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Leukemia (PH Wiernik, Section Editor)

Allogeneic Hematopoietic Stem Cell Transplantation for Older Patients With Acute Myeloid Leukemia

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Opinion statement

Acute myelogenous leukemia (AML) in the elderly is complex and has a poor prognosis, often characterized by higher risk cytogenetic and molecular features compared to that in younger patients. Rates of transplant have been limited by concern related to non-relapse mortality, as older patients have historically been considered medically unfit for the transplantation process. Reduced-intensity conditioning (RIC) for hematopoietic stem cell transplantation (HSCT) has been shown to provide similar efficacy to myeloablative methods, with decreased non-relapse mortality in the elderly and improved efficacy over non-transplant approaches with cytotoxic chemotherapy alone. Targeted non-cytotoxic and modified cytotoxic agents have emerged to further improve transplant outcomes for older AML patients. Validated comorbidity indices are useful tools to assess an individual's fitness for undergoing HSCT rather than chronological age alone. We believe HSCT is the primary curative treatment approach for many older AML patients, taking into account risk and comorbidities, particularly given the tendency of leukemia in this population to harbor an unfavorable disease profile. We use RIC and advocate for the addition of targeted agents if applicable. With continuing data in support of transplant for older AML patients, we anticipate that transplant rates in this population will continue to rise.

Introduction

Acute myeloid leukemia (AML) results from the proliferation of abnormal populations of clonal hematopoietic cells in the bone marrow, with the potential for spread into the blood and other organ systems. Like many malignancies, AML is more common in the older population, and the incidence of AML continues to rise. Approximately 55–75% of newly diagnosed AML occurs in patients over the age of 65 [1, 2], with a median age at diagnosis of 69 years [3].

Elderly AML, typically referring to AML in patients over the age of 60 [4], is a complex entity that presents difficult management decisions for hematologists. Although overall survival (OS) rates for AML have improved over the years, the survival for older patients continues to remain poor [3]. Several epidemiological studies have demonstrated 5-year survival rates of less than 10% in patients over age 60, whereas younger patients achieve rates up to 50% [2, 4, 5].

The conventional treatment approach to AML consists of induction chemotherapy followed by post-remission consolidation chemotherapy, followed by the consideration of allogeneic hematopoietic stem cell transplant (HSCT). Allogeneic transplant is a curative treatment modality for patients with AML, used in patients with cytogenetic and molecular factors associated with a high risk of recurrence. AML in older patients tends to harbor less favorable cytogenetic and molecular patterns than in younger patients, resulting in a higher risk for chemoresistance and relapse [6–8]. Therefore, elderly patients could benefit the most from the immunotherapeutic potential of allogeneic transplant.

This article aims to review recent literature surrounding the use of allogeneic HSCT in the older AML population, including outcomes of standard allogeneic HSCT, conditioning strategies, cytogenetic and molecular genetic considerations, comparison of outcomes achieved by conventional and novel agents without transplantation to outcomes after allogeneic HSCT, and newer therapies that may allow more elderly patients to become candidates for allogenic HSCT.

The challenge of applying the transplant strategy to the older population

In the entire population of AML patients, HSCT has been shown in large-scale analyses to be the most successful post-remission management strategy to prevent relapse [9]. However, the intensive conditioning regimens typically used to induce long-term leukemia-free survival (LFS) and complete remission (CR) can lead to increased toxicity in older patients and, ultimately, poorer outcomes [10]. The balance between the potential for treatment efficacy and toxicity is nuanced; a hematologist must consider many parameters in deciding whether to pursue allogeneic HSCT for an elderly patient with AML.

Conditioning regimens for AML in older patients

HSCT in the elderly AML population can be considered in the setting of post-remission therapy after complete response, post-induction therapy with residual disease present (although less efficacious), or after salvage therapy in relapsed/refractory disease. The conditioning regimen for HSCT is an important treatment decision. Conditioning therapies were initially developed to achieve

maximal myeloablation of the bone marrow cell population, in order to both eradicate disease and reduce the risk of rejection by reducing host immune function. Conventional myeloablative conditioning (MAC) regimens dating back to the 1970s provide high doses of chemotherapy, with or without total body irradiation (TBI) [11]. In the past, allogeneic HSCT was reserved for patients under the age of 60 mostly due to concerns of higher non-relapse mortality (NRM) in older patients from infectious and hematologic complications, superimposed on the potential morbidity from graft-versus-host disease (GVHD) [12]. However, with the development of reduced-intensity conditioning (RIC) regimens, older patients with higher comorbidity indices [13] have increasingly been able to tolerate HSCT, and this treatment modality has been considered more frequently [12, 14].

