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The who, how and why: Allogeneic transplant for acute myeloid leukemia in patients older than 60 years

Sarah A. Wall[1], **Steven Devine**[2], and **Sumithira Vasu**[2]

[1]Hematology and Medical Oncology Fellowship, Ohio State University, Columbus, OH, USA

[2]Division of Hematology, Ohio State University, Columbus, OH, USA

Abstract

Acute myelogenous leukemia (AML) is primarily a disease of the elderly, and as such, our approach to treatment needs to be tailored to address an aging population. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative treatment for intermediate and high risk AML, and until recently, its use had been limited to a younger population and dependent on availability of a donor. Advances in conditioning regimens, supportive care, and the use of alternative donor sources have greatly expanded access to this therapy. In this review, we summarize the challenges and unique biological aspects of treatment with allogeneic stem cell transplantation in this group of patients older than 60 years. We also highlight areas of ongoing research including measurement of residual disease prior to and following transplant, post-remission maintenance therapy, and natural killer cell immunotherapy. Finally, we propose future directions for AML treatment in an elderly and aging population.

Keywords

Acute myelogenous leukemia (AML); elderly; allogeneic hematopoietic stem cell transplantation (allo-HSCT); immunotherapy

Allo-HSCT is a potentially curative treatment option for patients with AML; however, historically, it had not been a viable option for many patients due to excessive toxicity. Reduced intensity conditioning (RIC) allo-HSCT has emerged as a less toxic alternative. It relies predominantly on a graft-versus-leukemia (GVL) effect, mediated by infused donor T cells, rather than the cytoreductive effect of a myeloablative conditioning regimen. The chemotherapy doses administered in RIC allo-HSCT do not result in myeloablation but rather are profoundly immunosuppressive to enable engraftment. Due to the less intensive nature of the conditioning regimen, this modality has allowed transplantation to be

Corresponding author: Sumithira Vasu, Starling-Loving Hall, 320 W. 10th Avenue, Columbus, OH 43210, USA, Sumithira.vasu@osumc.edu.

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performed safely in patients older than 60 years. The cut-off of 60 years was chosen based on many studies showing the negative prognostic effect of similar molecular groups in AML in patients > 60 years[1–4]. Chronologic age was once thought to be an important predictor of patient outcomes, largely related to the progressive decline of multiple organ systems with age; however, the use of functional assessments for individual patients has demonstrated that age may be "just a number". In some very fit elderly patients, myeloablative conditioning may be a viable approach to allo-HSCT.

Evidence to support the role for allo-HSCT in an elderly population is growing. Table 1 summarizes important studies establishing the role for RIC allo-HSCT in AML, a few of which are described in greater detail here. In a meta-analysis, more than half of patients older than 60 years undergoing allo-HSCT with non-myeloablative conditioning were either never hospitalized or hospitalized only overnight for stem cell infusion within the first 100 days after transplant with a 35% 5-year overall survival (OS)[5]. A retrospective comparison of RIC allo-HSCT with chemotherapy in patients aged 60–70 years with AML in first complete remission (CR) showed that allo-HSCT was associated with a significantly lower risk of relapse (32% vs 81% at 3 years, $p< 0.001$), higher non-relapse mortality (NRM) (36% vs. 4% at 3 years, $p< 0.001$), and longer disease free survival (DFS) (32% vs. 15% at 3 years, $p=0.001$)[6]. When outcomes after RIC allo-HSCT were compared across four different age groups: 40–54yrs, 55–59 years, 60–64 years and ≥ 65 years, a multivariate analysis showed that age had no significant impact on NRM, relapse, DFS or OS[7]. Despite these reports of favorable outcomes for elderly patients after allo-HSCT, and especially in comparison to chemotherapy alone, barriers and biases remain. Estey et al conducted a prospective feasibility analysis of RIC allo-HSCT in patients older than 50 years[8]. Of the ninety-nine patients who entered CR, only 53 were ever seen by the transplant service in consultation. Of those 53 patients, donors were available for 26 patients but RIC allo-HSCT was performed in only 14 patients. Of the 85 patients who achieved CR but did not undergo transplantation, up to 50% were deemed to be potential transplant candidates.

We have seen rapid change in outcomes in allo-HSCT over very short periods of time. This was highlighted in a study utilizing the National Marrow Donor Program (NMDP) registry and comparing outcomes in the years 2000–2004 with the years 2005–2009. The 3-year OS was significantly better in the more recent cohort for patients of all ages and notably improved for those ≥60 years old (35% vs. 25%, $p<0.001$). Interestingly, for older patients, the cumulative incidence of relapse did not improve significantly as was seen in younger cohorts; however, the improvement in OS was more substantially accounted for by decrease in NRM[9]. This study not only demonstrated that outcomes after allo-HSCT have improved across the board in a period of only 5 years, but it also suggests that this is a rapidly changing field and data may become outdated quite quickly. This leaves providers with the dilemma of trying to utilize the most up to date research in making treatment decisions while balancing whether there is enough mature evidence to support a given therapeutic endeavor. We explore in more detail some of the factors associated with allo-HSCT outcomes in the elderly and how these can direct clinical decision-making.

