To Transplant or Not to Transplant for Adult Acute Myeloid Leukemia: An Ever-Evolving Decision

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Abstract: In 2007, a group of experts charged by the American Society for Blood and Marrow Transplantation critically reviewed the available literature and summarized the indications for allogeneic hematopoietic cell transplantation versus chemotherapy in adults with acute myeloid leukemia. Much of the resulting position statement was based on studies conducted nearly 2 decades ago, and may not accurately represent current treatment. As a result of advances in both therapeutic regimens and supportive care, a number of recent studies have demonstrated clear and consistent improvements in the outcomes of patients receiving chemotherapy and allogeneic hematopoietic cell transplantation. In addition, prognostic accuracy has improved with the identification of mutations not detected by traditional cytogenetics. With these advancements in prognostic accuracy and treatment, it is now appropriate to revisit the indications for transplantation versus chemotherapy.

Introduction

In 2007, the American Society for Blood and Marrow Transplantation (ASBMT) Executive Committee adopted a position statement summarizing the indications for allogeneic hematopoietic cell transplantation (HCT) in the treatment of adult acute myeloid leukemia (AML; Table 1).[1] This statement was derived from a consensus reached by an expert panel following an evidence-based review of the literature.[2] The panel was able to make clear recommendations based on strong evidence for certain categories of patients. However, the review acknowledged that a lack of data prevented the resolution of many pressing questions surrounding allogeneic HCT for AML. Moreover, available data at the time were largely based on studies conducted in the mid 1990s. Since then, there have been clear improvements in AML prognostic studies, treatment techniques, and supportive care.

In successive frontline phase III studies conducted by the Southwest Oncology Group between 1981 and 2001, there has been progressive improvement in 5-year overall survival (OS; Figure

Table 1. Transplantation Versus Chemotherapy: 2007 ASBMT Position Statement

2007 ASBMT Position Statement	Shifting Construct
There is a survival advantage for allogeneic HCT vs chemotherapy for patients younger than 55 years with high-risk cytogenetics.	Patients with high-risk cytogenetic or molecular findings do poorly with chemotherapy alone. Allogeneic HCT has improved outcomes in even the highest-risk groups, such as those with monosomal karyotype, and confirms the position.
There is insufficient evidence to routinely recommend allogeneic HCT for patients with intermediate-risk cytogenetics, although this is a reasonable strategy.	Mutations not detected by traditional cytogenetics allow for better prognostication within the intermediate-risk cytogenetic group, identifying those who benefit from HCT (FLT/ITD) and those who do not (NPM1 and CEBPA).
There is no survival advantage for allogeneic HCT in patients younger than 55 years with low-risk cytogenetics.	Given the poor prognosis of high leukocytosis in AML with t(8;21), it is reasonable to consider allogeneic HCT. In CBF-AML, KIT mutations are associated with poorer outcomes, and may be a potential indication for HCT in the near future.
There are insufficient data to make a recommendation for the use of myeloablative regimens for patients older than 55 years.	As reducing the intensity of conditioning may lead to higher rates of relapse, it may be reasonable to pursue an allogeneic HCT with myeloablative conditioning in a select population of more fit patients as identified by validated metrics, such as the HCT-CI.
There are insufficient data to make a recommendation for RIC allogeneic HCT vs chemotherapy.	RIC regimens have demonstrated long-term remissions and decreased transplant-related mortality, resulting in similar overall survival when compared to ablative regimens, extending the therapeutic benefits of allogeneic HCT to patients of advancing age or with medical comorbidities.
For patients in second complete remission, allogeneic HCT is recommended if there is an available donor. Otherwise, an autologous HCT is recommended.	With alternative donor sources, nearly every patient has a donor. These transplantation techniques have been rapidly improving, and are currently being investigated in a prospective study to assess the benefits and risks of these approaches.[40]

AML=acute myeloid leukemia; ASBMT=American Society for Blood and Marrow Transplantation; CEBPA=CCAAT/enhancer-binding protein alpha; CI=comorbidity index; FLT=Fms-like tyrosine kinase; HCT=hematopoietic cell transplantation; ITD=internal tandem duplication; NPM1=nucleophosmin 1; RIC=reduced-intensity conditioning.