RIC protocols typically consist of fludarabine-based chemotherapy, with or without TBI, with chemotherapy dose and/or radiation dose reduced by at least 30% [11]. RIC relies on the post-transplant graft-versus-malignancy effect to compensate for the lower intensity chemotherapeutic response [15]. Furthermore, the increased levels of immunosuppression incorporated into non-myeloablative transplantation regimens may have the potential for better engraftment. Meta-analyses have demonstrated a lower risk of GVHD using reduced-intensity methods, possibly due to less chemotherapy-induced cell damage [16]. Despite NCCN guidelines supporting the use of RIC allogeneic HSCT in patients ≥ 60 years old with post-induction CR [17], allogeneic HSCT is met with concern as a suitable treatment option for this population. Comparisons of RIC-HSCT with MAC-HSCT have shown similar rates of relapse, although most prospective comparisons have included patients younger than 60 [18]. Retrospective data have suggested that non-myeloablative transplants may be as effective as myeloablative transplants in patients over age 50 [19, 20]. However, such studies are hypothesis-generating, rather than practice-changing, due to the inherent selection bias of retrospective studies.

Data from a phase III trial reported by Bornhauser et al. support the use of RIC-HSCT for the non-elderly AML population when compared to MAC-HSCT. This trial demonstrated that RIC resulted in reduced toxic effects compared with standard conditioning, without impacting efficacy. The majority of patients included were between 41 and 60 years of age. Patients who received RIC demonstrated fewer early in-hospital deaths and lower 12-month NRM than those who received standard conditioning. Most importantly, the relapse incidence (RI) did not differ significantly between conditioning groups, resulting in similar disease-free survival (DFS) and OS. Although this study did not include patients over the age of 60, it provided prospective data on the general outcome of RIC [21]. More recently, Devine et al. published a prospective phase II Cancer and Leukemia Group B (CALGB) trial that enrolled patients from 2004 to 2011 and included RIC-HSCT in 114 patients with AML between the ages of 60–74 with Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2 [22••]. This was the first major prospective investigation of HSCT in older AML patients. The conditioning regimen consisted of fludarabine 30 mg/m^2 for 5 days on days 7 through 3, with busulfan 0.8 mg/kg every 6 h for eight doses on days 4 and 3. Some patients also received antithymocyte globulin. Two-year LFS and OS were 42% and 48%, respectively. NRM was 15% at 2 years. There was a 44% cumulative incidence of relapse, which occurred at a median of 194 days (range 15–2041 days) after transplantation. The

cumulative incidence of grade ≥ 3 acute GVHD and extensive chronic GVHD was 3% and 11%, respectively. The cause of death was relapse in 75% of patients, followed by chronic GVHD in 9% of patients. Grade ≥ 3 toxicities were reported in 68% of patients. There were no primary graft failures, although two patients developed secondary graft failure requiring re-transplantation. The authors conclude that RIC-HSCT is well tolerated in the elderly population and confers better outcomes compared to historical outcomes of 2-year OS less than 20% with conventional non-HSCT therapy in similar patient populations [23]. The percentage of NRM (15%) is particularly encouraging, as it is similar to that in the general allogeneic HSCT population. Unfortunately, the distribution of baseline ECOG performance status in the patients was not reported, which would be useful to assess for selection bias in recruitment. These data represent our most up-to-date insight on RIC-HSCT in the elderly until a phase III trial is published comparing RIC to MAC or non-transplant therapy in this population.

Comparisons of AML therapy comparing RIC-HSCT to standard-dose chemotherapy without allogeneic HSCT have been limited to retrospective analyses. The data suggest that RIC-HSCT may compare favorably to standard-dose chemotherapy without transplantation [23–28]. There are relatively few studies analyzing this comparison in elderly patients. Farag et al. [28] examined AML patients specifically between ages 60–70 years, comparing outcomes in patients who underwent RIC with allogeneic HSCT ($n = 94$) to results from two prior randomized studies of patients who underwent induction and post-remission chemotherapy with or without an additional agent (interleukin-2 or Bcl-2) according to CALGB protocols ($n = 96$) [29, 30]. In these older patients, allogeneic HSCT was associated with significantly greater likelihood of LFS at 3 years (32% versus 15%) and lower RI at 3 years (32% versus 81%) [28]. This type of analysis of course has multiple limitations due to its retrospective nature, for example, selection bias and inability to conduct a donor-versus-no donor analysis. A prospective phase III trial by the European Group for Blood and Marrow Transplantation (EBMT) along with several cooperative groups was initiated, comparing consolidation RIC-HSCT to conventional consolidation chemotherapy without HSCT (NCT00766779). The trial included patients 60–75 years of age with AML in first CR. The RIC regimen included low-dose TBI, which was given to some patients on CALGB protocols in the retrospective study by Farag et al. [28] but was not included in the prospective phase II trial by Devine et al. [22••]. The trial was terminated early after accrual of 126 patients but may still provide prospective data comparing HSCT to conventional consolidative therapy and more information regarding the use of low-dose TBI in conditioning regimens for the elderly.

