION IN AML
The observation that animals given lethal doses of total-body irradiation (TBI) were protected from death by infusion of autologous [2], syngeneic [3], or allogeneic marrow [4] led to human studies in acute leukemia. Thomas and colleagues [5] hypothesized that lethal doses of TBI and cyclophosphamide could destroy leukemic cells, normal marrow, and the immune system of patients with leukemia, and that infusion of normal marrow from allogeneic histocompatible donors would rescue them. Thomas’s early studies in end-stage leukemias confirmed their hypothesis and established a new therapy. Although many advances have occurred, Thomas’s [5,6] original clinical work more than 30 years ago achieved results remarkably similar to those achieved today.

It is now understood that AML consists of a hierarchy of cells derived from rare leukemia stem cells, which retain the unique capacity for self-renewal [7]. Leukemic stem cells replenish the bulk population of leukemic cells that possess only limited potential for proliferation. Leukemic stem cells sustain and propagate human leukemia. They are exceedingly rare: as few as 1 in 1 million leukemia cells may be capable of initiating and sustaining leukemia in immunologically susceptible mice [8].

Like normal hematopoietic stem cells, leukemic stem cells are quiescent and resistant to chemotherapy agents, which are most effective in proliferating cells. They excrete toxic drugs by ATP-binding transporters and repair DNA injury efficiently. Leukemic stem cells, therefore, are generally not affected by conventional chemotherapy [9]. Virtually all patients
who achieve apparent eradication of malignant blasts and complete remission following induction chemotherapy will relapse as a result of undetectable residual leukemic stem cells if additional treatment is not given.

“Lethal” doses of TBI or drugs, for example, busulfan, destroy blast cells and may eliminate leukemic stem cells in a minority of cases, but the high relapse rate following syngeneic transplantation suggests that a graft-versus-leukemia (GVL) effect is required for eradication of leukemia in most patients [10]. The development of complete donor hematopoietic chimerism following nonmyeloablative preparative regimens demonstrates the capacity of donor immune cells to eradicate normal hematopoietic stem cells. Immunologically active donor T cells can also eliminate human acute myeloid leukemia stem cells, preventing the experimental development of human AML in mice [11] and curing AML in humans [12].

If the immunologic effect is of primary importance in eradication of leukemic stem cells, nonablative regimens designed to permit engraftment of donor immune cells with minimal toxicity would seem a wise strategy. Although patients with large blast burdens may not be susceptible to this approach because of rapid progression of disease, its apparent effectiveness in some patients lends credence to this theory.

THEORETIC BASIS FOR (AND AGAINST) AUTOLOGOUS TRANSPLANTATION

Autologous transplantation is limited by contamination of the stem cell product by malignant cells and the absence of an immunologic effect of allogeneic cells. Clinical results reveal less curative potential for autotransplantation than for syngeneic transplantation and less for syngeneic than for allogeneic transplantation, suggesting that both of these limitations are operative. Still, autologous transplantation cures some patients. Thus, in some instances, high-dose preparative therapy must eradicate leukemic stem cells, and the stem cell graft must not contain leukemic stem cells capable of engrafting [13] and giving rise to AML.

CLINICAL RESULTS

Allogeneic Transplantation in First Complete Remission (CR)

Treatment with an anthracycline and cytarabine achieves CR in 60%-80% of adults <60 years of age with newly diagnosed AML [14], but virtually all patients relapse without further treatment [15,16]. Options for postremission therapy include allogeneic HSCT, autologous HSCT, and consolidation chemotherapy. Thomas and coworkers [6] pioneered the use of HLA (human leukocyte antigen)-identical sibling donor marrow transplantation for patients with AML in first CR, achieving sustained leukemia-free survival (LFS) in more than half. Prospective studies comparing allogeneic HSCT with consolidation chemotherapy in the 1980s and early 1990s (Table 1) showed lower relapse rates in patients who underwent allogeneic HSCT, but higher treatment-related mortality (TRM) and no survival advantage [17-19].