1). Similar improvements have been noted by the British Medical Research Council and others.[3] How much of these improved outcomes are due to actual advances in the chemotherapeutic regimens and how much are due to better supportive care measures is uncertain. Nonetheless, when estimating trends for age-specific survival in patients reported to the Surveillance, Epidemiology, and End Results (SEER) Program database, Pulte and colleagues identified a significant improvement in 5- and 10-year survival between 2 eras 20 years apart (1980–1984 and 2000–2004) in most age groups.[4] Unfortunately, this improvement has not been uniform, and it was not seen in patients aged 75 years or older. The lack of improvement in elderly patients is likely due to biologic differences in the disease and patient comorbidities; additionally, a lower rate of referral to specialized cancer centers and hesitancy to aggressively treat such patients may also contribute to this lack of progress.[5]

Along with improved outcomes of chemotherapy, transplantation outcomes have been improving since the mid 1990s. The Seattle group published a report comparing the outcomes of over 2,500 patients receiving allogeneic HCT in 2 eras (1993–1997 and 2003–2007).[6] When comparing the earlier cohort to the latter, it was observed that the nonrelapse mortality (NRM) in the first 200 days after transplant decreased from 30% to 16% and the OS at 4 years increased from 37% to 53% (Figure 2). The improvements from era to era held true for the subgroup of patients who underwent HCT for AML, as the hazard ratio (HR) for NRM by day 200 and death from any cause in AML patients transplanted in the more recent era were 0.38 and 0.63, respectively. A similar study conducted by the group from the Karolinska Institute in Stockholm, Sweden, as well as a registry study of Eastern European countries by the European Group for Blood and Marrow Transplantation (EBMT), found equivalent improvements in OS after allogeneic HCT in recent transplants compared to those performed 1 or 2 decades earlier.[7,8] The Center for International Blood and Marrow Transplant Research (CIBMTR) recently reported an analysis of 5,972 patients younger than 50 years who underwent myeloablative (MA) allogeneic HCT for AML.[9] In patients who received a matched related donor (MRD) HCT in 2000–2004 (compared with those in 1985–1989), there was a relative risk reduction in transplant-related mortality (TRM) for AML patients