Application of novel agents to transplant conditioning

A novel liposomal formulation of cytarabine plus daunorubicin (CPX-351) at a molar ratio of 5:1 was compared to standard induction 7 + 3 chemotherapy in a phase III trial of secondary AML in elderly patients ages 60 to 75. The hazard ratio for survival of 0.69 ($p = 0.003$) favored CPX-351, with a superior CR/CRi rate of 47% compared to 33% ($p = 0.016$). Toxicity was similar in both groups [31•]. An exploratory analysis of this trial evaluated HSCT-related outcomes for the two study arms. Of the 309 patients enrolled into the trial, 91 patients who

achieved CR/CRi went on to receive allogeneic HSCT (34% from the CPX-351 arm, 25% from the 7 + 3 arm, $p = 0.098$). Rates of CR/CRi going into transplant were similar between both groups; however, the CPX-351 group had doubled the percentage of patients over the age of 70 (31% versus 15%). Kaplan-Meier estimates demonstrated improved post-transplant survival in patients who received induction CPX-351, with HR 0.46 ($p = 0.0046$) [32]. These findings indicate that CPX-351 is a more effective bridge to transplant than standard chemotherapy in older patients with poor prognosis due to secondary AML [31•, 32].

In the modern era, sophisticated radiation therapy systems have been developed for delivery of TBI, such as radioimmunotherapy. This technique integrates a medically targeted approach to deliver radiation more directly to hematopoietic cell populations through monoclonal antibodies that target progenitor leukocyte antigens (e.g., anti-CD33, anti-CD45, and anti-CD66) [33]. Lauter et al. published results from a phase II prospective trial in which older AML patients received anti-CD66 antibodies conjugated to 188-Rhenium along with RIC (fludarabine and busulfan) plus alemtuzumab (for in vivo T cell depletion) prior to allogeneic HSCT. This trial compared 22 AML patients (ages 54–76, median 65) who received the study regimen to a historical control group who received the same RIC regimen alone. The study arm showed lower rates of severe acute GVHD and lower systemic toxicity, particularly lower hepatotoxicity. However, the estimated relapse rate and survival were similar between the two groups [34]. Subsequently, a group from the same institution performed a phase II study to determine whether a dose reduction of alemtuzumab would facilitate an improved relapse rate via a mechanism of less stringent T cell depletion to foster enhanced graft-versus-malignancy effect. There were no differences in relapse or mortality [35]. Thus, to date, radioimmunotherapy plus RIC in the elderly has been shown to be feasible and may reduce acute GVHD but has not been shown to favorably influence relapse or survival.

Impact of cytogenetics and molecular mutations on transplant outcomes in the older AML population

AML is a heterogeneous disease, with a spectrum of severity based on cytogenetic and molecular profiles. Oran et al. [36•] retrospectively compared morbidity and mortality endpoints between older and younger AML patients receiving HSCT, and further subdivided each population based on disease characteristics. The study analyzed 464 patients with AML in CR1 who underwent allogeneic HSCT from 2001 to 2014; of these patients, 110 were ≥ 60 years old. Patients were separated into groups according to the modified European Leukemia Net (ELN) classification, which included favorable (FLT3-ITD wild-type), intermediate-I (normal cytogenetics, FLT3-ITD mutant), intermediate-II (cytogenetic abnormalities not characterized as favorable or adverse), and adverse (any number of adverse deletions, translocations, or rearrangements). The outcomes among elderly patients aged ≥ 60 years were compared to those among younger patients within each group. Not surprisingly, older patients generally had poorer 3-year LFS and higher RI. This was true

for all risk groups except intermediate-I (normal cytogenetics, FLT3-mutant) in which the older age group actually showed no significant differences compared to younger patients in terms of RI (28% versus 36%), LFS (50% versus 53%), and OS (55% versus 57%, respectively). The authors found this result striking; however, the sample size of elderly intermediate-I patients in the retrospective study was small, consisting of only 19 patients. In addition, the modified ELN for cytogenetically normal (CN) patients is based on FLT3-ITD status without the status of other mutations (NPM1, CEBPα, IDH, ASXL1). Nonetheless, older patients with the FLT3-ITD mutation demonstrated quite impressive LFS after allogeneic HSCT (51% at 3 years), comparable to their younger counterparts (53% at 3 years). The authors concluded that allogeneic HSCT may be a particularly good treatment choice for these older patients, but further verification is required that should include larger studies to validate the modified ELN as an appropriate tool for risk classification in older AML patients [36•].