Since 1995, 6 cooperative group trials have examined the role of HSCT in AML in first remission (Table 1) [20-25]. Patients with HLA-identical sibling donors were offered allogeneic transplantation (“genetic randomization”), whereas others were generally randomized between autologous transplantation and intensive consolidation chemotherapy (ICC). Lower relapse rates in patients undergoing allogeneic HSCT conferred improved or equivalent LFS and similar survival compared to ICC.

Autologous Transplantation in First Remission

Although favorable results for autologous transplantation in patients with AML in first CR have been reported, there is no definitive data indicating that this approach is superior to ICC. In the Groupe Ouest Est Leuemieres Aigues Myeloblastiques (GOELAM) trial, in which the ICC group received high doses of cytarabine (HiDAC), which provides more effective consolidation than standard doses of cytarabine [26], there was no benefit in LFS for autotransplant compared to ICC [21], similar to the US intergroup trial [22]. Two separate meta-analyses of 6 randomized studies demonstrated that autologous bone marrow transplantation modestly prolonged event-free survival (EFS) but not overall survival (OS) compared to consolidation chemotherapy or no further treatment in adults with AML in first CR [27,28]. Because autotransplantation in first CR provides no clear advantage over chemotherapy, its routine use is unwarranted and shortsighted because it jeopardizes the safety and effectiveness of subsequent allogeneic transplantation in those who relapse and are candidates for this procedure.

Cytogenetics and Other Risk Factors

An assortment of factors that influence outcome following treatment with chemotherapy alone or with transplantation have been identified. The factors that are critical to determining the best treatment in an individual are those that differentially affect the results of transplantation and consolidation chemotherapy. Analysis of several Southwest Oncology Group (SWOG) studies showed that older age adversely affected transplant outcome more than chemotherapy outcome, and that higher white blood cell count at diagnosis and a requirement for more than 1 induction cycle to achieve remission adversely affected chemotherapy outcome but not transplant outcome [29,30]. AML related to prior therapy, after accounting for cytogenetics, is
not associated with an adverse prognosis following allogeneic transplantation [31,32] as it is with chemotherapy alone [33].

Genetics largely determines the biologic behavior of AML and is the most powerful prognostic factor [34,35]. Specific genetic abnormalities affect results achieved with ICC and transplantation differentially. Patients with favorable cytogenetics producing aberrant core binding factor, including inversion (16), and translocation (8;21) fare better with HiDAC consolidation. The North American Intergroup trial [22], stratified according to cytogenetic risk [36], showed superior 5-year survival for patients with unfavorable cytogenetics who underwent allogeneic transplantation (44%) compared to autologous transplantation (13%) or ICC (15%). Meta-analysis of randomized studies confirmed the OS benefit of allogeneic HSCT for patients with poor-risk cytogenetics (coefficient of +0.24 on metaregression analysis) and suggested improved OS in the intermediate-risk group (coefficient of +0.09) [37].

The recent Dutch-Belgian Hemato-Oncology Co-operative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) trial demonstrated superior LFS with allogeneic HSCT for both intermediate and poor-risk groups [25]. Risk stratification included induction cycles needed to achieve CR, and white cell count, in addition to cytogenetics. Meta-analysis of 4 cooperative group (including the HOVON-SAKK study) trials of 4000 AML patients in CR1 demonstrated a 12% OS benefit at 4 years for patients with poor or intermediate risk cytogenetics who had an HLA-identical donor. Allogeneic HSCT was superior for patients whose apparent risk of relapse with ICC exceeded 35% [25].

