Introduction

Acute myeloid leukemia (AML) is a disease of the elderly. According to the Surveillance, Epidemiology and End Results Program, the incidence of AML in the United States is 3.6 per 100,000, with approximately 13,000 new cases diagnosed annually and a median patient age of 67 years. Compared to younger patients, AML in older adults (arbitrarily defined as age > 55 to 60 years) is frequently associated with a variety of adverse prognostic factors including history of antecedent hematologic disorders, higher incidence of poor-risk cytogenetics, increased expression of P-glycoprotein in myeloid blasts, and compromised performance status. Following standard induction chemotherapy regimens, less than 50% of patients achieve complete remission, and the long-term survival is poor. Reduced-intensity conditioning regimens decrease treatment-related toxicity and can be used in older AML patients and in younger AML patients with medical comorbidities.

Reduced-intensity Conditioning Allogeneic Hematopoietic Cell Transplantation in Adults With Acute Myeloid Leukemia

Mehdi Hamadani, MD, Mohamad Mohty, MD, and Mohamed A. Kharfan-Dabaja, MD

Background: Acute myeloid leukemia (AML), whether de novo or arising from antecedent hematologic disorders in elderly patients, is less likely to be curable with standard chemotherapy regimens used for younger patients. Allogeneic hematopoietic cell transplantation (allo-HCT) is currently the most efficient anti-leukemia treatment for AML and has shown a survival advantage in younger patients with intermediate- or poor-risk cytogenetics.

Methods: The authors review their experience as well as the published data regarding the role of reduced-intensity conditioning (RIC) allo-HCT in adults with AML. MEDLINE/PubMed and EMBASE/Ovid were searched, as well as reference lists of relevant articles, conference proceedings, and ongoing trial databases.

Results: Elderly patients with AML have a poor survival for all cytogenetics subgroups (except for acute promyelocytic leukemia) and higher rates of transplant-related mortality with myeloablative allo-HCT. RIC regimens have been shown to decrease procedure-related toxicity and have emerged as an attractive treatment modality in AML patients not suitable for myeloablative conditioning regimens. While prospective data comparing outcomes of AML patients undergoing RIC allo-HCT vs conventional chemotherapy alone are not yet available, RIC allo-HCT is a reasonable option for high-risk older patients and for younger AML patients with medical comorbidities who achieve a first or subsequent remission. The application of RIC for patients with refractory disease or untreated relapse as well as the use of alternative donors should be considered within the context of clinical trials.

Conclusions: RIC allo-HCT is a safe and effective treatment modality in high-risk elderly AML patients and in younger AML patients with medical comorbidities.
elderly AML patients achieve complete remission (CR), and long-term survival is rare. According to a study from the Cancer and Leukemia Group B (CALGB 8461), the 5-year overall survival (OS) rate of older AML patients with good-, intermediate-, and poor-risk cytogenetics receiving conventional chemotherapies was 19%, 7%, and 0%, respectively. Other cooperative groups studies have reported similar dismal outcomes in this particular population.

While myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) has improved survival outcomes of at least certain subgroups of younger AML patients, this has not been the case for elderly patients, mainly due to higher rates of nonrelapse mortality (NRM). Improvement in NRM rates using the so-called nonmyeloablative (NMA) or reduced-intensity conditioning (RIC) regimens has broadened applicability of allo-HCT in elderly patients or in younger patients with comorbidities in whom the use of standard myeloablative conditioning regimens is contraindicated.

To critically review the role of RIC allo-HCT in AML, it is important to recognize that the myeloablative intensity of different conditioning regimens vary significantly and that the distinction between truly myeloablative regimens and RIC regimens is not precisely defined. The latter is further complicated by the recent advent of the so-called myeloablative reduced-toxicity conditioning (RTC) regimens that are associated with improved NRM rates. The European Blood and Marrow Transplantation (EBMT) group" and the Center for International Blood and Marrow Transplant Research (CIBMTR) recently attempted to clarify the differences in NMA, RIC, and myeloablative regimens. Henceforth, we refer to NMA, RIC, and myeloablative regimens strictly as defined recently, which in a few instances may be different from the description used in the original reports. In this paper, we review the role of NMA or RIC allo-HCT in older (or unfit) adults with AML, and we discuss the issues related to the timing of allografting, the significance of conditioning regimen intensity, and the alternative donor allo-HCT in this particular population.