What subtypes of AML benefit from allogeneic transplant?

Traditionally, allo-HSCT has shown survival advantage when the risk of relapse exceeds 35–40%. Patients with unfavorable karyotype or FLT3ITD mutated AML benefit from transplant. Patients with normal karyotype, accounting for 45% of *de novo* AML cases in patients older than 60, fall into the intermediate risk category[1]. A study of genomics showed more alterations in patients older than 60 years compared to the younger cohort and it has been suggested that this genomic instability may contribute to a poorer prognosis for older patients[10]. The prognostic implications of select genomic alterations will be addressed here, but it should be noted that this is an area of active research, particularly for mutations that are targetable by available drugs or those in development. CN-AML is increasingly recognized as a molecularly heterogeneous disease[11]. The original European Leukemia Network (ELN) classification published in 2010 incorporated NPM1, FLT3ITD and CEBPA, in addition to cytogenetics, in risk-stratification of AML[12]. An update in 2017 now includes RUNX1, ASXL1, and TP53 as adverse risk mutations[13].

Allo-HSCT has been shown to confer a survival benefit in FLT3ITD mutated AML; however, relapse risk remains high even after allo-HSCT indicating need for investigation of maintenance strategies[14]. NPM1 mutations are typically considered to carry a favorable prognosis; however, the effect may be mitigated by the presence of other molecular mutations. Schmid et al found that cumulative incidence of relapse, DFS, and OS after allo-HSCT did not differ significantly in patients with CN-AML according to NPM1*mut* vs. NPM1*wt* status but that FLT3 status was an important predictor of all 3 outcomes[15]. For this retrospective study, the median patient age was 51 years with a maximum of 71 and there was a trend in age noted among molecular subgroups with a median age of 52 years for NPM1*wt*/FLT3*wt*, NPM1*mut*/FLT3*wt*, and NPM1*mut*/FLT3ITD, and of only 47 years for the NPM1*wt*/FLT3ITD subgroup (p=0.05). While elderly patients did not make up a majority of the subjects in the study, this trend in age is interesting because the NPM1*wt*/FLT3ITD group with a younger median age was more likely to require at least 2 induction courses to achieve CR and had poorer outcomes in terms of incidence of relapse, DFS, and OS. The NPM1*wt*/FLT3ITD group was also more likely to receive myeloablative conditioning but did not experience a higher rate of NRM. This study demonstrates the prognostic importance of molecular subtype which is further emphasized by better outcomes in subgroups with older median age.

The effect of NPM1 mutation has been studied specifically in the elderly population. In a study of adults 60 or older with newly diagnosed AML, 60% of enrolled patients achieved CR after intensive chemotherapy and 92% of those CR patients went on to complete up to 4 cycles of intermediate dose cytarabine. The patients with non-monosomal or normal karyotype AML and *NPM1mut* had the longest median continuous CR and the highest 5 year OS compared with core-binding factor, monosomal karyotype, and non-monosomal or normal karyotype with *NPM1wt* disease[16]. The SAL-AML 2003 study compared adult patients up to 60 years old receiving allo-HSCT to those without donors. In secondary analysis of patients with intermediate risk karyotype and NPM1*mut*, there was no significant difference in 3-year OS between consolidative chemotherapy and allo-HSCT; however, relapse risk was higher in the chemotherapy group and treatment-related mortality (TRM)

was higher in the allo-HSCT group[17]. In the absence of data for outcomes in elderly patients receiving RIC allo-HSCT in this specific molecular group, enrollment of such patients in clinical trials evaluating allo-HSCT may provide information regarding transplant outcomes.

For patients with predictors of adverse risk disease, the outcome of allo-HSCT has also been studied. Translocations involving 11q23 are most frequently associated with previous chemotherapy, specifically topoisomerase II inhibitors, but can occur *de novo*. These translocations are associated with poor outcomes and assigned to the intermediate or adverse risk group depending on which specific translocation has occurred. In the largest report of 11q23 AML patients, a significant difference in 2-year OS was found depending on translocation with t(9;11) and t(11;19) faring better at 64% and 73%, respectively than t(6;11) and t(10;11) at 40% and 24%, respectively ($p<0.0001$). In multivariate analysis, these trends in translocations were again demonstrated as were poorer outcomes for patients receiving RIC, older than 40, and undergoing transplant in CR2 rather than CR1[18]. This study included patients up to 67 years of age, but outcomes in elderly patients with mutations involving *11q23* have not been studied independently.