Patients with intermediate-risk cytogenetics fare better with high-dose cytarabine consolidation than with standard doses [34]. The role of HLA-identical sibling transplantation in patients in first remission with intermediate-risk cytogenetics remains controversial. Genetic abnormalities undetectable with standard cytogenetic analyses can be used to segregate the nearly 50% of patients with normal cytogenetics into less favorable (partial tandem duplications of MLL gene, FLT3 internal tandem duplications [FLT3-ITD], high expression of BAALC) [38-40] or more favorable risk (nucleophosmin [NPM1] or CEBP-alpha transcription factor gene point mutation) [41,42] groups.

Analysis of 4 trials assigning patients with normal cytogenetics and an HLA-matched sibling donor to allogeneic transplantation in first CR showed that patients whose leukemia was NPM1+/FLT3-ITD had no improvement in OS or LFS with transplantation, whereas patients with other combinations more than doubled

<table>
<thead>
<tr>
<th>Author (Reference) Year (Cooperative Group)</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Relapse Rate (%)</th>
<th>Leukemia-Free Survival (%)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harousseau [23] 1997 (GOELAM)</td>
<td>Allo versus C versus Auto</td>
<td>73 75 71</td>
<td>37 45 55</td>
<td>49 48 43</td>
<td>55 52 58</td>
</tr>
<tr>
<td>Cassileth [22] 1998 (ECOG/CALGB/SWOG)</td>
<td>Allo versus C versus Auto</td>
<td>113 116 117</td>
<td>29 48 61</td>
<td>43 34 34</td>
<td>46 43 52</td>
</tr>
<tr>
<td>Burnett [21] 1998 (MRC AML-10)</td>
<td>Auto versus no further treatment</td>
<td>— 190 191</td>
<td>— 37 58</td>
<td>— 53 40</td>
<td>— 57 45</td>
</tr>
<tr>
<td>Cornelissen [25] 2007 (HOVON-SAKK)</td>
<td>Donor versus no donor</td>
<td>326 165 398</td>
<td>†32 †59 †48</td>
<td>†37 †54 †46</td>
<td></td>
</tr>
</tbody>
</table>

Allo indicates allogeneic; auto, autologous; C, chemotherapy; NR, not reported.
Relapse rates, disease-free survival and overall survival shown above are at 4 years with the following exceptions. 1. Leukemia free survival reported by Appelbaum et al. is at 5 years. 2. Relapse rate and leukemia-free survival reported by Archimbaud is at 7 years. 3. Leukemia free and overall survival reported by Burnett et al. is at 7 years.
†In HOVON-SAKK study relapse rate, disease-free survival and overall survival of patients getting chemotherapy or autologous-HSCT is (not provided separately, rather it is) reported together as “no donor” group.
their 4-year LFS with allogeneic-HSCT (47% versus 23%) [43]. Although further study is needed, these genetic aberrations are detectable by commercially available tests, and their apparent prognostic impact justifies their use in combination with other factors to help determine treatment in selected patients.

It is critical to recognize the limitations of the comparative trials. They employ “genetic randomization” and are not truly randomized. Many use consolidation regimens that are inferior to HiDAC in favorable and intermediate-risk groups. The studies use intent-to-treat analyses, but have high “dropout” rates (except in the HOVON-SAKK trial where compliance was 82%) of patients randomized to receive an allograft [44], underestimating the effect of HSCT. Analysis by cytogenetic risk categories is confounded by small numbers of patients: individuals with poor-risk cytogenetics assigned to allogeneic-HSCT in MRC AML-10, SWOG/ECOG, EORTC/GIMEMA AML-10, and HOVON-SAKK were 13, 18, 64, and 36, respectively. Last, induction and consolidation chemotherapy, transplantation preparative regimens, graft-versus-host disease (GVHD) prophylaxis, supportive care measures, and even cytogenetic risk categories (Table 2) are not uniform, complicating comparisons and summarizations.