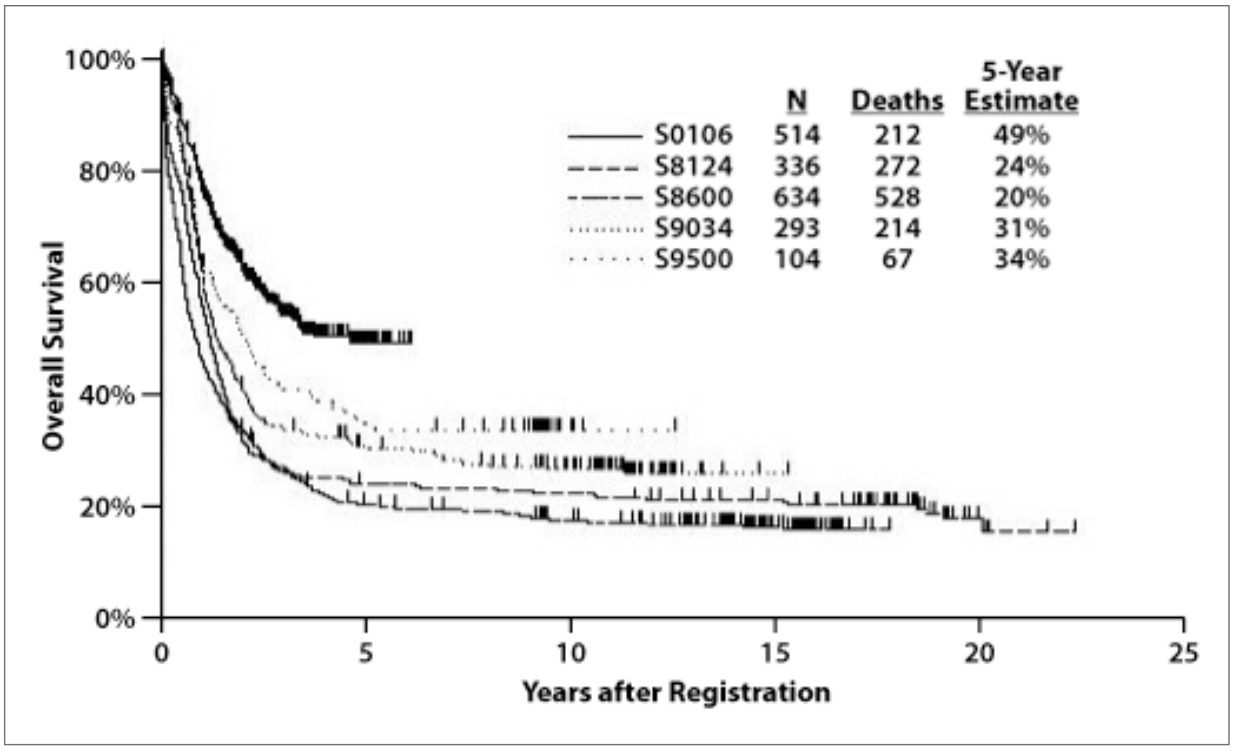

Figure 1. Overall survival for patients with newly diagnosed acute myeloid leukemia treated on Southwest Oncology Group trials initiated in 1981 (S8124), 1986 (S8600), 1990 (S9034), 1995 (S9500), and 2001 (S0106). As shown, survival improved steadily with time. Courtesy: Fred Hutchinson Cancer Research Center.

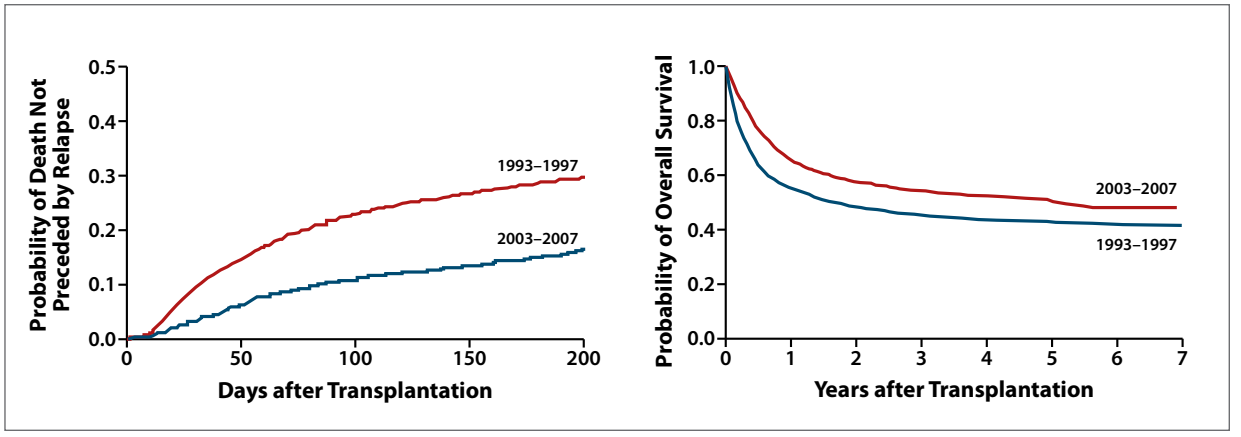

Figure 2. Comparison of nonrelapse mortality and overall survival in patients receiving allogeneic transplants from 1993–1997 versus 2003–2007.[6]

transplanted in first or second remission (50% and 25%, respectively; *P*<.001 for both) in a multivariate model adjusting for changes in patient and disease characteristics over time. Similar risk reductions were seen in those who underwent an unrelated donor transplant (URD) in first (27%; *P*=.09) or second (42%; *P*<.001) remission.