Another subtype that carries a poor prognosis is TP53 mutated AML. In a study of patients with adverse cytogenetic risk AML undergoing allo-HSCT, 40 of 97 patients (41%) were identified as TP53*mut*. The 3-year OS for TP53*wt* was 33% and only 10% for TP53*mut* ($p=0.002$). While the median age in this study was only 51 years with a range of 18 to 67, the median age was significantly higher in the TP53*mut* group (55 v. 43 years, $p<0.01$)[19]. These survival data were based on initial treatment with standard induction regimens, but that may not be the best approach. In a prospective, uncontrolled trial of decitabine induction, patients with TP53 mutations and transfusion-dependent MDS, relapsed AML, or AML and age greater than 60 years had a 12.7 month median OS compared to historical value of 4–6 months. Furthermore, patients with TP53 mutations who went on to allo-HSCT experienced the same survival benefit as those with wild-type TP53[20]. Further studies highlighting important differences in incidence of TP53*mut* by age and exploring the use of decitabine induction with or without consolidative allo-HSCT will be crucial to better direct the use of currently available therapies (ClinicalTrials.gov Identifier: NCT03063203). Our practice has been to transplant patients with TP53 mutation only in the setting of clinical trials, preferably evaluating post-transplant maintenance strategies or GVHD prevention studies.

What is the impact of donor source?

Traditionally, choice of post-remission therapy has too often relied on a "genetic randomization" which has resulted in only patients with a human leukocyte antigen (HLA)-matched sibling proceeding to allo-HSCT. However, with recent analyses showing comparable survival between matched related donor transplants and well-matched unrelated donor transplants, this modality has been increasingly applied to patients >60 years[21]. In a multi-center prospective phase II trial of allo-HSCT in older patients (median age 65 years), the majority (52%) received grafts from unrelated donors. Overall DFS and OS at 2 years after transplantation were 42% and 48%, respectively, compared with patients receiving MUD grafts, in whom DFS was 40% and 2-year OS was 50%[22].

For many patients of diverse racial or ethnic backgrounds, an unrelated donor cannot be identified. For these patients, three alternative graft sources can be considered: (i) umbilical cord blood (UCB), (ii) haploidentical related donor and (iii) mismatched unrelated donor (MMUD). Each graft source has its own unique set of challenges and complications post-transplant, as summarized in a recent review[23]. Currently in the US, the same patient evaluated in different geographic areas could be offered any of these three sources depending on center preferences. UCB transplants are associated with slow immune recovery which may result in debilitating viral infections and consequent TRM. Haploidentical transplants use strategies for in-vivo T cell depletion with either alemtuzumab or post-transplantation cyclophosphamide, and as such, are associated with high rates of relapse and graft failure. Less is known about MMUD in RIC transplants, but the best studied mismatch relates to HLA-C which is associated with increased grade 3 or 4 acute GVHD, increased NRM and worse 2-year OS. Recently a permissive HLA-C mismatch has been identified. In patients mismatched at the HLA-C*03:03/C*03:04 alleles, there were no differences in outcomes when compared with an 8/8 matched group[24]. There is a currently available randomized trial conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN 1101) evaluating efficacy of haploidentical vs. UCB transplant in patients up to 70 years old.

A recent Center for International Blood and Marrow Transplant Research (CIBMTR) analysis studied patients with AML over age 50 and in first CR who received alternative-donor transplants[25]. Graft sources were either adult unrelated donor (URD) with the majority being 8/8 HLA matched or UCB transplantations. Neutrophil recovery by day 28 was lower in UCB (69%) compared with 8/8 HLA-matched URD (97%) and 7/8 HLA-matched (91%) recipients ($p<0.001$). Three-year TRM was higher and DFS lower with UCB versus 8/8 HLA-matched URD (3-year TRM: 35% v. 27% and DFS: 28% v. 39%, respectively). TRM was highest in 7/8 HLA-matched URD (41%, $p=0.01$), but DFS was similar (34%, $p=0.39$). Three-year chronic GVHD was the lowest in UCB at 28% versus 53% and 59% in 8/8 and 7/8 HLA-matched URD recipients, respectively. Three-year survival was 43% in 8/8 HLA-matched URD, 37% in 7/8 URD and 30% in UCB ($p=0.002$). This study shows that allo-HSCT for AML in first CR with any of these grafts extends DFS for more than one third of older patients, but at the cost of increased chronic GVHD with URD use and increased TRM with poorer survival outcomes with UCB use.