Medical therapy alone for elderly patients with FLT3-mutated AML does not appear to confer longer survival at this time. Whitman et al. [23] examined patients aged ≥ 60 years with this mutation, treated with cytarabine-based induction regimens from CALGB protocols, followed by consolidation, accompanied by additional investigational drugs in some patients. Patients had 10% likelihood of being disease-free at 3 years, and 14% likelihood of survival at 3 years. Patients between ages 60–69 years with the FLT3-ITD mutation had poorer survival and treatment outcomes compared to their wild-type age-matched counterparts, with the exception of patients aged ≥ 70 years. The authors concluded that patients aged 60–69 may benefit from the more aggressive therapies afforded to younger patients in order to combat the higher mortality associated with harboring the FLT3-ITD mutation. Of note, recent results of a phase III trial evaluating the addition of midostaurin to standard induction 7 + 3 chemotherapy demonstrated a survival advantage when incorporating the drug into the standard chemotherapy regimen, but patients aged 60 years and above were not included in the trial [37].

A summary of the prominent studies described is presented in Table 1.

Patient-specific considerations for HSCT

While we tend to consider elderly AML as patients above the age of 60, a patient's complete medical picture is more clinically relevant than chronological age alone. Indices for age combined with medical comorbidities have been developed to aid physicians in calculating a patient's biologic age. A commonly used index, called the hematopoietic cell transplantation comorbidity index (HCT-CI), scores comorbidities of all major organ systems and has become a useful tool in decision-making. The prospective validation of this index is currently ongoing [13].

Several studies have been published to further aid physicians in deciding whether to offer transplant. The EBMT transplantation risk score, initially established for chronic myeloid leukemia, has now been expanded to assess risk score for multiple hematologic disorders that can be treated with transplant, including AML. A risk score from 0 to 5, based on five criteria, is assigned a score of 0, 1, or 2: patient age class (< 20, 20–40, or > 40 years old), disease stage (early, intermediate, or advanced), donor type (HLA-identical sibling or

Table 1. Summary of key studies and results for hematopoietic stem cell transplant in elderly AML patients

Study authors	Year of study data	Age range	No. of patients ≥ 60/total patients	Type of study	Subject of study	Result
McClune et al. [14]	1995–2005	40–79	195/545	Retrospective	Outcomes after RIC-HSCT for different age cohorts: 40–54, 55–59, 60–64, > 65	Comparing age cohorts: • No difference in NRM at 1 year ($p = 0.29$) or 4 years ($p = 0.66$) • No difference in RI at 2 years ($p = 0.87$) • No difference in LFS or OS at 2 years ($p = 0.81$, $p = 0.74$, respectively)
Alyea et al. [19]	1997–2002	50–71	Unknown/152	Retrospective	Non-MAC vs. MAC in patients > 50	• Improved NRM in non-MAC vs. MAC ($p = 0.01$) • Trend for higher RI in non-MAC ($p = 0.052$) • Trend for improved OS in non-MAC at 2 years ($p = 0.06$) • No difference in PFS at 2 years ($p = 0.24$)
Bornhäuser et al. [21]	2004–2009	18–60	0/195	Prospective phase III	RIC-HSCT vs. MAC-HSCT in non-elderly patients	RIC-HSCT showed: • Decreased NRM at 1 year ($p = 0.05$), but no overall difference in NRM ($p = 0.21$) • No difference in RI ($p = 0.74$), LFS (0.47), or OS ($p = 0.29$) • Decreased in-hospital mortality for patients 41–60 ($p = 0.006$)
Devine et al. [22••]	2004–2011	60–74	114/114	Prospective phase II	RIC-HSCT for elder patients	Outcomes at 2 years: • OS 48% • LFS 42% • RI 44% • NRM 15%
Whitman et al. [23]	Duration of CALGB trials: 9720 (1998–2002), 9420 (1995–1997), 8525 (1982–1990), 8923	60–83	243/2243	Retrospective	CN FLT3-ITD vs. FLT3-WT AML patients > 60 treated with	FLT3-ITD patients ages 60–69 had: • Shorter LFS ($p = 0.007$) • Shorter OS ($p < 0.001$)

Table 1. (Continued)