Improvements in transplant outcomes were observed when analyses were restricted to patients with matched siblings, where advances in human leukocyte antigen (HLA) typing would not be expected to play any role, and when restricted to those receiving myeloablative transplant regimens, ruling out the recent adoption of reduced-intensity preparative regimens as the reason. The biggest changes have been the avoidance of severe organ dysfunction, severe acute graft-versus-host-disease (GVHD), and infectious complications in the most recent era.[6] These changes are likely due to avoidance of the most intensive regimens, targeting of busulfan, prevention of liver toxicity with

ursodiol, improved microbial surveillance, and prevention and treatment with reduced complications from cytomegalovirus and fungal infections.

In addition to improvements in chemotherapy and transplant outcomes, a third area of advancement over the last decade has been continued refinement in our understanding of the molecular heterogeneity of AML, and the application of this understanding to disease risk profiling. This field is rapidly evolving, but the largest impact to date has been in segregating patients with intermediate-risk disease into several distinct categories. With these advances in prognostic capabilities, as well as in the nontransplant and transplant care of AML patients, it is appropriate to reconsider the indications for chemotherapy versus transplantation for adult AML.

Transplantation Versus Chemotherapy for Intermediate-Risk AML in CR1

ASBMT Position Statement: *There is insufficient evidence to routinely recommend allogeneic HCT for patients with intermediate risk cytogenetics [in first remission (CR1)], although this is a reasonable strategy.*[1]

Throughout the 1990s, risk categorization of AML was based on cytogenetics. In 2002, the Cancer and Leukemia Group B (CALGB) reported 5-year survivals of 55%, 24%, and 5% for patients segregated into favorable-, intermediate-, and poor-risk cytogenetic groups.[10] In this report, cytogenetically normal AML (CN-AML, 48% of all patients) represented the majority in the intermediate-risk group, and the group as a whole demonstrated a heterogeneous clinical outcome. Since then, the identification of mutations or overexpression of several genes not identified by traditional cytogenetics allows for better segregation into risk groups.

Among these mutations, internal tandem duplication (ITD) of FMS-like tyrosine kinase 3 (FLT3) is the most common indicator of adverse prognosis. Several large studies have shown that isolated FLT3/ITD is detected in approximately one-third of patients with CN-AML, and is associated with a leukemia-free survival (LFS) of 20–25% at 2 years, with a worse outcome if both alleles are mutated. In a multivariate model adjusting for patient and disease characteristics, the AML Study Group Ulm found that mutant FLT3 had a sizeable adverse impact on remission duration and OS (HR, 2.35 and 2.11, respectively) in patients with CN-AML.[11] In order to assess the utility of HCT in this high-risk population, the EBMT analyzed the results of 206 patients with CN-AML who underwent myeloablative HCT in CR1, based on FLT3 mutational status.[12] At 2 years, the presence of FLT3/ITD portended an increase risk of relapse after HCT (30% vs 16%; P=.006). However, they observed a noteworthy 58% LFS at 2 years for patients with mutated FLT3, a significant improvement over the 20–25% reported with chemotherapy alone.

Mutations in nucleophosmin 1 (NPM1) and CCAAT/enhancer-binding protein alpha (CEBPA) impair hematopoietic differentiation and have been frequently found in CN-AML (up to 50% and 20%, respectively). Isolated mutations in NPM1 and CEPBA are favorable prognostic markers, with higher remission rates, better relapse-free survival, and improved OS reminiscent of outcomes seen in patients with favorable-risk cytogenetics such as inv(16) or t(8;21). If patients with isolated NMP1 or CEBPA mutations are removed from the intermediate-risk group, there is a clearer benefit for HCT in this heterogeneous population. A donor versus no-donor analysis was conducted in 872 patients with CN-AML.[13] Among the 135 patients with mutant NPM1 without FLT3/ITD, there was no benefit for the donor group, most of whom were treated with allogeneic transplantation, as compared with the no-donor group (HR for relapse or death during CR, 0.92; 95% confidence interval [CI], 0.47–1.81). Conversely, there was a clear benefit to having a donor and therefore proceeding to transplant among the remaining patients with CN-AML (HR, 0.61; 95% CI, 0.40–0.94).