Haploidentical donors are also a viable option. Ciurea et al compared haploidentical donors to MUD in adult patients of all ages[26]. Predictably, the majority of patients receiving myeloablative conditioning were younger than 50 while the majority receiving RIC were older than 50. In patients receiving RIC, the incidences of acute and chronic GVHD and NRM were significantly lower for haploidentical transplants compared with MUD. While relapse incidence at 36 months was higher in the haploidentical group, no significant difference in OS was found. In another study of haploidentical RIC transplants, patients were subdivided into groups by age (50–59 years, 60–69 years, and 70–75 years)[27]. There were no significant differences between the age groups in terms of OS, DFS, NRM, time to count recovery, and relapse. The only significant difference was a higher rate of grade 2–4 acute GVHD in the age 70–75 group (52% v. 37% v. 24% in descending order, $p=0.009$), but there was no difference in rate of grade 3–4 acute GVHD or chronic GVHD. A major

limitation of the study for our purposes is that patients with AML made up only 24% of the total population. Even so, these 2 major trials, along with the others summarized in Table 2, show that donor availability is no longer the obstacle that it once was.

Our approach to donor selection for patients older than 60 years is to use a matched related donor whenever one exists. The next preferred option is the use a MUD. If a matched donor is not available, donor selection will ideally be directed by clinical trial enrollment, particularly on BMT CTN 1101, comparing UCB and haploidentical sources that was outlined above. If patients do not qualify due to lack of haploidentical donor and/or UCB, we will carefully consider the use of a single-antigen mismatched URD with post-transplantation cyclophosphamide on trial (ClinicalTrials.gov Identifier: NCT02793544) while being mindful of the potentially narrow therapeutic window left after accounting for the relative increase in risk of TRM and GVHD. For patients ineligible for both BMT CTN 1101 and mismatched URD with post-transplant cyclophosphamide trials, we will consider a haploidentical donor off trial; however, the risk of GVHD remains a concern, especially in our much older patients. Outcome data regarding impact of GVHD on readmissions, hospital length of stay, quality of life is needed to assess long-term impact of allo-HSCT in patients >60 years.

What is the impact of donor age?

With increasing age in the US population, donors are also older. A recent CIBMTR study showed grafts from older sibling donors are preferred over younger unrelated donors[28]. A total of 1415 related donor recipients were compared with 757 recipients of unrelated donors. Recipients of MUD grafts had higher risks of grade 2–4 acute GVHD ($p< 0.001$) and chronic GVHD ($p<0.0001$) than recipients of older sibling donors. As a result, older sibling donors may become the preferred graft choice over younger well-matched unrelated donors. This data, along with the data on alternative donor sources presented above, is changing the approach to allo-HSCT in elderly patients with AML. Instead of asking whether or not a patient has an available donor source, we can now ask the more important question: should the patient be offered allo-HSCT based on his individual risk of relapse and treatment-related mortality?

How are patients assessed for risk of transplantation-related mortality?

Comorbidity scores

Sorror et al developed a method to assess comorbidities before transplant called the Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI)[29]. The HCT-CI looks at objective measures to define hepatic, cardiac, pulmonary, renal, neurologic and psychiatric comorbidities. When the HCT-CI was developed, the cohort studied had a median age of 44.8 years with a maximum age of 72.7 years, so elderly patients were included. The authors did not evaluate the risk associated with increasing age because it is typically accounted for in decision to refer for transplant and in selection of conditioning regimen; however, they did adjust for age in their model and suggested an age-graded score that was later developed. When age was included in the HCT-CI model, it was included as a binomial variable with patients assigned one additional point for age greater than or equal to 40 years old[30]. Its use

has not been widely adopted with many contributing factors, but chief among them being the limited contribution to the overall HCT-CI score as age carries only a small weight as a risk factor. In a study at Fred Hutchinson Cancer Research Center (FHCRC), 125 recipients of non-myeloablative regimens were studied[31]. Multivariate analyses showed that high HCT-CI scores and high disease risk were the most significant factors predicting NRM and OS. The HCT-CI worksheet is available on the CIBMTR website and an online calculator is also available to compute the HCT-CI score (http://www.qxmd.com/calculate-online/hematology/hct-ci).