### Unrelated Donor Transplantation in First CR

Less than 30% of patients have an HLA-identical sibling donor [45]. Adult matched unrelated donor (URD) or cord blood transplantation are options in patients lacking sibling donors. Approximately 11 million HLA-typed volunteer donors are currently registered in the Bone Marrow Donors Worldwide file (www.bmdw.org). The probability of finding an HLA-A, -B, -C, -DR, and –DQ match by high-resolution DNA typing is 35%-40% for a Caucasian [46] and less for some minorities. Recent reports show similar rates of acute GVHD (aGVHD), TRM, relapse rate, and OS in patients with standard-risk hematologic malignancies undergoing HLA-identical sibling transplantation compared to HLA-allelic-matched URD (10 of 10) transplantation [47,48]. The risk of GVHD, graft failure, and mortality increases with an increasing number of HLA disparities between the recipient and donor [49], and disparities are tolerated more poorly by older patients. In a series of 161 patients in first CR treated with variably matched unrelated transplants, the 5-year LFS was 50% [50]. High graft cell doses and CMV seronegativity were favorable prognostic factors.

The 5-year OS for patients with unfavorable cytogenetics undergoing URD transplantation in CR1 was 30% in a CIBMTR/NMDP (National Marrow Donor Program) study [51], which compares favorably with survival rates below 15% reported for such patients with autologous-HSCT or ICC [36]. The German AML 01/99 trial prospectively studied patients with AML in first CR at high risk for relapse based on unfavorable cytogenetic abnormalities or more than 5% blasts on day 15 marrow. Four-year survival was 68%, 56%, and 23%, respectively, for those who underwent sibling, unrelated, and autologous transplantation (P < .01) [52]. URD transplantation is

<table>
<thead>
<tr>
<th>Study</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
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<tbody>
<tr>
<td>ECOG/SWOG</td>
<td>* inv16, t(16;16), 16q-</td>
<td></td>
<td>* -5/5q-</td>
</tr>
<tr>
<td></td>
<td>* t(8;21) without -9q and CK</td>
<td></td>
<td>* -7/7q-</td>
</tr>
<tr>
<td></td>
<td>* t(15;17)</td>
<td></td>
<td>* t(6;9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* t(9;22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* abnormal 3q, 9q, 11q, 20q, 21q, and 17p</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* CK</td>
</tr>
<tr>
<td>MRC AML-10 [95]</td>
<td>* inv16, t(16;16), 16q-</td>
<td></td>
<td>* -5/5q-</td>
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<tr>
<td></td>
<td>* t(8;21)</td>
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<td>* t(15;17)</td>
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<td>* abnormal 3q</td>
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<td>* CK</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>* All other cytogenetic abnormalities</td>
</tr>
<tr>
<td>EORTC/GIMEMA AML-10</td>
<td>* t(8;21)</td>
<td></td>
<td>* -5/5q-</td>
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<tr>
<td></td>
<td>* inv16, t(16;16), 16q-</td>
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<td>* t(8;21)</td>
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<td>* abnormal 3q</td>
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<td></td>
<td></td>
<td></td>
<td>* All other cytogenetic abnormalities</td>
</tr>
<tr>
<td>HOVON-SAKK</td>
<td>* inv16, t(16;16), 16q-</td>
<td></td>
<td>* -5/5q-</td>
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<td></td>
<td>* t(8;21)</td>
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<td>* -7/7q-</td>
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<td>* inv16, t(16;16), 16q-</td>
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<td>* abnormal 3q</td>
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<td></td>
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<td>* t(9;22)</td>
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<td></td>
<td>* abn(11q23)</td>
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<tr>
<td></td>
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<td>* CK</td>
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</table>

CK indicates complex karyotype; NN, normal karyotype.
appropriate for younger patients with AML in CR1 with high-risk cytogenetics. Transplantation using well-matched URD might also be considered for selected patients with normal cytogenetics and unfavorable genetic abnormalities or otherwise at high risk for relapse who lack significant comorbidities.