**Patient Selection for RIC Transplantation**

The decision to use NMA or RIC regimens for AML patients undergoing allo-HCT is not always clearly delineated, and significant variations exist in the selection criteria used by transplant centers around the world. Poor outcomes of elderly patients following myeloablative allo-HCT are well established. Sorror et al evaluated the impact of a priori medical comorbidities on transplant outcomes by using the Hematopoietic Cell Transplantation — Comorbidity Index (HCT-CI) and reported significantly higher NRM rates and inferior OS in patients with an HCT-CI score of ≥3. While not validated in prospective clinical trials, it is becoming increasingly common practice to offer RIC allo-HCT to AML patients of advanced age (generally > 50 to 55 years) and/or an HCT-CI > 2 (regardless of age), or to those with a prior history of autologous transplantation or poorer performance status.

Elderly AML patients undergoing allo-HCT represent a highly selected cohort, with the procedure not being offered to a vast majority of this high-risk population. Estey et al prospectively assessed the feasibility of RIC allo-HCT in 259 older AML patients. In this series, 46 of 99 patients who achieved a CR were not referred for evaluation for allo-HCT because of perceived advanced age of the patient, medical comorbidities, physician bias, or patient preference. Of the 53 patients in CR who were referred for a transplant consultation, a compatible HLA-matched donor; whether sibling or unrelated donor, was not found in 27 cases (51%). Ultimately, only 14 of 26 patients who had a suitable HLA-matched donor available underwent RIC allo-HCT, representing only 14% of patients achieving a CR and 5% of patients originally included in the study. This finding underscores the importance of caution in interpreting results of RIC transplantation because it represents a selected cohort of “better fitted” AML patients with chemosensitive disease.

Following is a review of the published literature addressing the role of RIC allo-HCT for AML patients in first CR (CR1), those beyond CR1, and those with refractory disease or untreated relapse. Where possible, these data are interpreted relative to expected outcomes in older patients with chemotherapy alone or with outcomes following myeloablative conditioning (in younger patients).

**The Role of RIC Transplantation for AML in CR1**

The optimal management of older AML patients achieving CR1 remains controversial, with the majority of patients expected to relapse when treated with consolidation chemotherapy alone. Registry data from EBMT and CIBMTR and from large multicenter retrospective studies have shown 2-year leukemia-free survival (LFS) and OS rates of approximately 40% and 50%, respectively, for AML patients in CR1 undergoing RIC allo-HCT. Table 1 summarizes selected prospective clinical trials that included AML patients in CR1 undergoing either NMA or RIC allo-HCT.

The largest prospective (phase II) clinical trial published to date by the Seattle consortium evaluated the role of NMA conditioning with 2 Gy total body irradiation (TBI) with or without fludarabine (90 mg/m2 total dose) in 122 patients with AML. Durable engraftment was achieved in 95% of cases, with relatively acceptable rates of acute and chronic graft-vs-host disease (GVHD). Analysis of 51 AML patients in CR1 included in this study demonstrated a 2-year OS rate of 51%. This finding, together with the lower risk of relapse noted in patients receiving allografts from unrelated donors, highlighted the importance of the immune-mediated graft-vs-leukemia effects in AML patients receiving a truly NMA conditioning regi-
men. Kohrt et al.\textsuperscript{33} recently reported 3-year LFS and OS rates of 48\% and 50\%, respectively, in CR1 AML patients undergoing allo-HCT following NMA conditioning with total lymphoid irradiation and antithymocyte globulin.