Geriatric assessments

The HCT-CI score has stream-lined the approach to risk assessment before transplant; however, for patients older than 60 years, a functional assessment would provide additional information on occult limitations. The goal of these assessments is to identify concerns in the pre-transplantation period and intervene when possible. A comprehensive geriatric assessment (CGA) has been studied in patients >50 years who were eligible for HSCT[32]. The CGA utilizes self-reported information and performance based objective test results to assess and quantify comorbidities, physical and mental function, level of frailty and nutrition. The CGA was assessed in 166 patients, 44% of whom had high HCT-CI. Disability was present in 40% of the patients and 25% were noted to be frail, as defined by a functional measure of frailty incorporating walk speed, grip strength, and self-reported physical activity, exhaustion, and weight. Self-reported physical and mental function was significantly lower than population age-group norms. A functional assessment such as the CGA uncovers a substantial prevalence of undocumented limitations in functional status, disability and frailty in older allogeneic HSCT patients.

This is a fertile area for ongoing research in improving outcomes post-transplant. A recent secondary analysis of a BMT CTN study of pre-transplantation exercise and stress management training pre-transplant evaluated the predictive value of patient-reported outcomes for post-transplant morbidity and mortality[33]. The physical component scale of the Medical Outcomes Study Short Form-36 Health Survey (SF-36) incorporates patient self-assessment of physical function, bodily pain, limitations in daily activities, and general health. Lower pre-transplant SF-36 physical component scores were correlated with increased mortality (HR for 10-point decrease in score, 1.40 (1.18–1.66), $p<0.001$). Of the original 336 patients, 236 survived to day 100 and completed the SF-36 again. Pre-transplant and post-transplant physical component scores were compared and for every 10-point decrease in a given patient score, the risk of TRM increased as did the risk of all-cause mortality (HR for TRM, 3.57, $p<0.001$; HR for all-cause mortality, 1.83, $p<0.001$).

Patient-reported outcome tools like the SF-36 are increasingly incorporated into pre-transplant work-up and should continue to be an area of interest for research to better establish their predictive value and the role for peri-transplant intervention. Performance of a CGA is a time-intensive process. This limitation has been cited across the oncologic literature as a major obstacle to its routine use. At our institution, a multi-modality geriatric clinic has been established to evaluate octogenarians with hematologic malignancies and offer guidance in terms of tolerability of chemotherapy or immunotherapy, but this has not

yet included allo-HSCT candidates. Our current practice includes the use of HCT-CI in conjunction with a comprehensive assessment by physical and occupational therapy to identify physical limitations and treat them prior to, during, and after transplant. We are working toward extending the geriatric clinic to include younger patients being considered for allo-HSCT. The role of the clinic will continue to be objective assessment of functional status, but will also allow for "pre-habilitation" of patients with identified limitations so as to reduce their risk of TRM.

How do we increase efficacy of transplants?

Minimal residual disease (MRD) post-induction/consolidation

The role of MRD measurement in AML will be to integrate with presenting features at diagnosis, much like its use in acute lymphoblastic leukemia (ALL), to prognosticate and aid in therapeutic decision-making. Unlike ALL, several logistic challenges in MRD detection in AML have resulted in few prospective risk stratified studies of AML patients[8]. These challenges are due to inconsistencies in thresholds to determine MRD, uncertainties in informative time points, sampling frequency, and lack of standardized assays. Despite these challenges, several retrospective and observational studies have shown the value of MRD in risk stratification, though the majority included only younger patients. In patients younger than 60 years, MRD detected after induction and consolidation as assessed by flow cytometry was shown to be associated with a high risk of relapse[34]. A comprehensive review of MRD is beyond the scope of this article; however, many of the key studies are summarized in Table 3 with emphasis on those trials focusing on elderly patients or those with a median population age of >50 years.

It is generally accepted that ELN favorable risk patients do not need allo-HSCT and ELN adverse risk patients require allo-HSCT at first CR. MRD detection has been shown to carry prognostic significance within each risk group. Buccisano et al showed that incorporation of MRD distinguished two categories of patients: (i) low risk: patients with favorable or intermediate-risk karyotype who were MRD negative after consolidation; and (ii) high risk: unfavorable-risk karyotype, FLT3ITD mutated patients, or MRD positive favorable or intermediate karyotype patients[35]. A retrospective analysis by Araki et al demonstrated significant benefit after allo-HSCT for MRD negative patients compared with those with MRD positivity by multiparametric flow cytometry (MFC) or active disease[36]. In fact, MRD positive patients behaved similarly to those with active disease with relapse risk of 67% and 65%, respectively (compared to 22% in MRD negative patients) and 3-year OS of 26% and 23%, respectively (compared to 73% in MRD negative patients). Prospective trials in Europe now routinely incorporate MRD in risk-adapted treatment approaches for AML. These findings have led to the conclusion that MRD status should determine need for HSCT irrespective of cytogenetic risk.