**Umbilical Cord Blood Transplantation (UCBT)**

The easy and rapid availability of a prescreened, HLA-typed product makes UCBT an attractive option for patients without a HLA-matched sibling or adult unrelated donor. Transplantation using cord blood is associated with lower GVHD rates for the degree of HLA-mismatching. UCBT is an appropriate alternative when a well-matched URD is not available within a reasonable time [53-58]. Limited experience with UCBT and the low stem cell dose available from individual cord units has limited the use of UCBT in adults with AML, but the use of multiple units from different donors may improve engraftment [58]. Expansion of the current pool of cord blood units could markedly extend the application of transplantation, particularly to minority populations underrepresented in adult registries.

**Comorbidities**

Although the role of genetics and other factors in predicting the behavior of AML have received considerable attention, factors that determine the risk of TRM have received less emphasis, but are of at least equal importance. Older age and poor performance status are appropriately used in patients in first CR to select consolidation chemotherapy over allogeneic transplantation where the adverse risk of these factors is magnified. But systematic assessment of comorbidities is rare [59]. The hematopoietic cell transplantation comorbidity index, developed by Sorror and colleagues [60,61], is the most influential risk factor for nonrelapse mortality and survival in patients with AML in first CR who undergo allogeneic transplantation. Evaluation and scoring take <10 minutes. The same index has predictive value for chemotherapy-treatment of AML [62] and for reduced intensity transplantation [63]. It should be used to estimate treatment-related risk and to guide decisions on treatment. The judgment to perform allogeneic transplantation in first remission must balance the increased risk of TRM with transplantation against the extent to which transplantation decreases the risk of relapse in an individual patient. The potential for delayed complications, particularly chronic GVHD (cGVHD), following transplantation is also an important consideration. Most transplantation survivors, however, are healthy and active.

**Allogeneic Transplantation for Primary Refractory AML**

For the approximately 30% of patients with AML who fail to achieve CR with standard induction chemotherapy, allogeneic HSCT is the lone curative option [64]. Table 3 illustrates the outcome of transplantation in studies containing at least 50 patients with primary induction failure [65-69]. Patient characteristics and inclusion criteria are heterogeneous, and the number of failed induction chemotherapies varies. The 3-year LFS is approximately 20% to 30%. Favorable prognostic factors include availability of an HLA-identical sibling [66,67], good performance status [66], young age [66], fewer cycles of induction chemotherapy [65,69], good-or intermediate-risk cytogenetics [67], and low tumor burden [65,69]. It is essential to consider allogeneic transplantation early in the course of patients who do not achieve remission with initial therapy.

**Transplantation for AML beyond First Remission**

Chemotherapy offers little chance of cure for AML patients who relapse. Despite higher rates of TRM and relapse and substantially lower LFS [46] than transplantation in first CR, allogeneic HSCT still provides the best prospect for cure [70,71]. For patients who previously underwent autologous or allogeneic HSCT in first remission, however, the likelihood of successful allografting is markedly reduced [70].

Patients in first relapse nearly always receive chemotherapy in an attempt to achieve second CR. The 3-year LFS, however, was nearly 30% in 2 studies of transplantation in untreated first relapse [72,73]. Because less than half of those who undergo reinduction therapy will obtain second CR, where allotransplantation is curative in only about 30%, more patients might be cured with allotransplantation in early relapse. Candidates for allotransplantation who are not transplanted in first CR should have early identification of potential donors to permit timely transplantation at relapse. They should have their blood counts monitored closely and undergo marrow examination for abnormal counts, permitting some to undergo allotransplantation in untreated early relapse. For those with sibling donors, rapid transplantation can often be accomplished. Matched URD usually require months for identification and procurement, but initial survey of URD can speed this process in patients who do not undergo allogeneic transplantation in first CR. Patients lacking potential donors can have autologous stem cells procured while in first remission.