To our knowledge, only two prospective clinical trials (have specifically addressed the role of RIC allo-HCT for AML patients in CR1. Grigg et al\textsuperscript{34} reported a 2-year LFS rate of 68\% and an OS rate of 56\% in 34 CR1 AML patients. The NRM was 15\%, with 37\% cumulative incidence of disease relapse at 2 years. The second study, which specifically addressed the role of RIC transplantation for AML in CR1, included 31 patients and reported an impressive 2-year LFS rate of 76\%, with low rates of relapse (18\%) and NRM (9\%).\textsuperscript{35} It is plausible that these encouraging outcomes are due in part to intensive consolidation chemotherapy (± high-dose therapy and autologous transplantation) given to all patients before RIC allo-HCT, which might not be feasible in most AML patients > 60 years of age. More importantly, these results highlight the significance of adequate disease control with intensive consolidation therapy before RIC allo-HCT. Ongoing clinical trials such as CALGB 100103 and EBMT will provide additional data regarding the role of RIC in AML patients in CR1.

While these prospective studies have helped to establish the feasibility of RIC transplantation for AML patients in CR1,\textsuperscript{17,31-36} it is important to recognize their limitations, such as (1) inclusion of a heterogeneous group of AML patients with respect to remission status at time of allografting, (2) lack of homogeneous criteria to select patients for NMA or RIC regimens among the studies, (3) lack of uniformity regarding the intensities of preparative regimens, and (4) use of various GVHD prophylactic strategies in the studies. These limitations make direct comparison between these trials difficult. The median age of patients included in these trials (50 to 55 years) is still lower than the median age at diagnosis for AML patients, suggesting that this approach continues to be offered to a selective cohort of relatively younger AML patients. Moreover, unlike young AML patients in whom cytogenetics and genomic risk stratification have helped established the role of myeloablative allo-HCT in CR1, no such prospective data are available for patients undergoing RIC allografting. Recent data from EBMT showed 2-year LFS rates of 64\%, 57\%, and 38\% in CR1 AML patients with good-, intermediate-, and poor-risk cytogenetics,\textsuperscript{37} which compares favorably to survival rates in respective cytogenetic groups with standard chemotherapy alone.\textsuperscript{9} With the understanding of aforementioned limitations, it appears that a subset (approximately 35\% to 45\%) of CR1 AML patients who receive an NMA or RIC allo-HCT do achieve long-term LFS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Age (Range)</th>
<th>No. of CR1 AML Patients</th>
<th>Unrelated Donors</th>
<th>Conditioning</th>
<th>Relapse</th>
<th>Leukemia-Free Survival</th>
<th>Overall Survival</th>
<th>Transplant-Related Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Lima et al\textsuperscript{17}</td>
<td>58 (22–75)\textsuperscript{a}</td>
<td>11 None</td>
<td>Flu-Mel Flu-AraC-Id</td>
<td>40%\textsuperscript{a}</td>
<td>33% (3 yrs)\textsuperscript{a}</td>
<td>40% (3 yrs)\textsuperscript{a}</td>
<td>30% (1 yr)\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>Blaise et al\textsuperscript{35}</td>
<td>52 (26–60)</td>
<td>31 None</td>
<td>Flu-Bu-ATG</td>
<td>18%</td>
<td>76% (2 yrs)</td>
<td>79% (18 mos)</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>van Besien et al\textsuperscript{36}</td>
<td>52 (17–71)\textsuperscript{a}</td>
<td>9 54%\textsuperscript{a}</td>
<td>Flu-Mel-C</td>
<td>32% (1 yr)\textsuperscript{a}</td>
<td>38% (1 yr)\textsuperscript{a}</td>
<td>48% (1 yr)\textsuperscript{a}</td>
<td>11.1%\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Grigg et al\textsuperscript{34}</td>
<td>45 (19–60)</td>
<td>34 None</td>
<td>Flu-Cy</td>
<td>37% (2 yrs)</td>
<td>56% (2 yrs)</td>
<td>68% (2 yrs)</td>
<td>15%\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Valcarcel et al\textsuperscript{31}</td>
<td>53 (21–70)\textsuperscript{a}</td>
<td>59a None</td>
<td>Flu-Bu</td>
<td>44% (4 yrs)\textsuperscript{a}</td>
<td>39% (4 yrs)\textsuperscript{a}</td>
<td>42% (4 yrs)\textsuperscript{a}</td>
<td>20% (4 yrs)\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>Kohrt et al\textsuperscript{33}</td>
<td>54 (21–67)\textsuperscript{a}</td>
<td>38a 45%\textsuperscript{a}</td>
<td>TLI-ATG</td>
<td>NR</td>
<td>48% (3 yrs)</td>
<td>50% (3 yrs)</td>
<td>3% to 4% (1 Yr)</td>
<td></td>
</tr>
<tr>
<td>Gyurkocza et al\textsuperscript{84b}</td>
<td>60 (5–74)\textsuperscript{a}</td>
<td>160 45%\textsuperscript{a}</td>
<td>TBI ± Flu</td>
<td>39% (5 yrs)</td>
<td>NR</td>
<td>37% (5 yrs)</td>
<td>18% = Sib 29% = MUD (5 yrs)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Data for AML patients in CR1 not reported separately.
\textsuperscript{b} This retrospective study included patients enrolled on prospective trials at Fred Hutchinson Cancer Center, Seattle, Washington.
\textsuperscript{c} Transplant-related mortality not reported in the manuscript.
Is RIC Allo-HCT for AML in CR1 Superior to Chemotherapy Alone?