Study authors	Year of study data	Age range	No. of patients ≥ 60/total patients	Type of study	Subject of study	Result
	(1990–1993), 10,201 (2003–2006)				medical therapy without HSCT	• Twice the risk of relapse or death • No difference in outcomes between FLT3-ITD vs. WT in patients > 69 years old Outcomes at 3 years for WT patients ages ≥ 60: • LFS 18% • OS 23%
Mohty, et al. [23]	1993–2003	26–65	Unknown/95	Retrospective	RIC-HSCT vs. chemotherapy	RIC-HSCT at 7-year analysis showed: • Improved LFS ($p = 0.0002$) • Improved OS ($p = 0.003$) • TRM in 3 patients (12%)
Russell et al. [24]	2002–2009	35–64	Unknown/1701 (679 patients 55–64)	Retrospective, first endpoint from the study	RIC-HSCT vs. chemotherapy	RIC-HSCT at 5 years showed: • Lower RI ($p = 0.002$) • No difference in OS ($p = 0.2$)
Russell et al. [24]	2002–2009	35–44	0/141	Retrospective, second endpoint from the study	RIC-HSCT vs. MAC-HSCT	RIC-HSCT at 5 years showed: • No difference in RI ($p = 0.7$) • Improved OS overall (67% vs. 50%) but not significant when adjusted for donor type ($p = 0.11$) • Lower NRM ($p = 0.03$)
Kurosawa et al. [25]	1999–2006	50–70	Unknown/953	Retrospective	RIC-HSCT vs. chemotherapy	RIC-HSCT showed • Reduced RI (22% vs. 62%, $p < 0.001$) • Higher NRM (21% vs. 3%, $p < 0.001$) • Longer LFS (56% vs. 29%, $p < 0.001$)

Table 1. (Continued)

Study authors	Year of study data	Age range	No. of patients ≥ 60/total patients	Type of study	Subject of study	Result
						• Longer OS (62% vs. 51%, $p = 0.012$)
Farag et al. [27]	1998–2006	60–70	190/190	Retrospective	RIC-HSCT vs. chemotherapy (CALGB protocols 9720 and 10,201)	RIC-HSCT at 3 years showed: • Significantly longer LFS (32% vs. 15%, $p = 0.001$) • Lower RI (32% vs. 81%, $p < 0.001$) • Higher but not significant OS (37% vs. 25%, $p = 0.08$) • Higher NRM (36% vs. 4%, $p < 0.001$)
Lancet et al. [30, 31]	2012–2014	60–75	309/309	Prospective phase III	CPX-351 induction versus 7 + 3 induction for secondary AML	CPX-351-based induction showed: • Reduced 100-day mortality post-transplant (9.6% vs. 20.5%) • Improved OS ($p = 0.46$) • Higher rates of CR (47.7% vs. 33.3%, $p = 0.016$) • Similar grade 3–5 adverse events (92% vs. 93%)
Lauter et al. [32]	2003–2006	44–76	Unknown/44	Prospective phase II	RIC-HSCT with vs. without	radioimmunotherapy
RIC with	radioimmunotherapy showed non-significant improvements in: • Median OS (11.1 vs. 8.45 months, $p = 0.772$) • Median LFS (11.8 vs. 4.87, $p = 0.697$) • Similar RI (~41% each) • NRM (13% vs. 32%, p value not reported)					
	2001–2014		110/464	Retrospective		

Table 1. (Continued)

Study authors	Year of study data	Age range	No. of patients ≥ 60/total patients	Type of study	Subject of study	Result
Oran et al. [34]		18 to > 67			RIC-HSCT by modified ELN risk profile and by age < 60 vs. > 60	Older patients > 60 vs. < 60 at 3 years had mostly poorer but still impressive outcomes: • LFS (20.2–49.8% vs. 44.6–67.8%) • OS (19.7–55.3% vs. 52.9–70.4%) • RI (31.1–49% vs. 15.4–39.8%) • True for all risk groups except for CN-FLT3 which showed similar LFS (51% vs. 53%), RI (28 vs. 36%), and OS (55% vs. 75%) Among older > 60 patients: • TRM 19.4% at 1 year • Higher risk profile group OS 37.6% at 3 years

RIC reduced-intensity conditioning, *HSCT* hematopoietic stem cell transplant, *NRM* non-relapse mortality, *RI* relapse incidence, *LFS* leukemia-free survival, *OS* overall survival, *MAC* myeloablative conditioning, *PFS* progression-free survival, *CALGB* Cancer and Leukemia Group B, *CPX-351* liposomal cytarabine-daunorubicin, *CR* complete remission, *CN* cytogenetically normal, *FLT3-ITD* Fms-like tyrosine kinase 3-internal tandem duplication, *WT* wild-type, *AML* acute myeloid leukemia, *TRM* treatment-related mortality, *ELN* European LeukemiaNet classification