Timing and frequency of MRD assessment varies depending on relapse kinetics specific to each type of AML. For leukemia with slow relapse kinetics such as favorable risk core-binding factor or NPM1*mut* disease, peripheral blood testing would be adequate[37]. With the tremendous molecular heterogeneity of AML, it is unlikely that a single method or follow-up strategy would encompass clinically relevant monitoring of MRD. Rather, detection of

specific markers prospectively with outcomes of risk-adapted therapies might answer definitively the prognostic value of MRD. What has been clearly demonstrated is that patients who are MRD positive at transplant are at higher risk of relapse than those who are MRD negative, regardless of cytogenetic risk or patient age[38]. The use of an MRD risk-adapted approach in elderly AML patients may be able to identify patients for appropriate clinical trials, for example, MRD positive patients could be enrolled in trials studying post-transplant maintenance while patients with higher risk of NRM could be enrolled in trials evaluating novel GVHD prevention strategies.

Strategies to mitigate risk of relapse

Although RIC allo-HSCT has provided access to a curative therapy for patients older than 60 years, it is associated with a relapse rate as high as 40–50%[22]. MRD monitoring and post HSCT maintenance strategies were essential to pre-emptively address the problem of relapse[39, 40]. Due to the increasing recognition of the value of MRD, attention has been focused on MRD monitoring in both the pre- and post-transplant settings resulting in studies of most appropriate conditioning regimens as well as pre-emptive treatment of relapse and treatments for frank relapse after allo-HSCT.

Hypomethylating agents and the immunomodulatory drug, lenalidomide, have been the best studied strategies, either as single agents or in combination with DLI. These drugs are also appealing in an elderly population because they are routinely used and fairly well tolerated therapies in an older demographic. Treatment with lenalidomide was associated with a 60% incidence of GVHD[41]. Multiple groups have evaluated azacitidine as a single agent or in combination with DLI[42–45]. Complete and partial remissions have been observed along with conversion from mixed chimerism to full donor chimerism. Goodyear et al reported that regulatory T cells were expanded with azacitidine resulting in decreased incidence of GVHD while preserving GVL[46]. This was also reported by Schroeder et al in their population of patients treated with azacitidine and DLI[47]. While these studies addressed frank relapse, an approach studying CD34 chimerism has been pioneered by the German group[48]. Platzbecker et al used azacitidine for imminent relapse defined as CD34 chimerism <80%. Over 80% of patients responded with increase in donor chimerism but 65% eventually relapsed indicating a need for evaluation of novel agents in the maintenance setting.

The use of decitabine maintenance following allo-HSCT has also been evaluated. Pusic et al treated 22 patients in CR following allo-HSCT with various doses of decitabine (5, 7.5, 10, and 15mg/m^2/day × 5 days every 6 weeks) with no maximum tolerated dose reached[49]. Nine of 22 patients completed all 8 planned cycles of treatment and all remained in CR at follow-up. Of the remaining 13 patients, only 4 were alive at follow-up with 3 in CR and 1 with CNS relapse. No assessment of MRD was made but retrospectively, the authors felt that 2 of the relapsing patients were already exhibiting signs of imminent relapse at the time of enrollment.

For older AML patients, improvement in detection of MRD and its impact on relapse risk will be crucial in planning their treatment course. Elderly patients without detectable disease at transplant may be able to avoid the greater toxicity associated with higher-intensity conditioning while deriving the same benefit of transplant via RIC. On the other hand,

patients with detectable disease will be better equipped to make decisions about their treatment based on not only the risk of TRM but potentially a more accurate representation of relapse risk. Further prospective study is certainly necessary to definitively reach these conclusions.

Cellular-based immunotherapy without transplant

Another area of research has been infusion of NK cells outside of the setting of allo-HSCT. While this paper focuses on the treatment with allo-HSCT, exploring cellular-based immunotherapies like adoptive transfer of NK cells is a logical extension of our knowledge of immune function in AML and reconstitution of the immune system following allo-HSCT. In a promising first-in-human phase I trial, nine patients with relapsed/refractory AML were conditioned with fludarabine and cyclophosphamide then received infusion of pre-activated NK cells[50]. Of the nine, four achieved CR with or without count recovery and the overall response rate was 55%. The median age was 71 (60–77 years). Trials evaluating expanded or in vivo cytokine activated NK cells for elderly patients outside of a transplant setting are being evaluated including at our institution (ClinicalTrials.gov Identifier: NCT02316964).

Why has there not been a prospective randomized trial to document efficacy of allo-HSCT?