Studies using a genetic randomization (ie, a donor vs no donor comparison) in their design have provided additional knowledge of the role of myeloablative allo-HCT for AML in CR1. However, such prospective data are not yet available in the context of RIC allo-HCT. When comparing the outcomes of studies evaluating the role of RIC allo-HCT in older adults to clinical trials where chemotherapy alone was used for such patients, there are obvious limitations because transplant studies have an inherent selection bias for relatively younger, healthier patients who not only achieve but also maintain disease remission until allo-HCT.

Interestingly, when the results of the MD Anderson study (described previously) assessing the prospective feasibility of RIC in elderly AML patients were analyzed, using a donor-vs-no-donor comparison, the donor group had a better relapse-free survival. Mohty et al retrospectively performed a genetic randomization through a donor-vs-no-donor comparison in 95 adult AML patients in CR1. The HLA-matched sibling donor group included 35 patients, and the no-donor group comprised 60 patients. In an intention-to-treat analysis, LFS was significantly higher in the donor group (54 vs 30% at 4 years). The LFS advantage in the donor group was even stronger when analysis was restricted to the 25 patients who actually received RIC allo-HCT with fludarabine, busulfan, and antithymocyte globulin. A significant benefit regarding OS was also seen in the donor group, both by intention-to-treat analysis and by limiting analysis to patients who actually underwent allo-HCT. An update of this study showed that the LFS advantage persisted in the donor group (72% vs 24%) at 7 years. While these data provide useful clinical information, a prospective randomized study is needed to address this issue.

Prospective clinical trials randomizing elderly AML patients to chemotherapy alone vs induction chemotherapy followed by NMA or RIC allo-HCT will clarify the role of RIC transplantation in elderly AML patients in CR1. Ongoing trials, accessible at www.clinicaltrials.gov, include the TransAtlantic Leukemia Group 1/02 (NCT00342316), the EBMT-ALWP01/2008 (NCT00766779), and the SU1122007-874 (NCT00568653).

The Role of RIC Transplantation for AML Beyond CR1

Chemotherapy alone offers little chance of cure for AML patients with relapsed disease. Information addressing the role of RIC transplantation in AML beyond CR1 is limited. A multicenter retrospective analysis from the Cooperative German Transplant Study reported 2-year LFS rates of 52%, 40%, and < 20% for AML patients in CR1, in CR2, and with advance disease, respectively, emphasizing that RIC allo-HCT should be considered earlier in the course of the disease. Registry data from EBMT demonstrated a 2-year LFS rate of 55% for CR2 AML patients with RIC transplantation. AML patients who are beyond CR1 represent only a minority of patients accrued in published prospective clinical trials (Table 2). Acknowledging the limitations of available data, it appears that approximately 30% to 35% of AML patients beyond CR1 can be expected to be leukemia-free 2 to 3 years following RIC allo-HCT. Interestingly, the outcomes of AML in CR2 patients who receive NMA allo-HCT preparative regimens are encouraging (2- to 3-year LFS rates of approximately 40% to 50%), with acceptable rates of NRM. In the absence of randomized prospective outcome data of AML patients beyond CR1, an NMA or RIC allo-HCT should be strongly considered for these patients whenever possible as it provides the best prospect of cure.