unrelated donor), and donor-recipient sex match/mismatch (specifically, an increased score for a male recipient with female donor). The authors propose a risk-benefit scheme for AML based on disease classification: for low-risk AML, transplant is considered worthwhile only if the risk score is low at 0–1; for intermediate-risk disease, a score of up to 3 should be considered for HSCT; and for high-risk disease, any score (0–5) should be considered for transplant. This risk scheme does not specifically consider comorbidities, and notably places all patients over age 40 in a high-risk category [38]. Focusing on the older population, Sorror and Etsey published a composite analysis of risk assessment tools and known risk factors related to outcomes after HSCT. They concluded that factors with strong evidence for impact on outcomes include the HCT-CI score, cytogenetics and specific mutations (e.g., FLT3), disease status (e.g., CR1 vs. CR2 or relapsed disease), and performance status. Age alone was not shown to be an independent poor prognostic factor. Ultimately, the authors provide a general recommendation that the only risk groups who would not benefit from HSCT over chemotherapy are those with exceptionally high HCT-CI scores (of 8 or higher) combined with additional risk factors [39].

Apart from survival and relapse outcomes, it is important to consider quality of life (QOL) with respect to transplant. A study assessing transplant type and the associated QOL examined allogeneic HSCT, autologous HSCT, and intensive chemotherapy for patients with AML. The findings demonstrated significant relative decrease in QOL for those undergoing allogeneic HSCT [40].

Donor source for transplant in elderly AML

Autologous transplant has the advantage of obviating the need for long-term immunosuppressive therapy. However, the disadvantages of autologous transplant include the absence of graft-versus-leukemia effect, and the impact of preparative conditioning on organ function that might preclude further therapy should there be a late relapse. A large retrospective study of patients with AML aged 50 and older compared autologous peripheral blood stem cell transplantation (PBSCT) to RIC allogeneic human leukocyte antigen (HLA)-identical PBSCT. Even though the allogeneic group had more advanced disease at the time of transplant, patients receiving allogeneic transplant showed a lower risk of relapse without increase in NRM, and superior survival [41].

Additional factors that influence the use of allogeneic HSCT in the elderly include the source of stem cells, strategy of transplantation, and post-transplant QOL. Identifying HLA-matched donors for the elderly remains a challenge compared to younger patients, due to the higher chance of having a sibling who is no longer alive or has comorbidities that render them unable to provide a graft. The rise of haploidentical transplantation using post-transplant cyclophosphamide regimens has increased the number of potential donors for elderly patients by including their children as potential donors. Retrospective data for patients over the age of 50 with standard- to intermediate-risk cytogenetics suggest that donor type may not be a major prognostic factor, although there may be some importance in the highest risk groups [42]. Several analyses have sought to assess outcomes based on donor type, stratified as haploidentical donor, matched-related donor (RD), and matched-unrelated donor (UD) [43]. Results have been inconsistent. An analysis of AML and

myelodysplastic syndrome patients with median age 60 reported similar outcomes for the three groups, with a trend for improved DFS favoring matched-RD or matched-UD over a haploidentical donor ($p = 0.12$) [44]. A different study of these three donor types in patients over 55 years old with a variety of hematologic malignancies (approximately one-third AML) found improved outcomes favoring haploidentical and matched-RD. Specifically, patients who received a haploidentical donor demonstrated a trend for improved OS compared to matched-UD ($p = 0.08$), and significantly improved DFS ($p = 0.02$), NRM ($p = 0.01$), and incidence of severe GVHD ($p = 0.03$) [45]. One analysis in patients receiving grafts from PBSCs compared outcomes of haploidentical HSCT based on age cohorts (≤ 55, 55–65, and > 65 years), demonstrating worse survival in the oldest age cohort. However, when compared to a matched control cohort who underwent matched-UD HSCT, survival in the haploidentical cohort did not differ among patients with ages > 65 years. Despite inherent selection bias in such study design, it represents the potential to increase the rate of elderly HSCT by increasing the donor pool without reducing efficacy [46].

The source of cells being harvested—mobilized PBSCs versus bone marrow—is still being investigated. A large EBMT analysis of adult AML patients younger than age 60 demonstrated improved neutrophil and platelet recovery with PBSCT, but higher rates of chronic GVHD [47]. Similar findings were reported in a phase III trial that included 48 sites in North America, in which patients were under the age 65 years, half of whom had a diagnosis of AML. Two-year survival, acute GVHD, and relapse incidence were similar in patients randomized to transplantation via PBSCs versus bone marrow. However, graft failure was more frequent in the bone marrow group (9% vs. 3%, $p = 0.002$) and incidence of chronic GVHD was greater in the PBSC group (53% vs. 41%, $p = 0.01$) [48]. A Cochrane review on this topic had similar conclusions. NRM was lower in patients receiving PBSCT ($p = 0.02$). In intermediate-risk AML, LFS did not significantly differ by stem cell source; however, in advanced AML, LFS was improved in the PBSCT group. Unfortunately, this data is not specific to the elderly AML population; the review noted that many of the studies available excluded patients > 55 years old, with the oldest accepted patients 65 years old [49].