The 5 year LFS of patients undergoing URD HSCT in CR1 and CR2, at Fred Hutchinson Cancer Center were 50% and 28%, respectively [50]. Results of URD transplantation in patients not in remission...
are significantly affected by disease burden (bone marrow blasts >20%, blasts in peripheral blood >5000/μL, or both) and number of prior treatments [50,74]. Patients with advanced disease who do not achieve remission with salvage chemotherapy experience TRM rates approaching 50% and only 10%-15% achieve sustained LFS with allotransplantation [75].

Autologous Transplantation in Second CR

Autologous HSCT results in sustained LFS in selected patients in second or subsequent CR [76-78]. EBMT registry data demonstrate sustained LFS in 35% of patients undergoing autologous HSCT in second CR [78]. Longer duration of CR1, M3 subtype, grafts harvested in CR1, and younger patient age are associated with improved survival [76-78]. Patient selection appears to be largely responsible for the favorable results obtained in many trials of autologous transplantation. Among 741 patients (enrolled in MRC AML 10 and 12 trials) who achieved a second CR, 480 underwent HSCT (116 = sibling allogeneic transplants, 192 = autograft, and 154 = matched URD). The 5-year OS of patients undergoing HSCT was superior to those receiving further chemotherapy (39% versus 22%). The 5-year survival rates for patients undergoing sibling, URD, and autologous transplantations were 54%, 40%, and 33%, respectively [79].

Reduced-Intensity Conditioning (RIC)

RIC limits the toxicity and lowers the transplant-related mortality of allogeneic transplantation. Most RIC studies in AML are retrospective or nonrandomized prospective series, and include heterogeneous patients (often including some with myelodysplastic syndromes). Information on cytogenetics is unfortunately limited. Table 4 lists the studies utilizing RIC regimens in AML (and MDS) patients that included at least 50 patients.

No prospective, randomized trials comparing myeloablative (MA) with RIC regimens in AML have been performed; however, retrospective comparisons have been reported [80,81]. The Acute Leukemia Working Party of EBMT [81] used registry data to compare 315 recipients of RIC with 407 patients who received MA conditioning prior to HLA-matched sibling allografts. Over 70% of patients were in CR1 or CR2. At 2 years, TRM was significantly lower (18% versus 36%), but relapse rates significantly higher (41% versus 24%) in the RIC group. LFS and OS were not significantly different. For patients, mostly in first or second CR, who received a matched related or URD allograft following RIC, Hegenbart reported a relapse rate of 39%, LFS of 44%, and OS of 48% at 2 years. TRM was significantly higher in the URD group (22% versus 10%) [82].

Seventy percent of patients with AML are over the age of 55 years [83] and are at high risk of TRM with ablative allogeneic transplantation. Although RIC studies have included many elderly patients, they have also included younger patients with and without compromised organ function. Table 5 lists those studies where the median age was >60 years. Alyea et al. [80] detected no significant difference in LFS and OS at 2 years in a RIC group (20% and 28%) compared to a myeloablative group (31% and 34%) in a retrospective comparison of 152 patients older than 50 years. Hegenbart et al. [82] demonstrated that 2-year OS and LFS, in patients over the age of 60 years (45% and 42%) was similar to that of the whole cohort of patients aged 17 to 74 years.

In general, patients older than 60 years show lower TRM and similar OS and LFS compared to those

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Table 3. Retrospective Studies Looking at Allogeneic Stem Cell Transplantation for Primary Refractory AML