Table 2. — Prospective Clinical Trials Evaluating the Role of Reduced-Intensity Conditioning Allogeneic Transplantation in Acute Myeloid Leukemia (AML) in Second Complete Remission (CR) or Beyond

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Age (Range)</th>
<th>No. of CR ≥ 2 AML Patients</th>
<th>Unrelated Donors</th>
<th>Conditioning</th>
<th>Relapse</th>
<th>Leukemia-Free Survival</th>
<th>Overall Survival</th>
<th>Transplant-Related Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Lima et al17</td>
<td>58 (22–75)</td>
<td>13</td>
<td>None</td>
<td>Flu-Mel/Fu-AraC/Id</td>
<td>40%</td>
<td>33% (3 yrs)</td>
<td>40% (3 yrs)</td>
<td>30% (1 yr)</td>
</tr>
<tr>
<td>van Besien et al38</td>
<td>52 (17–71)</td>
<td>4</td>
<td>54%</td>
<td>Flu-Mel-C</td>
<td>32%</td>
<td>38% (1 yr)</td>
<td>48% (1 yr)</td>
<td>33% (1 yr)</td>
</tr>
<tr>
<td>Hegenbart et al32</td>
<td>57 (17–74)</td>
<td>39</td>
<td>52%</td>
<td>TBI ± Flu</td>
<td>34%</td>
<td>44% (2 yrs)</td>
<td>61% (2 yrs)</td>
<td>13% = Sib</td>
</tr>
<tr>
<td>Kohrt et al33</td>
<td>54 (21–67)</td>
<td>38</td>
<td>45%</td>
<td>TLI-ATG</td>
<td>NR</td>
<td>50% (3 yrs)</td>
<td>37% (3 yrs)</td>
<td>3% to 4% (1 yr)</td>
</tr>
</tbody>
</table>

C = alemtuzumab, AraC = cytarabine, ATG = antithymocyte globulin, Bu = busulfan, Flu = fludarabine, Id = idarubicin, Mel = melphalan, MUD = matched unrelated donor, Sib = matched sibling donor, TBI = total body irradiation, TLI = total lymphoid irradiation, NR = not reported.

* Data for AML patients in CR ≥ 2 not reported separately.
The Role of RIC Transplantation in Refractory AML

Patients with refractory AML are particularly challenging. Few retrospective studies or case series limited to a small subset of highly selected patients receiving a myeloablative allo-HCT have been reported in the literature.43-45 A large CIBMTR study has recently reported a remarkable 3-year OS rate of 42% with matched-sibling myeloablative allo-HCT in a subset of refractory AML patients who had a good performance status, no circulating blasts, a prior CR duration of > 6 months, and no poor-risk cytogenetics.46 The role of RIC in refractory AML, however, is more controversial. The retrospective Cooperative German Transplant Study reported an LFS rate of 49% for AML patients with < 5% blasts in the bone marrow at the time of allografting, compared to only 14% for those with > 20% myeloblasts.47 It is likely that these poor outcomes are caused in part by the fact that most NMA or RIC regimens cannot provide adequate disease control to allow sufficient time for immune-reconstitution and development of graft-vs-leukemia effects.47

Unlike myeloablative transplantation in young adults, surprisingly a number of prospective studies for NMA or RIC allo-HCT included AML patients with refractory (active) disease or those in untreated relapse (Table 3). In the MD Anderson experience, treatment-related mortality of AML patients not in remission at the time of allografting was unacceptably high, with an LFS rate of 20% at 3 years.17 No benefit of RIC over NMA conditioning was seen for this cohort. Similarly, van Besien et al36 reported a 1-year LFS rate of only 25% in patients with refractory disease. Four of 7 patients in remission at 1 year relapsed during the second year. One might speculate that poor outcomes noted in these studies underscore the fact that in cases of progressive leukemia, NMA or RIC regimens are not sufficiently effective to control the disease long enough to allow a graft-vs-leukemia effect to develop.