Other somatic mutations have been identified and are being developed as prognostic markers. Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations often occur in the presence of NPM1 and appear to confer a worse prognosis in CN-AML without the FLT3/ITD mutation, regardless of NPM1 status.[14,15] Mutations in the genes encoding DNA methyltransferase 3A (DNMT3A) are present in 30–40% of patients with CN-AML. DNAMT3A mutations are associated with a lower frequency of complete response, poorer OS,[16] and a shorter LFS.[17]

It is likely that future prognostic models incorporating novel mutations will be able to better identify patients in the current intermediate-risk group who should and should not be routinely considered for allogeneic HCT. One such approach is integrated genetic profiling, which optimizes clinical outcome prediction by integrating a larger number of known biomarkers into a predictive model, rather than relying on individual or small sets of biomarkers.[18,19] This approach has been proven to be a powerful clinical tool in other heterogeneous malignancies, such as the 21-gene recurrence score in breast cancer.

The identification of somatic mutations via molecular techniques in patients with intermediate-risk cytogenetics is rapidly changing the indication for allogeneic HCT in this population. The European LeukemiaNet has added FLT3, NPM1, and CEBPA to traditional

cytogenetics as determinants of good-, intermediate-, and poor-risk groups in an updated prognostic system.[20] For some patients who were considered intermediate risk at the time of the 2007 ASBMT position statement, there is now a clear indication for HCT (those with FLT3 mutations). For others, there is evidence that HCT does not have an advantage over chemotherapy (NPM1- or CEBPA-mutated in the absence of FLT3 mutation). Other markers are still under investigation and will require more studies to determine their ability to predict outcome in a continuously changing array of prognostic information.

Transplantation Versus Chemotherapy for Favorable-Risk AML in CR1

ASBMT Position Statement: *There is no survival advantage for allogeneic HCT in patients under age 55 with low risk cytogenetics [in CR1].*[1]

Despite the significant reduction in TRM in the most recent era, a significant risk of morbidity and mortality is still associated with allogeneic HCT. To better define the role of HCT in patients with favorable-risk AML, the EBMT compared results of 325 patients with core binding factor AML (CBF-AML; eg, inv[16] or t[8;21]) in CR1 who underwent allogeneic HCT (145 patients) versus autologous HCT (180 patients).[21] The study concluded that both autologous and allogeneic transplantation resulted in similar 5-year LFS (59% for allogeneic and 66% for autologous; *P*=.5) and incidence of relapse (27% vs 32%, respectively; *P*=.45). TRM was significantly higher in the allogeneic group (14% vs 2%, respectively; *P*=.003). A conclusion that can be drawn from this study is that the benefit of a graft-versus-leukemia (GVL) effect from an allogeneic HCT was negated by the increased transplant-related toxicity in this population with the most chemotherapy-sensitive AML. To quantify relapse-free survival and OS benefit of allogeneic HCT for AML in CR1, Koreth and associates conducted a systematic review and meta-analysis of prospective trials that evaluated patients with AML in CR1.[22] Of the patients included from 24 trials, 547 patients with low-risk cytogenetics were analyzed, and no benefit with allogeneic HCT was seen in relapse-free survival (HR, 1.06; 95% CI, 0.80–1.42) or OS (HR, 1.07; 95% CI, 0.83–1.38) as compared to non-allogeneic HCT treatments.