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>No. of Patients</th>
<th>Disease Burden (% Blasts in Marrow)</th>
<th>No. of Prior Regimens</th>
<th>Donor Type</th>
<th>Leukemia-Free Survival</th>
<th>Overall Survival</th>
<th>Relapse Rate</th>
<th>Treatment-Related Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biggs [65]</td>
<td>88</td>
<td>25%</td>
<td>≥2</td>
<td>mSib</td>
<td>21% at 3 years</td>
<td>NR</td>
<td>62% at 3 years</td>
<td>44%</td>
</tr>
<tr>
<td>Michallet [66]</td>
<td>69</td>
<td>NR</td>
<td>NR</td>
<td>mSib</td>
<td>9% at 5 years</td>
<td>13% at 5 years</td>
<td>NR</td>
<td>51%</td>
</tr>
<tr>
<td>Fung [67]</td>
<td>68</td>
<td>36%</td>
<td>≥2 (82%)</td>
<td>mMUD</td>
<td>31% at 3 years</td>
<td>30% at 3 years</td>
<td>51%</td>
<td>NR†</td>
</tr>
<tr>
<td>Esteve [68]</td>
<td>346</td>
<td>NR</td>
<td>NR</td>
<td>mMUD</td>
<td>18% at 2 years</td>
<td>25% at 2 years</td>
<td>57% at 2 years</td>
<td>25%</td>
</tr>
<tr>
<td>Wong [69]</td>
<td>53</td>
<td>23%</td>
<td>NR</td>
<td>mMUD</td>
<td>26% at 2 years</td>
<td>29% at 2 years</td>
<td>NR</td>
<td>62%</td>
</tr>
</tbody>
</table>

mSib indicates HLA-identical sibling donor; mmSib, 1 antigen mismatched related donor; MUD, matched unrelated donor; mMUD, mismatched unrelated donor; NR, not reported; TRM, treatment-related mortality; CR, complete remission.

*Data available for 55 patients only.
†Study claimed TRM comparable to figures with allogeneic transplant in first CR, but no figures were provided.
<table>
<thead>
<tr>
<th>Author (Year) (Reference)</th>
<th>Design</th>
<th>Disease Category</th>
<th>Patients in CR (%)</th>
<th>Donor Type (%)</th>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Relapse Rate (%)</th>
<th>Leukemia-Free Survival (%)</th>
<th>Overall Survival (%)</th>
<th>TRM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sayer (2003) [96]</td>
<td>Retrospective</td>
<td>AML</td>
<td>22.1</td>
<td>44-MRD 44-MUD 11-MMUD 1-MMUD 1-MMRD 47-MUD 40-MRD</td>
<td>FB/TBI</td>
<td>113</td>
<td>25.7 (2 years)</td>
<td>29 (2 years)</td>
<td>32 (2 years)</td>
<td>53 (2 years)</td>
</tr>
<tr>
<td>de Lima (2004) [97]</td>
<td>Retrospective</td>
<td>AML + MDS</td>
<td>14</td>
<td>47-MUD 40-MRD 13-MMRD 38.7-MRD 61.3-MUD</td>
<td>FM</td>
<td>62</td>
<td>30</td>
<td>32 (3 years)</td>
<td>35 (3 years)</td>
<td>30 (1 year)</td>
</tr>
<tr>
<td>Ho (2004) [98]</td>
<td>Prospective series</td>
<td>AML + MDS</td>
<td>58-MRD55.3-MUD</td>
<td>46-MUD 43-MRD 8-MMUD 6-MMUD</td>
<td>FBC</td>
<td>62</td>
<td>24-MRD ≥10.5-MUD</td>
<td>61-MRDS9-MUD (1 year)</td>
<td>73-MRDS7-MUD (1 year)</td>
<td>5-MRD 21-MUD (1yr)</td>
</tr>
<tr>
<td>Van Besien (2005) [99]</td>
<td>Prospective series</td>
<td>AML + MDS</td>
<td>37</td>
<td>44-MUD 43-MRD 8-MMUD 6-MMUD</td>
<td>FMC</td>
<td>52</td>
<td>40 (2 years)</td>
<td>38 (2 years)</td>
<td>39 (2 years)</td>
<td>33 (2 years)</td>
</tr>
<tr>
<td>Aoudjhane (2005) [81]</td>
<td>Retrospective registry</td>
<td>AML</td>
<td>71</td>
<td>MRD FB/TBI</td>
<td>315</td>
<td>41 (2 years)</td>
<td>40 (2 years)</td>
<td>47 (2 years)</td>
<td>18 (2 years)</td>
<td></td>
</tr>
<tr>
<td>Tauro (2005) [100]</td>
<td>Prospective series</td>
<td>AML + MDS</td>
<td>55.3</td>
<td>46-MRD 54-MUD</td>
<td>FMC</td>
<td>76</td>
<td>34.2 (3 years)</td>
<td>37 (3 years)</td>
<td>41 (3 years)</td>
<td>19-MRD 24-MUD (1 year)</td>
</tr>
<tr>
<td>Martino (2006) [101]</td>
<td>Retrospective registry</td>
<td>AML + MDS</td>
<td>≥30.7</td>
<td>MRD FB/M/C/TBI</td>
<td>215</td>
<td>45 (3yrs)</td>
<td>33 (3yrs)</td>
<td>41 (3 years)</td>
<td>22 (3 years)</td>
<td></td>
</tr>
<tr>
<td>Hegenbart (2006) [82]</td>
<td>Prospective series</td>
<td>AML</td>
<td>74</td>
<td>48-MRD 34-MUD 18-MMUD</td>
<td>F/TBI</td>
<td>122</td>
<td>39 (2 years)</td>
<td>44 (2 years)</td>
<td>48 (2 years)</td>
<td>16 (2 years)</td>
</tr>
</tbody>
</table>