To address the issue of disease control, Schmid et al48 used a strategy of sequential cytoreduction (with fludarabine, high-dose cytarabine, and amsacrine) followed immediately by RIC transplantation and planned prophylactic donor lymphocytic infusions in a cohort of 75 patients with high-risk AML or myelodysplastic syndrome (MDS). Using this intensive strategy, 44 AML patients with active disease had encouraging 2-year LFS and OS rates of 48% and 51%, respectively. These data support the concept of pretransplant “disease debulking” therapy with augmentation of graft-vs-leukemia effects with donor lymphocytic infusions. Further study of this strategy is warranted.

Recognizing the importance of cytoreduction before NMA or RIC allo-HCT in patients with refractory AML, different investigators have evaluated the feasibility of immunoconjugates (eg, gemtuzumab ozogamicin)19 or radioiodinated monoclonal antibodies (131I-labeled CD45 antibody)20 to specifically target disease in the marrow and other sites of leukemia. Encouraging preliminary results have been reported (Table 3). Others have attempted to improve transplantation outcomes by early RIC allo-HCT during induction chemotherapy-induced aplasia,51 by incorporating novel agents as part of conditioning regimens,52 or by adding lower doses of hypomethylating agents to reduce the risk of leukemia relapse following transplantation.53 Follow-up in most reported studies remains short, and the long-term efficacy and safety of these approaches remain unknown. While some of the

Table 3. — Prospective Clinical Trials Evaluating the Role of Reduced-Intensity Conditioning Allogeneic Transplantation in Acute Myeloid Leukemia (AML) Patients With Refractory/Active Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of AML Patients Not in Complete Remission</th>
<th>Conditioning</th>
<th>Relapse</th>
<th>Leukemia-Free Survival</th>
<th>Overall Survival</th>
<th>Transplant-Related Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Lima et al17</td>
<td>70</td>
<td>Flu-Mel Flu-AraC-Id</td>
<td>NR</td>
<td>20% (3 yrs)</td>
<td>23% (3 yrs)</td>
<td>34% (1 yr)</td>
</tr>
<tr>
<td>van Besien et al36</td>
<td>28</td>
<td>Flu-Mel-C</td>
<td>39%</td>
<td>25% (1 yr)</td>
<td>37% (1 yr)</td>
<td>33% (1 yr)</td>
</tr>
<tr>
<td>Schmid et al48</td>
<td>40†</td>
<td>TBI-Cy-ATG</td>
<td>NR</td>
<td>48% (2 yrs)</td>
<td>51% (2 yrs)</td>
<td>26% (1 yr)</td>
</tr>
<tr>
<td>Bornhauser et al49</td>
<td>27</td>
<td>Flu-Mel Flu-TBI†</td>
<td>38% (2 yrs)</td>
<td>35% (2 yrs)</td>
<td>39% (2 yrs)</td>
<td>30% (2 yrs)</td>
</tr>
<tr>
<td>Pagel et al50</td>
<td>39</td>
<td>TBI-Flu</td>
<td>40% (1 yr)</td>
<td>NR</td>
<td>38% to 46% (1 yr)</td>
<td>22% (1 yr)</td>
</tr>
</tbody>
</table>

C = alemtuzumab, Cy = cyclophosphamide, AraC = cytarabine, ATG = antithymocyte globulin, Flu = fludarabine, Id = idarubicin, Mel = melphalan, NR = data for patients with active disease not reported, TBI = total body irradiation.

† Data includes 4 patients with refractory myelodysplastic syndrome.
†† Data includes 22 patients with refractory AML and 18 with untreated relapse.
††† Five patients received myeloablative TBI doses.
‡‡‡ 38% for patients with AML refractory to chemotherapy, and 46% for AML in untreated relapse.
* Data for refractory AML patients not reported separately.
reported studies do identify a small subset of AML patients with refractory disease who might benefit from RIC allo-HCT (with or without some form of additional peritransplant therapy), such an intervention should be performed within the context of a clinical trial.