New strategies to reduce morbidity and NRM focus on reducing GVHD. Depletion of certain T cell subsets within the allograft is in early clinical development and may lead to improved QOL associated with allogeneic transplantation, thereby making hematologists less reluctant to consider transplantation in the elderly. Early studies of haploidentical allogeneic HSCT suggest that grafts depleted of T cell receptor (TCR) α/β-expressing cells have fast and stable engraftment, low rates of GVHD, and improved immune recovery [50]. A single-arm trial presented at the 2017 American Society of Hematology annual meeting demonstrated favorable clinical outcomes in adults undergoing HSCT with TCR α/β depletion [51]. Moreover, the alloreactivity of transplanted grafts has been attributed to naïve T cells. Single-arm studies of haploidentical HSCT grafts depleted of the naïve T cell subset CD45RA have shown rapid T cell reconstitution, absence of GVHD, and less infection-related mortality [52].

Effect of minimal residual disease for older AML patients undergoing HSCT

Elderly patients who achieve minimal residual disease (MRD)-negative CR prior to HSCT have been shown to achieve improved outcomes with respect to both survival and RI compared to MRD-positive elderly patients. Unfortunately, elderly AML patients are significantly less likely to reach a post-consolidation MRD negative state [53]. Walter et al. analyzed AML patients with MRD who underwent myeloablative and non-myeloablative conditioning, and assessed the interaction of MRD on outcomes, stratified by use of non-MAC or MAC. The non-myeloablative cohort, although not exclusively containing elderly AML patients, closely resembled this population, as the non-MAC cohort patients were significantly older, had increased comorbidities, and had more unfavorable cytogenetics. For patients going into transplant with CR but MRD-positive disease, non-myeloablative conditioning was associated with improved outcomes compared to MAC, with improved 3-year OS (41% versus 25%), longer LFS (33% versus 13%), lower RI (57% versus 63%), lower NRM (10% versus 23%), and lower acute grade 3–4 GVHD (0% versus 27%) [54]. These findings are encouraging for the treatment of MRD-positive older patients, who can be considered candidates for HSCT with non-MAC, which may lead to better outcomes for these patients.

Strategies for relapsed/refractory disease

Relapsed AML after first allogeneic HSCT is associated with poor survival rates. Remission is required prior to allogeneic transplantation to optimize the likelihood of long-term survival; however, remission rates in relapsed/refractory AML continue to be poor [55]. Current treatment options that give the possibility of long-term survival are donor lymphocyte infusion (DLI) or second allogeneic HSCT. Comparisons of second allogeneic HSCT to DLI are limited to retrospective series. The largest and most recent analysis evaluated 418 patients at multiple centers in Europe who received DLI or second allogeneic HSCT from 1992 to 2014. Patients who received DLI were older, had shorter time from first allogenic HSCT to relapse, and were less frequently in remission prior to receiving the allograft. Rates of 5-year OS were similar in each group (15% vs. 19%, $p = 0.86$). For patients who were in remission at the time of receiving the allograft, the 5-year RI for those who received DLI versus second HSCT was not significantly different (64% vs. 56%, $p = 0.64$). In patients who were not in remission at the time of receiving the allograft, the 5-year LFS was very poor, 10% vs. 6% in the DLI and second HSCT, respectively ($p = 0.03$). NRM was significantly lower with DLI compared to second HSCT (9% vs. 31%, $p < 0.0001$) [56]. Therefore, for the older population of patients who have relapsed after HSCT, DLI may be a favorable choice, as the morbidity of a second allogeneic HSCT is high and would be poorly tolerated in heavily pretreated elderly patients [56, 57].

As Gale and colleagues suggest, the number of patients who become transplant ineligible due to reinduction alone may offset those who derive benefit from repeat transplantation. Indeed, the true morbidity and mortality associated with attempting to achieve a second complete remission is unknown, as studies of transplant outcomes have not consistently reported these pre-transplant statistics [58].

Novel agents given with or without cytotoxic chemotherapy may improve the historically poor remission rates to make more elderly patients eligible for allogeneic HSCT, however.