MRD indicates matched related donor; MUD, matched unrelated donor; MMUD, mismatched inrelated donor; MMRD, mismatched related donor; NR, not reported; TRM, transplant-related mortality; CR, complete remission; F, fludarabine; M, melphalan; B, Busulphan, A, Cytarabine (Ara-C); I, Idarubicin; C, Alemtuzumab (Campath); TBI, total-body irradiation.
undergoing MA conditioning [63,84-86]. Follow-up, however, is too short to fully evaluate late TRM and relapse. RIC regimens seem a reasonable option in older patients in remission who have significant co-morbidities. These older patients have poor prognoses with ICC. They should be enrolled on well-designed clinical trials. Specific criteria to identify patients likely to fare better with RIC regimens must be established.

The Future

No simple algorithm is sufficient to determine treatment in individual patients. Attention to the cumulative risk of multiple comorbidities can improve patient selection for transplantation. Better identification and characterization of the entirety of genetic abnormalities will improve risk stratification. For example, the impact of FLT3-ITD on survival in patients with a normal karyotype depends not merely on its presence but on the ratio of mutant to wild-type FLT3 [87]. The KIT-D816 mutation does not appear to influence survival in patients with a normal karyotype, but has a negative impact on survival in patients with t(8;21) where it occurs more commonly [88].

Methods such as high resolution single nucleotide polymorphisms arrays identifies previously unrecognized genetic lesions that will almost certainly be clinically relevant [89]. More meaningful characterization of the biologic behavior of an individual’s leukemic cells might require more sophisticated methods such as gene expression profiling [90] or techniques designed to identify differences in signaling biology [91]. Advances in immunophenotyping and cell separation [92] may permit the characterization of signaling pathways in leukemic stem cells [91], providing targets in the only cells capable of maintaining the leukemia hierarchy.

The ultimate goal of such work is to systemically administer agents that selectively eradicate leukemic stem cells and spare normal hematopoietic stem cells. More immediately, the use of agents that can be used in vitro to selectively eradicate leukemic stem cells, while sparing normal hematopoietic stem cells [93], could improve autotransplantation. Agents that can be administered systemically to effectively kill both normal and leukemic stem cells [94] would require allogeneic or autologous (purged) rescue. These and other applications of basic work would make HSCT more effective in a broader range of patients.

REFERENCES


64. Song KW, Lipton J. Is it appropriate to offer allogeneic hematopoietic stem cell transplantation to patients with primary refractory acute myeloid leukemia? Bone Marrow Transplant. 2005;36:183-191.