**The Role of Dose Intensity in the Context of RIC**

The inverse correlation between the intensity of the conditioning regimen and the risk of disease relapse, particularly in AML, is well known. However, higher conditioning regimen intensity is also directly proportional to poorer NRM. As a result, the optimal conditioning regimen in AML with the best therapeutic index remains undefined. A number of retrospective studies have compared outcomes of patients >50 years of age undergoing either NMA or RIC transplantation against myeloablative allo-HCT, and these studies have mostly shown improvement in NRM and possibly OS with the former. However, these less intense regimens also result in significantly higher risk of relapse in most studies but not all. Comparisons of RIC or RTC transplants against myeloablative allo-HCT have shown similar results, with NRM rates favoring less intense regimens at the cost of higher relapse rates, while limited comparisons of RTC regimens vs myeloablative conditioning suggest improved regimen-related toxicity with RTC without differences in relapse rates or cumulative incidence of NRM.

In the context of NMA and RIC allo-HCT, the regimen with the best risk-to-benefit ratio is more controversial. A study by de Lima et al retrospectively compared outcomes of MDS and AML patients undergoing NMA conditioning (fludarabine, cytarabine and idarubicin) to those receiving RIC (fludarabine and melphalan) transplants. More favorable outcomes regarding relapse rates and LFS were observed following the RIC regimen but at the expense of a higher NRM. No difference in survival was seen between the groups. Interestingly, for refractory AML, neither regimen provided a benefit in terms of reduced risk of relapse. Shimoni et al retrospectively compared fludarabine-busulfan–based RIC against transplantation with fludarabine-melphalan–based RIC. The melphalan-containing RIC was associated with more intense myelosuppression and higher NRM; however, OS was not better in the busulfan-containing group because of higher rates of disease relapse. This study highlights the fact that seemingly similar and dose-equivalent RIC regimens may have markedly different outcomes and should not be assumed to have an equal therapeutic index. At this time, the optimal conditioning regimen for older AML patients remains to be determined. Until then, the choice of preparative regimen for these patients will continue to depend on transplant center preference and physician bias. Ongoing studies such as the Bone Marrow Transplant Clinical Trials Network (BMT-CTN) study 0901 will help address this issue.

**Myeloablative Conditioning Regimens With Reduced Toxicity**

In the last 2 decades, the use of RIC regimens has increased steadily, mainly due to the associated lower rates of NRM. However, concerns regarding increased risk of disease relapse with such regimens have led others to develop myeloablative conditioning regimens (the so-called RTC regimens), with regimen-related toxicity significantly lower than that expected with traditional myeloablative regimens. In a cohort of 96 patients with advanced AML or MDS, de Lima et al reported that combining fludarabine with myeloablative doses of once-daily busulfan as transplant conditioning produced encouraging disease control, with impressive rates of NRM (3% at 1 year). In CR1 AML patients undergoing unrelated donor allo-HCT, RTC with fludarabine and busulfan appears to provide an encouraging 3-year LFS rate of 70%, with an acceptable NRM rate of 15% at 3 years. While myeloablative RTC regimens have been successfully employed, even in elderly patients with advanced myeloid malignancies, prospective randomized studies showing their superiority over RIC regimens are not available, and limited retrospective data suggest comparable outcomes following allo-HCT with fludarabine and busulfan-based RIC and RTC.

**RIC for Therapy-Related or Transformed AML**

AML with a history of antecedent hematologic disorders and therapy-related AML (t-AML) are increasing in prevalence with the aging of the population and with improved survival of patients treated with chemotherapy or radiotherapy for other malignancies. Outcomes of patients with t-AML, when treated with standard chemotherapy regimens alone, are disappointing. While a small subset of patients with t-AML (approximately 25% to 30%) can become long-term survivors following myeloablative allo-HCT, such intensive conditioning regimens are frequently not feasible in this high-risk patient cohort due to advanced age, medical comorbidities, and prior high-dose therapy. Registry data from EBMT suggest that compared to myeloablative conditioning, RIC allo-HCT in patients with t-AML or MDS is associated with higher relapse rates, lower NRM, and no significant difference in OS. Considering the uniformly poor outcomes of patients with t-AML with standard therapies, performing RIC allo-HCT (at least in patients achieving CR) is reasonable.