The case for allogeneic HCT in patients with low-risk AML is not completely closed, as some patients with low-risk cytogenetics have been found to harbor other factors associated with a poorer prognosis, perhaps lowering the threshold for HCT. For example, multiple groups have reported on the negative prognostic impact of leukocytosis (white blood cell [WBC] count >25.4 x 10^9/L) in patients with t(8;21).[23-25] The French AML Intergroup reported an estimated 3-year survival of 74% for patients with a low WBC index (<2.5, the product of WBC by the ratio of marrow blasts) compared with 47% in patients with a high WBC index (>20).[25] A similar effect was seen on relapse, with an estimated 3-year relapse rate of 20% for patients with a low WBC index, and 61% for those with a WBC index greater than 20.

As seen in patients with intermediate-risk AML, the identification of novel mutations is continually refining prognostic accuracy. Mutations in the KIT gene, found in approximately 20–30% of patients with CBF-AML, have been associated with a poor prognosis. In 110 patients with CBF-AML treated on CALGB protocols, the presence of a KIT mutation was associated with increased 5-year cumulative incidence of relapse in both inv(16) (56% vs 29%) and t(8;21) (70% vs 36%).[26] When adjusted for sex, the presence of mutated KIT was associated with a lower OS in inv(16) (HR 3.9, 95% CI, 1.4–10.7) but not in t(8;21).

There have been few recent, prospective, comparative studies of transplant versus chemotherapy for favorable-risk AML; as such, there is insufficient evidence to change the ASBMT recommendations. Given the poor prognosis of high leukocytosis in AML with t(8;21), it is reasonable to consider allogeneic HCT in CR1 for this subset of patients. Some may also suggest transplantation for patients with CBF-AML harboring a KIT mutation, as these patients have a higher incidence of relapse than what would be expected as a whole for patients with low-risk cyogenetics. KIT mutations present a possible therapeutic target for tyrosine kinase inhibitors, and if proven to be disease modifying, this approach may impact the indication for allogeneic HCT in patients harboring KIT mutations.

Transplantation Versus Chemotherapy for Unfavorable-Risk AML in CR1

ASBMT Position Statement: *There is a survival advantage for allogeneic HCT versus chemotherapy for patients under age 55 with high-risk cytogenetics.*[1]

The ASBMT recommendations of 2007 were based on the results of prospective trials in which patients with AML in CR1 with donors were allocated to allogeneic transplantation and those without donors were treated with consolidation chemotherapy. In patients with high-risk cytogenetics, OS appeared to be improved with allogeneic transplantation.[27] Since the ASBMT recommendations were published, subsequent meta-analyses have come to similar conclusions.[22,28] There is now an appreciation that within the subgroup of patients with unfavorable cytogenetics, those with a monosomal karyotype have a particularly poor prognosis. In an effort to

address the question of whether the increased antitumor effects associated with allogeneic transplantation were sufficiently potent to benefit this very difficult group of patients, Fang and colleagues reviewed the outcome of allogeneic transplantation in 432 patients with AML.[29] The 4-year survival in those with a monosomal karyotype was 25%, which was considerably worse than the 56% survival observed in those without, but significantly better than the expected 0–4% survival associated with chemotherapy. Thus, the ASBMT conclusions continue to be appropriate for this patient population.

Transplantation Versus Chemotherapy for Adult AML in Patients Older Than 55 Years

In 2007, the ASBMT expert review panel sought to determine whether or not patients older than 55 years should undergo allogeneic HCT. This group represents a majority of patients with AML, as the incidence of AML is much higher in the population older than 65 years than younger than 65 years (12.2 vs 1.3 cases per 100,000, respectively). The care of older patients with AML is more likely to be complicated by medical comorbidities; consequently, a major concern is transplant-related toxicity that is too high to justify this approach over chemotherapy. Thus, the ASBMT divided this issue into 2 questions: 1) Should patients be transplanted using a myeloablative preparative regimen? and 2) Are there data to show that allogeneic HCT using a reduced-intensity regimen is superior to chemotherapy?

