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BRIEF COMMUNICATION

Allogeneic transplantation outcomes amongst a contemporary cohort of high-risk myelodysplastic syndrome and acute myeloid leukemia patients aged ≥70 years

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Targeted therapy

Abstract
Allogeneic hematopoietic stem cell transplantation (HSCT) is an integral therapy for patients with hematological malignancies, myelodysplasia, and bone marrow failure. Its use has been increasing over the past decade, as understanding of the treatment and its related toxicities has led to changes in patient selection, conditioning regimens, and post-transplant care. Older (age ≥65 years) patients are often considered unfit for transplantation; however, more recent data suggest that older patients, when selected appropriately, tolerate transplantation well. We report our institutional experience with HSCT in patients aged ≥70 years. A cohort of 22 patients underwent HSCT. Median overall survival was 5.16 years [95% confidence interval (CI): 1.5–8.7 years], and median post-transplant survival was 2.2 years (myelodysplastic syndrome: median 1.3 years, 95% CI: 4.7 months–2.2 years; acute myeloid leukemia: median not reached). Thirty-day mortality following HSCT was 9.5% (*n* = 2). These data provide further support for the use of HSCT in selected older patients, and highlight the impact of HSCT

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on overall survival among a patient cohort primarily of acute myeloid leukemia and myelodysplasia.

Introduction

Muffly et al. [1] recently published the Center for International Blood and Marrow Transplant Research (CIBMTR) experience regarding the increasing use of HSCT in patients aged 70 years and older, highlighting the dynamic landscape in treatment optimization for older patients with acute myeloid leukemia (AML). Despite a reported recent increase in the number of patients over the age of 70 years who proceed to HSCT, it is sobering to reflect that this increase reflects approximately 4% of newly diagnosed AML in this age bracket [1]. AML is the leading indication for HSCT, and given the average age of AML at diagnosis is 67 years, there is a large population of potential transplant patients over the age of 70 years. Older patients (over age 65 years) harbor more comorbidities, have higher risk disease, and have worse outcomes with aggressive treatments than their younger counterparts have [2]. However, older adults with AML have dismal outcomes without aggressive therapy when compared to younger patients with similar risk disease; therefore, this target group of patients may have the largest opportunity to benefit from HCT [11,12]. The use of reduced-intensity conditioning and nonmyeloablative regimens has been shown to decrease the risk of treatment-related mortality (TRM). However, a reduction in TRM may be at the expense of increased risk of relapse [3,12]. This imbalance may be subject to reversal with exploration of novel adjuvant options for post-transplant maintenance therapy to reduce relapse [6–9]. These are current areas of extensive clinical investigation.

Results: Our institutional experience with HSCT, particularly in high-risk older patients with AML, supports these recent endorsements to expand transplantation to older adults. We reviewed a contemporary cohort of patients age 70 years and older who underwent HSCT between 2013 and December 2017 [$n = 22$, 10 with AML and 12 with myelodysplastic syndrome (MDS)]. Patient demographics are demonstrated in Table 1. Two patients had intermediate-risk AML (1 cytogenetically normal, 1 with dicentric chromosome 20), and two had adverse-risk AML based on molecular characterization (1 FLT-3 TKD D835, 1 *TP53* mutated). The majority of AML patients developed secondary AML fromantecedent MDS.

AML patients underwent intensive induction with 7 + 3 or equivalent regimens. Three patients received liposomal daunorubicin/cytarabine on protocol per the Celator trial (NCT01696084), and four patients received hypomethylating agents (decitabine or azacytidine) as pretransplant maintenance. All patients received reduced-intensity conditioning with either busulfan/fludarabine/total body irradiation (Bu/Flu/TBI) or fludarabine/melphalan [4,5,13]. Patients with AML were either in first complete remission (CR1) or had no morphological evidence of disease on bone marrow examination at the time of HSCT. Twenty-one (95%) patients had matched unrelated donors. Eighteen patients received a 12/12 HLA-matched HSCT, and four patients an 11/12 HLA-matched HSCT. Two patients had a permissive mismatch at the DPB1 allele (12/12); one MDS patient had a DRB1 mismatch; one AML and one MDS patient had a B antigen mismatch; and one MDS patient had a C antigen mismatch. One patient underwent an HLA-matched sibling donor HSCT for MDS. Donor source was peripheral blood in 21 (95%) patients, and bone marrow in one patient. Graft-versus-host disease (GVHD) prophylaxis was based on the conditioning regimen, with Bu/Flu/TBI patients receiving cyclosporine A and mycophenolate mofetil, and those conditioned with fludarabine/melphalan receiving tacrolimus

Table 1 Hematopoietic stem cell transplantation demographics.[a]

Median age, years	71 (range 70–77)
Disease	$n = 22$ (%)
AML ($n = 10$)	
De novo	4
Favorable risk	–
Intermediate risk	2
Adverse risk	2
Secondary AML	5
Therapy-related AML	1
MDS ($n = 12$), n (%)	
Myelodysplasia unclassifiable	3 (13)
MDS with excessive blasts 1	3 (13)
MDS with excessive blasts 2	5 (22)
MDS with multilineage dysplasia	1 (4)
Median HCT-CI ($n = 22$)	2.5 (range 0–8)
Median Karnofsky Performance Score	80 (range 70–100)
Disease status prior to HSCT, n (%)	$n = 22$
First complete remission	9 (39)
No response/stable disease	9 (39)
Hematological improvement	1 (4)
Primary indication failure	2 (9)
Progressive disease	1 (4)
Conditioning regimen	
Busulfan/fludarabine/TBI	17
Fludarabine/nelphalan	5

Note. AML = acute myeloid leukemia; HSCT = hematopoietic stem cell transplantation; MDS = myelodysplastic syndrome; TBI = total body irradiation.