Three major advances have dramatically expanded access to allo-HSCT for patients >60 years: (i) Allele based typing of matched unrelated donors and increasing use of related haploidentical donors leading to better donor selection and improved outcomes, (ii) increasing use of reduced-intensity conditioning regimens, and (iii) improvement in supportive care with antifungals and transfusions. These advances have resulted in improved survival rates as demonstrated by retrospective review of the transplant program at FHCRC[51]. Comparison of cohorts transplanted between 1993–1997 and 2003–2007 demonstrated improvement in OS despite a significant increase in the median patient age (37.4 years v. 47.2 years) with a maximum age at transplant of 78.9 years more recently compared with only 67.8 years in the previous decade. It is now no longer a question of donor availability but one of efficacy of allo-HSCT over conventional chemotherapy in reducing relapse risk. The role for prospective trials is as important as ever, especially in the areas of MRD-directed interventions and immunotherapies that may potential spare toxicities associated with traditional cytotoxic chemotherapy.

With increasing recognition of the molecular heterogeneity of AML and prognostic value of mutations, a prospective randomized study would require hundreds of patients and would be difficult to accrue. The German AML Study Group recently completed a prospective study (AML96) examining the feasibility of a risk-adapted post-remission treatment strategy including related and unrelated allo-HSCT for high risk AML patients and related allo-HSCT and auto-HSCT for standard risk AML patients in a multi-center setting (ClinicalTrials.gov Identifier: NCT00180115). This multi-center study should provide insights into long term survival in different cytogenetic groups. The aforementioned BMT-CTN 1101 comparing haploidentical and UCB transplants for patients without a suitable matched donor should also contribute further insight into alternative donor sources.

Conclusion

Reduced-intensity transplant has broadened access to curative therapy for older patients with AML. Increasing understanding of the molecular heterogeneity of AML along with the knowledge of consistently lower response rates in elderly AML will likely result in more transplants in older patients. Chronological patient age is no longer a “hard” contraindication to transplant, rather objective measures of comorbidities such as the HCT-CI and functional measures such as the CGA provide a better picture of the risk of TRM. While transplant can be safely performed in patients >60 years, relapse remains a major cause of post-HSCT mortality. Clinical trials evaluating novel immunomodulatory drugs for treatment of relapse or for use in the maintenance setting is an area of active research. Though hurdles remain for prospective randomized trials evaluating efficacy of allo-HSCT in AML, participation in clinical trials remains our best hope for improving transplant outcomes for adult AML patients.

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Practice Points

- Physiologic measures, rather than chronologic age, are likely better predictors of tolerance of chemotherapy and allo-HSCT.
- Increasing use of alternative donor sources, the advent of RIC, and improvements in supportive care have made allo-HSCT more accessible to appropriately selected elderly AML patients.
- Allo-HSCT outcomes have improved significantly over time despite an aging population.

Research Agenda

- Improving pre-transplant functional status assessment
- Incorporation of risk-adapted treatment strategy based on the presence or absence of MRD prior to allo-HSCT
- Role for post-transplant maintenance therapy in patients at highest risk for relapse

Table 1

Summary of reduced-intensity HSCT trials in AML.

Publication	Type of study	Number of patients	Age range (years)	Follow-up (months)	Incidence of relapse (%)	NRM (%)	DFS (%)	OS (%)
Sorror[5]	Retrospective	372	60–75	55	41	27	32	35
Farag[6]	Retrospective	94	60–70	36	32	36	32	37
Koreth[52]	Retrospective	158	60–71	34	54.6	10	35	46
Chevallier[53]	Retrospective	600	60–65	23.7	25	32.3	46.2	49.2
Devine[22]	Prospective	114	60–74	40	47	14	39	46
Niederwieser[54]	Prospective	132	60–74	96	40.5	28.7	32.5	35.5

Table 2

Transplant outcomes between the alternative graft sources with reduced-intensity conditioning regimens using institution-specific conditioning regimens.

Study	Total patients	AML/MDS patients	Incidence of Grade II-IV aGVHD (%)	Incidence of cGVHD (%)	1-year NRM (%)	1-year relapse (%)	1-year OS (%)
Haplo							
Ciurea[55]	28	22	19	20	40	40	22
Luznik[56]	68	27	34	5	15	51	46
Brunstein[57]	50	22	32	13	7	45	62
UCB							
Brunstein[57]	50	29	40	25	24	31	54
Brunstein[58]	110	41	59	23	26*	31*	45*
Cutler[59]	32	13	9.4	12.5	34¶	34¶	53¶
MMUD							
Pidala[60]	45	24	64	43	26	23	55
Koreth[61]	23	10	13	41	0	29	75

*3-year outcome data, 1-year was not available

¶2-year outcome data, 1-year was not available

Table 3

Studies defining minimal residual disease detection for various markers.