The ASBMT concluded: *There are insufficient data to make a recommendation for the use of myeloablative regimens for patients over age 55. There are insufficient data to make a recommendation for reduced intensity conditioning (RIC) allogeneic HCT vs. chemotherapy [in CR1].*[1]

Recently, Kurosawa and coworkers completed a retrospective analysis of 1,036 AML patients aged 50–70 years who achieved first remission.[30] At 3 years, patients who underwent allogeneic HCT in CR1 had a lower cumulative incidence of relapse compared with patients who did not receive allogeneic HCT (22% vs 62%; $P<.001$), but they had a higher nonrelapse mortality (21% vs 35%, respectively; $P<.001$). Nonetheless, patients who underwent allogeneic HCT had better LFS (56% vs 29%, respectively; $P<.001$) and OS (62% vs 51%, respectively; $P=.012$). Of the 152 patients who underwent HCT, 39% were conditioned with myeloablative regimens. There was no significant difference in the 3-year OS from CR1 in the patients who were conditioned with myeloablative versus RIC regimens (63% vs 61%; $P=.571$). Although patients who were conditioned with a myeloablative regimen were younger (median age, 52 years vs 58 years), there was no difference in disease risk between the myeloablative and RIC groups. An analysis of cumulative relapse or TRM was not provided for these subsets. This was a retrospective study and, as such, there are likely inherent biases in the selection of patients for allogeneic HCT and the choice between myeloablative and RIC conditioning. Nonetheless, the analysis suggests that allogeneic HCT is a reasonable option for fit older patients with AML and that an ablative conditioning regimen can be used with relative safety in a select subpopulation.

The HCT-comorbidity index (HCT-CI) may be a useful tool for identifying patients with an acceptable risk of TRM with myeloablative conditioning, in order to overcome the higher relapse rates seen with RIC regimens relative to myeloablative regimens.[31] In a retrospective analysis of 71 patients aged 50 years or older who underwent HCT (myeloablative, 35 patients; RIC, 36 patients), Takasaki found that in addition to disease risk, higher HCT-CI score and an HLA-mismatched donor were predictors of increased nonrelapse mortality and poorer OS.[32] Conditioning regimen intensity (myeloablative vs RIC) was not found to be a predictor of OS or nonrelapse mortality.

Although some patients can tolerate myeloablative conditioning with an acceptable risk of TRM, this may not be the case for the majority of patients older than 55 years. Without a myeloablative regimen reducing leukemic burden, is GVL alone enough to improve outcomes over that of chemotherapy? Long-term remissions have been demonstrated with RIC, where it would not be expected with chemotherapy alone.[33,34] Sorror and associates reported the outcomes of 372 patients aged 60–75 years who were enrolled on prospective clinical transplant protocols and underwent allogeneic HCT with RIC for advanced hematologic malignancies (55.64% with acute leukemia or myelodysplastic syndrome/myeloproliferative neoplasm).[35] The conditioning regimens were primarily 2-Gy total body irradiation (TBI) with or without fludarabine 90 mg/m^2, therefore relying almost entirely on the GVL effect. The 5-year cumulative incidence of nonrelapse mortality was 27%, and relapse was 41%. This resulted in a 5-year LFS of 32% and OS of 35%. Disease risk and HCT-CI correlated with OS in multivariate models, where stratification by age was not associated with a worse outcome, and increasing age did not correlate with GVHD or organ toxicity.

Several retrospective studies comparing myeloablative and RIC regimens in patients with AML have been published. The EBMT compared the results of 434 AML patients aged 50 years and older who were conditioned with either RIC (58%) or a myeloablative regimen (42%) prior to an unrelated donor transplant.[36] As expected, patients conditioned with RIC had lower