Targeting isocitrate dehydrogenase (IDH) mutations may be particularly useful in the elderly population due to the epigenetic mechanism of action, as opposed the cytotoxic mechanism and high rates of cytopenia with other therapies. IDH mutations alter the normal function of the Krebs cycle in the conversion of isocitrate to α-ketoglutarate. The downstream effect of the mutated pathway leads to histone hypermethylation and blockage of cellular differentiation. The IDH1 and IDH2 mutations are found in approximately 5–10% and 10–15% of AML, respectively. In the phase I/II trial of the IDH1 inhibitor Ivosidenib, CR was achieved in 21%, with median duration of 9 months and approximately 9% of patients going on to allogeneic HSCT [59]. In the phase I/II study of the IDH2 inhibitor enasidenib, the overall response rate was 40% in patients with a median age of 67 years, with severe toxicity limited to 12%. CR was achieved in 19% of patients, of whom the median survival was 20 months, and 11% of patients went on to receive allogeneic HSCT [60•]. Importantly, treatment with enasidenib can lead to prolonged stable disease with the possibility of achieving delayed remission. Approximately 40% of patients treated with enasidenib maintained stable disease beyond treatment day 90, of whom approximately 25% subsequently achieved CR at median treatment day 130 [61]. This strategy of inducing differentiation of the malignant cell via a mutated pathway is very attractive for use in the elderly, as a small subset who achieves remission after relapsed/refractory disease may become eligible for HSCT.

Multiple oral tyrosine kinase inhibitors (TKI) have been studied in FLT3-mutated AML. In the relapsed/refractory setting, a phase II trial of salvage quizartinib monotherapy demonstrated a CR rate of 54% in elderly patients (median age 70) with FTL3-ITD mutations [62]. However, remissions are short-lived, and resistance is conferred by acquired on-target mutations with high levels of clonal heterogeneity [63]. The second-generation TKI, gilteritinib, has recently demonstrated promising activity in elderly AML. In a phase I/II trial with median age above 60 and a substantial percentage of patients above 70, gilteritinib demonstrated a 40% overall response rate in relapsed/refractory AML [64]. This was achieved while demonstrating acceptable toxicity profile at the established dose for the phase III trial, which is currently underway. Gilteritinib is also being evaluated for its role in the setting of post-allogeneic HSCT maintenance therapy for patients with FLT3 mutations, trial currently in accrual (NCT02997202).

Summary

AML in the elderly population represents the majority of patients with the disease, yet optimal management approaches for these patients are less studied

and more complex. Older patients carry a wide range of risk profiles, which, compounded by medical comorbidities, portend higher relapse and mortality rates. More recently, investigators have paid increasing attention to the incorporation of allogeneic HSCT into the treatment for older patients with AML, and prospective studies are accruing, which may build a substantiated foundation for considering this treatment strategy. Allogeneic HSCT for older patients has been shown to provide significant improvement in OS and RI compared to conventional non-transplant therapies, but toxicity of standard conditioning regimens and the need for prolonged immunosuppression remain major limiting factors. Although transplantation has been utilized less frequently in the older population than their younger counterparts, rates of transplantation in the elderly are rising. The transition to RIC and increased use of haploidentical donors have led to a shifting focus toward optimizing the graft-versus-malignancy effect. This has been a seminal change in allowing older patients to undergo HSCT, which has shown acceptable toxicity and tolerability. Older patients with higher risk disease profiles, such as the FLT3-ITD mutation and secondary AML, require specific focus and may benefit substantially from novel therapies followed by transplantation. Targeted therapy has evolved rapidly and broadly, and there is likely substantial promise in this avenue to improve rates of remission, making more elderly patients better candidates for allogeneic HSCT. Targeted radioimmunotherapy may also represent a more effective way to incorporate radiation into RIC regimens, although this concept is still in a relatively early investigative phase.

Thus far, trials that focus on older AML patients frequently do not include patients greater than 70 years old. As a result, many conclusions pertaining to elderly AML cannot definitively be applied to patients above this age. However, treating physicians should focus on the concept of biologic age, which incorporates medical comorbidities and is more prognostic for outcomes and treatment tolerability than chronologic age alone. Multiple risk assessment tools are now available to aid in this evaluation, such as the HCT-CI.

Elderly AML is a varied and complex entity, and thus the management strategy requires a thorough molecular workup, individualized clinical consideration, and extensive discussion with the patient regarding the variety of options available for their care.

Compliance with Ethics Guidelines

Conflict of interest

Rebecca Levin-Epstein declares that she has no conflict of interest. Caspian Oliai declares that he has no conflict of interest. Gary Schiller reports the following outside the submitted work: grants from AbbVie; grants, personal fees, and speakers' bureau involvement from Agios; grants from Actinium; grants from Ambit; grants, personal fees, and speakers' bureau involvement from Amgen; grants from Ariad; grants from Array Biopharma; grants and personal fees from Astellas; grants and grant-reviewer activities from Leukemia and Lymphoma Society; grants from BioMed Valley Discoveries; grants from Boehringer Ingelheim; grants from Celator; grants and speakers' bureau involvement from Celgene; grants from Forma; grants from Cyclacel; grants from Daiichi Sankyo; grants and speakers' bureau involvement from Incyte; grants and speakers' bureau involvement from Janssen; grants and consultant contract

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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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