Study	Design	Patients	MRD detection method	Findings
LAIP				
Buccisano et al[35]	Observational Assessed post-induction and post-consolidation	>60 yo: 61 <60 yo: 149	■ MFC ■ >0.00035 RLCs	■ Elderly patients less likely to reach MRD negative status post-consolidation compared to younger (11% vs. 28%, p=0.009) ■ MRD negativity resulted in longer 5-year DFS for both elderly (57% vs. 13%, p=0.0197) and younger patients (56% vs. 31%, p=0.0017). ■ 5-year CIR higher in MRD positive elderly patients (83% vs. 42%, p=0.045) and in younger patients but not statistically significant (59% vs. 24%); Two-fold higher 5-year CIR in elderly MRD negative compared to younger MRD negative, but did not reach statistical significance
*Willekins et al[62]	Retrospective PB and BM samples on CBF-2006 trial	94	■ RQ-PCR RUNX1/AB L1 ratio >0.001%	■ BM molecular CR in 30%; not predictive of risk of relapse (9% MRD+ BM for 2 years while remaining in morphologic CR and MRD− PB) ■ Persistent PB molecular CR over 2 year follow-up was associated with a lower risk of relapse (4-year cumulative incidence, 8.2%) ■ PB molecular relapse, confirmed on a subsequent sample, predicted hematological relapse (4-year cumulative incidence, 86.9%) within a median time interval of 3.9 months
CBFA [t(8;21)]				
Hoyos et al[63]	Retrospective Samples from AML99 and AML03	150 (40 were >50 yo)	■ RQ-PCR ■ AML1/ET O <40 copies/10^4 ABL cells ■ CBFβ/MYH11 <39 copies/10^4 ABL cells	■ Age and MRD status were not directly compared in statistical analysis ■ Age >50 years was associated with lower CR rates (72% vs. 94%, p=0.002) and was an adverse factor in terms of OS ■ High copy number MRD after induction for both AML1/ETO and CBFβ/MYH11 was associated with increased relapse by multivariate analysis
*Kronke et al[64]	Retrospective Monitoring of PB and BM samples from AMLHD98A and AMLSG 07-04	245	■ RQ-PCR ■ NPM1/AB L1 recorded as continuous variable	■ MRD negativity after double induction associated with cumulative incidence of relapse (CIR) of 6.5% at 4 years compared to 53% for MRD positivity (P<0.001); OS was 90% v. 51%, respectively (p = 0.001) ■ MRD negativity after completion of therapy associated with CIR of 15.7% compared to 66.5% for MRD positivity (p<0.001). ■ In multivariate analysis, higher NPM1 transcript levels were a significant factor for risk of relapse and death both after double induction and completion of consolidation
NPM1				

Study	Design	Patients	MRD detection method	Findings
*Ivey et al[65]	Samples from NCRI AML17 trial; 2009–2012 development phase (retrospective), 2012–2014 validation phase (prospective, interventional)	346	■ RQ-PCR ■ NPM1/A BL1 ratio >0.001%	■ 15% with PB NPM1 positivity after second cycle of chemotherapy, associated with increased risk of relapse after 3 years (82% vs. 30%; hazard ratio, 4.80; 95% CI 2.95 to 7.80; P<0.001) and a lower rate of survival (24% vs. 75%; hazard ratio for death, 4.38; 95% CI, 2.57 to 7.47; P<0.001) ■ MRD only independent prognostic factor for death in multivariate analysis (hazard ratio, 4.84; 95% CI, 2.57 to 9.15; P<0.001) ■ Rising NPM1 transcript reliably predicted relapse ■ Preleukemic clone mutations remained detectable during ongoing remission after chemotherapy, but NPM1 mutations were detected in 69 of 70 patients at the time of relapse and provided a better marker of disease status.
*Grunwald et al[66]	Retrospective Evaluation of new assay for FLT3 BM samples only	28	Tandem Duplication-PCR compared with standard PCR	■ By TD-PCR, 25% of patients were MRD positive on day +60 BM but all tested MRD negative by standard PCR ■ 86% (6 of 7) post-HSCT MRD positive patients relapsed while only 10% (2 of 21) of MRD negative patients have relapsed ■ 65% (13 of 20) MRD positive patients converted to negative post-HSCT and only 1 has relapsed
WT1				
*DiGrazia et al[67]	Prospective, post allo-HSCT; MRD triggered IT (cessation CsA or DLI)	207	■ RQ-PCR ■ Group 1: ≥180 WT1 copies/10^4 ABL cells ■ Group 2: ≥100 WT1 copies/10^4 ABL cells	■ Cumulative incidence of relapse in patients receiving IT: 76% in group 1 vs. 29% in group 2 (p = 0.006) ■ In group 1, 35% receiving IT achieved MRD negativity and 23% remain in hematologic remission up to 10 years from DLI. In group 2, 96% achieved MRD negativity and 74% remain in hematologic remission