nonrelapse mortality at 2 years compared with patients who received myeloablative conditioning (25% vs 39%; *P*=.003). There was a higher cumulative incidence of relapse seen in the RIC group compared with the myeloablative group (42% vs 29%; *P*=.015). However, in a multivariate model adjusting for disease stage and cytogenetics, there was no significant difference between the RIC and myeloablative groups. The CIBMTR recently published a similar analysis of 5,179 patients with AML and myelodysplastic syndrome, including both those with related and unrelated donor sources.[37] The median age at the time of transplant was significantly younger for those who underwent myeloablative conditioning versus those who did not, with only 3% of patients in the myeloablative group older than 60 years. Results from the 407 patients who underwent nonmyeloablative (NMA, defined as TBI 2 Gy ± fludarabine or fludarabine + cyclophosphamide) conditioning regimens were reported separately from the 1,041 patients who underwent RIC. Adjusted TRM was similar among the 3 groups. NMA conditioning resulted in an inferior cumulative incidence of relapse, LFS, and OS at 5 years (43%, 24%, and 26%, respectively) when compared to myeloablative conditioning (32%, 33%, and 34%, respectively). There was no difference in relapse, LFS, and OS between RIC and myeloablative regimens. Of course, the issue of patient selection bias weighs heavily on the interpretation of these results.

As part of the LAM-2001 trial, myeloablative conditioning in younger patients was prospectively compared to RIC in older patients in first remission within the framework of a risk-adapted strategy.[38] After achieving CR with 1 or 2 courses of induction chemotherapy, patients with a matched sibling either proceeded to myeloablative conditioning and transplantation using bone marrow (age <50 years) or received a course of consolidation therapy prior to RIC and peripheral blood transplant (age 50–60 years). After induction therapy, 676 (82%) patients achieved a CR and 164 ultimately went on to HCT (117 with myeloablative conditioning and 47 with RIC). At 108 months, there was no significant difference between the cumulative incidence of relapse (21.7% vs 28.6%), LFS (63.4% vs 65.8%), or OS (68% vs 69.3%) between the myeloablative and RIC groups, respectively. Although this prospective study does not address the question in patients older than 60 years, it does suggest that RIC in the setting of appropriate pre-HCT cytoreduction can result in LFS and OS similar to myeloablative conditioning without excess TRM.

The majority of patients with AML are older than 55 years. At the time of the ASBMT position statement, there were insufficient data to make a recommendation for HCT with myeloablative conditioning or RIC in this population. Comorbidities play a large role in TRM and often trump chronologic age. Although still debated, the evidence toward the safety and efficacy of HCT is mounting, and HCT should be considered in appropriate patients older than 55 years. As reducing the intensity of conditioning can lead to higher rates of relapse, it may be reasonable to pursue an allogeneic HCT with myeloablative conditioning in a select population of more fit patients, as identified by validated metrics such as the HCT-CI. Nonetheless, the development of RIC (and NMA) regimens has decreased TRM, resulting in similar OS when compared to myeloablative regimens and extending the therapeutic benefits of allogeneic HCT to patients of advancing age or those with medical comorbidities.

Conclusion

Advances in both nontransplant and transplant therapies over the past 2 decades, as well as improvements in supportive care and prognostic models, have changed the indications for allogeneic transplantation versus chemotherapy for patients with AML. Although some questions have been answered since the ASBMT position statement, there are still many outstanding issues. With rapidly expanding biologic characterization of AML and improvements in both chemotherapy and transplantation, continued comparisons will need to be performed in order to fully understand the benefits of each approach in specific populations. Such studies, while difficult, are possible in the younger patient population. However, most patients diagnosed with AML are older than 55 years, and although there are retrospective data suggesting the utility of HCT in this population, there are no definitive prospective studies to date. Retrospective analyses in this setting are especially susceptible to the biases introduced by both treating physicians and patients in the choice of HCT versus chemotherapy, and, if HCT is pursued, the choice of conditioning regimen. Prospective studies in this patient population are particularly difficult because of patient comorbidities, as well as physician and patient treatment biases. Prospective data analyzed on an intent-to-treat basis but that has a high drop out rate cannot truly determine which therapy is best for a specific patient. Osler noted that, "In seeking absolute truth we aim at the unattainable and must be content with broken portions."[39] In the absence of conclusive prospective data and based on the available information, patients older than 55 years should be considered for HCT, as are those younger than 55 years. Reduction of conditioning intensity has reduced the toxicity associated with transplant, and relapse remains the most significant cause of failure.

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