[a] Based on 2017 European LeukemiaNet classification of AML, and 2016 revision to the World Health Organization Classification of myeloid neoplasms and acute leukemia [17,18].

and short course (15 mg/m^2 on Day + 1, then 10 mg/m^2 on Days 3, 6, and 11) methotrexate.

Outcome analysis was conducted using IBM® SPSS® version 24 software. Survival was determined via Kaplan—Meier curves using the log-rank test. Despite this older population (median age 71 years) of predominantly high-risk AML and MDS patients, the outcomes from HSCT were superior to expected disease outcomes without HSCT (Fig. 1). Median overall survival (OS) was 5.16 years [95% confidence interval (CI): 1.5—8.7 years]. Median post-HSCT survival was

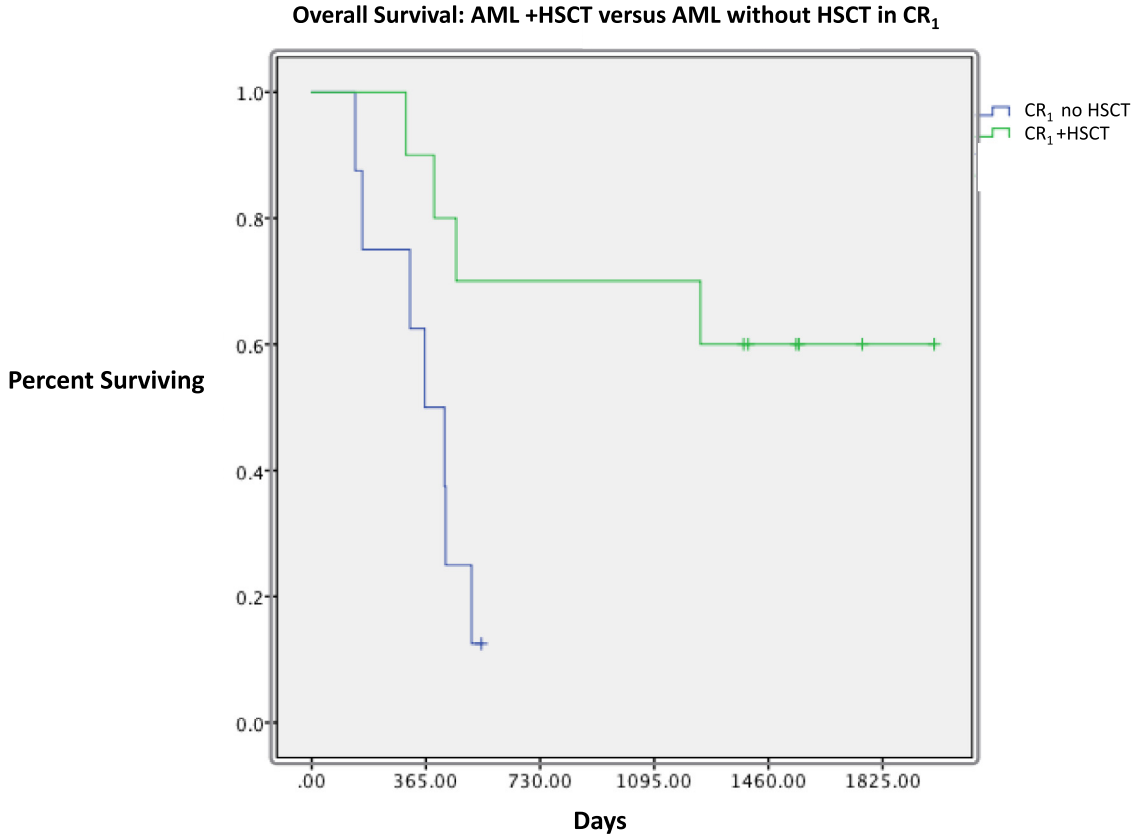

Fig. 1 Overall survival of patients with AML with and without HSCT in CR1. *Note*. AML = acute myeloid leukemia; CR1 = first complete remission; HSCT = hematopoietic stem cell transplantation.

Table 2 Overall survival and cause of death.