**Umbilical Cord Blood Transplantation**

The easy, rapid availability of a prescreened, HLA-typed product makes umbilical cord blood transplantation (UCBT) an attractive option for patients without a suitable HLA matched-sibling or unrelated donor. UCBT is associated with lower GVHD rates for the degree of HLA disparity, making it a reasonable alternative when
a suitable donor is not available.71-72 The low cell dose available from individual cord blood units has been the major limitation against the widespread use of UCBT in adults with AML or other hematologic malignancies. Preliminary data suggest that transplantation of multiple cord blood units from different donors — double cord transplants (DCTs) — is safe and feasible.73-76 A number of mostly retrospective studies of DCTs following a variety of NMA or RIC regimens (eg, fludarabine-TBI-cyclophosphamide; fludarabine-TBI-busulfan; fludarabine-melphalan-antithymocyte globulin) have included AML patients at various stages of remission and report 3-year OS and disease-free survival rates of approximately 30% to 35%, with acceptable rates of acute GVHD (for the degree of HLA mismatch), NRM, and graft rejection.71-76 Preliminary results from the Société Française de Greffe de Moelle Osseuse et de Thérapie Cellulaire and Eurocord’s multicenter phase II trial for RIC UCBT in patients with AML were presented in the 2010 meeting of American Society of Hematology.77 At 1 year, the rates of OS, LFS, relapse, and NRM for the 65 AML patients initially accrued on the study were 60%, 52%, 30%, and 18%, respectively.

Ongoing large multicenter trials (eg, BMT-CTN 0604) will help confirm the feasibility of this approach and determine its clinical efficacy. This could potentially result in increased use of UCBT in the future. Expansion of the current pool of cord blood units could markedly broaden applicability of this transplant modality, particularly in minority populations who are underrepresented in current volunteer hematopoietic cell donor databases.

**RIC Haploidentical Transplantation**

Virtually all AML patients (without an HLA-identical sibling donor) have at least one haploidentical related donor available. The theoretical risks of increased GVHD, NRM, graft rejection, and opportunistic infections associated with haploidentical transplantation have prevented routine use of this modality. However, with rigorous ex vivo T-cell depletion and an intense conditioning regimen (which is not suitable for older AML patients), Aversa et al78-80 reported encouraging LFS rates of 30% to 45% of AML patients depending on remission status at the time of allografting. A number of small single-institution studies81-83 that included patients with various hematologic malignancies have assessed the feasibility of a variety of NMA or RIC regimens for haploidentical transplantation. These seminal studies have provided important preliminary evidence about the feasibility of NMA/RIC haploidentical transplantation for hematologic malignancies. Continued research is needed to better define preferred conditioning regimens, methods and degree of T-cell depletion, and optimal CD34+ cell dose in the allograft. Although RIC haploidentical transplantation is a potentially curative option for AML patients lacking a suitable sibling or unrelated donor, we believe that at this time it should be performed only in experienced centers, within the context of clinical trials, especially in patients with poor-risk AML in CR1.

**Conclusions**

The number of NMA or RIC allo-HCTs performed in patients with AML has steadily increased over the last decade. The efficacy and feasibility data reviewed here support performing HLA typing and sibling and/or unrelated donor searches in newly diagnosed older AML patients who are able to tolerate this procedure. Offering NMA or RIC transplantation is a reasonable option for these older patients and for younger AML patients with medical comorbidities who achieve a first or subsequent remission. The application of NMA or RIC for patients with refractory disease or untreated relapse and the use of alternative donors should be considered within the context of clinical trials. Continued rigorous research efforts focusing on (1) the development of safer and more effective conditioning regimens, (2) novel methods to reduce the incidence and severity of GVHD without compromising the beneficial graft-vs-leukemia effects, (3) strategies to improve immune reconstitution following transplantation, and (4) increased availability of alternative-donor approaches are being pursued with the goal of ultimately achieving durable long-term remissions in older patients with AML.

**References**