Overall survival	1 year, %	2 years, %	3 years, %
AML + HSCT (*n* = 10)	90 (*n* = 9)	70 (*n* = 7)	70 (*n* = 7)
AML No HSCT (*n* = 17)	29 (*n* = 5)	0	0
AML CR1 No HSCT (*n* = 8)	50 (*n* = 4)	0	0
MDS + HSCT (*n* = 12)	90 (*n* = 10)	90 (*n* = 10)	45 (*n* = 5)
Median OS			
AML and MDS + HSCT (*n* = 22)		5.16 years (95% CI: 1.5—8.7 years)	
AML + HSCT (*n* = 10)		Not reached	
MDS + HSCT (*n* = 12)		5.1 years (95% CI: 1.8—8.5 years)	
AML CR1 no HSCT (*n* = 8)		361 days (95% CI: 207—514 days)	
Cause of death (*n* = 12)		*N* (%)	
Relapsed disease		3 (25)	
Acute GVHD		2 (16)	
Chronic GVHD		3 (25)	
Infection		2 (16)	
Organ failure		1 (8)	
New malignancy		1 (8)	

Note. AML = acute myeloid leukemia; CI = confidence interval; CR1 = first complete remission; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; MDS = myelodysplastic syndrome; OS = overall survival.

2.2 years (MDS: median 1.3 years, 95% CI: 4.7 months—2.2 years, AML: median not reached). Among this cohort, 2-year OS from diagnosis was approximately 77%. Nonrelapse mortality was 40% ($n = 9$) (Table 2). Thirty-day mortality following transplantation was 9.5% ($n = 2$). Cumulative incidence of relapse post-HSCT was 22% ($n = 5$), occurring a median 365 days post-HSCT. Two of three relapses in the AML cohort were in patients harboring FLT-3 ITD mutations on molecular analysis (1 patient was FLT-3 ITD$^+$ at diagnosis; the other was positive at post-transplant relapse). Both received post-HSCT FLT-3 targeted therapy with the multikinase inhibitor sorafenib in addition to donor leukocyte infusion. OS was not significantly different between patients with HCT-CI scores of 0—2 (median OS 5.1 years, 95% CI: 2.5—7.8 years) versus ≥3 (median OS 2.0 years, 95% CI: 2.0—8.5 years).

Acute GVHD occurred in 16 (72%) patients with a median Grade 2 (range 0—4). Acute GVHD was the primary cause of death in two MDS patients undergoing HSCT. Chronic GVHD occurred in 11 (52%) patients, and was limited in one and extensive in 10 (7 patients with mild extensive GVHD, and 3 with moderate extensive GVHD). Chronic GVHD was the cause of death in three patients. Among the patients with acute or chronic GVHD listed as cause of death, three of five (66%) had an 11/12 HLA mismatched donor (B, C, and DRB1 allele), which has been correlated with higher rates of acute GVHD and inferior OS outcomes compared to fully matched patients undergoing HSCT [19].

A contemporary cohort of our institutional patients aged ≥70 years with high-risk AML who did not undergo HSCT, despite achieving CR1 following induction chemotherapy ($n = 8$), had a median OS of 13 months (95% CI: 7.3—18 months). Institutional AML patients that failed to achieve remission ($n = 9$), had a median OS of 5 months (95% CI: 3.4—5.7 months). In comparison, the median OS was not reached amongst AML patients in the HSCT cohort ($n = 10$). The non-transplant cohort had a 30-day mortality rate of 11% ($n = 2/17$), with one patient dying during induction chemotherapy. One-, 2-, and 3-year OS between groups can be seen in Table 2.

Conclusion: Our institutional results demonstrate that HSCT is tolerable and effective for patients aged ≥70 years with AML/MDS and is associated with improved outcomes compared to historical cohorts of patients aged >70 years not undergoing HSCT [20]. While the retrospective nature makes direct comparison between cohorts difficult due to the potential confounding from selection bias, these data highlight the impact of transplantation on OS in older patients with MDS/AML. The CIBMTR data validate the feasibility and tolerability of this treatment and shed light on the recognition of the growing importance of an early discussion between oncologists and their patients on the role of HSCT in the treatment of their disease. While newer agents are being approved for treatment of AML in older adults, the median OS without HSCT is still ~1 year. Further work is critical to identify the patients best suited for HSCT, as well as understanding the role of other providers (palliative care, physical therapy, nutritionists, and psychologists) prior to HSCT and throughout the peritransplant and early post-HSCT periods, to enhance the emotional and functional status of these patients and potentially impact both treatment-related toxicity and quality of life [10,11,14,16]. Additional studies delineating the selection of the conditioning regimen and GVHD prophylaxis schedule that are best balanced — that is, the approaches that offer the lowest TRM and highest benefit of graft-versus-leukemia effect (and thereby the lowest risk of relapse) — are needed and are particularly relevant to this patient population. Equally as paramount is identification of appropriate HSCT candidates based on validated risk models among older adults that incorporate an individual's comorbidities, coupled with simultaneous assessment of the risk of TRM and disease risk by transplant-knowledgeable physicians. Such steps are necessary to guide final treatment decisions since chronological age alone is not a deterrent to successful HSCT [10,11,15].

Authors' contribution

CL, GM, RC, BHL, RM: drafting and revision of the manuscript, and acquisition and analysis of clinical data. UB, JL, ET, KHD, LN: acquisition of clinical data and revision of the manuscript.

Conflict of interest

The authors have no conflict of interests to disclose.

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