

Outcomes of Pediatric Patients with Therapy-Related Myeloid Neoplasms

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Abstract

Long-term outcomes after allogeneic hematopoietic cell transplantation (HCT) for therapy-related myeloid neoplasms (tMNs) are dismal. There are few multicenter studies defining prognostic factors in pediatric patients with tMNs. We have accumulated the largest cohort of pediatric patients who have undergone HCT for a tMN to perform a multivariate analysis defining factors predictive of long-term survival. Sixty-eight percent of the 401 patients underwent HCT using a myeloablative conditioning (MAC) regimen, but there were no statistically significant differences in the overall survival (OS), event-free survival (EFS), or cumulative incidence of relapse and non-relapse mortality based on the conditioning intensity. Among the recipients of MAC regimens, 38.4% of deaths were from treatment-related causes, especially acute graft versus host disease (GVHD) and end organ failure, as compared to only 20.9% of deaths in the reduced intensity conditioning (RIC) cohort. Exposure to total body irradiation (TBI) during conditioning and experiencing grade III/IV acute GVHD were associated with worse OS. In addition, a diagnosis of therapy related myelodysplastic syndrome and having a structurally complex karyotype at tMN diagnosis were associated with worse EFS. Reduced-toxicity (but not reduced-intensity) regimens might help to decrease relapse while limiting mortality associated with TBI-based HCT conditioning in pediatric patients with tMNs.

Introduction

Risk-adapted, dose-intensified, and multimodal regimens have improved cure rates for pediatric patients with cancer in recent decades. One in 900 adults younger than 45 years is a survivor of pediatric cancer.¹ The continued improvement in outcomes of pediatric cancer has led to a commensurate increase in survivors, which is expected to increase late sequelae of intensive chemotherapy.

Therapy-related myeloid neoplasms (tMNs) remain a devastating late complication in long-term survivors² and have been reported in children and adolescents treated for hematologic malignancies and solid tumors.^{3,4} Therapy-related acute myeloid leukemia (tAML) accounts for approximately 10%–20% of AML cases⁵ and develops in approximately 0.8%–6.3% of survivors at a median of approximately 3–5 years from initial treatment exposure.⁶ Patients with tAML have worse outcomes than do patients with de novo AML, with a median survival of <1 year from diagnosis.^{5,7} Allogeneic hematopoietic cell transplantation (HCT) is the only treatment that offers the possibility of long-term cure.^{8,9} However, even with HCT, the overall survival remains a dismal 22%–35%. Specifically, the non-relapse mortality (NRM) remains high at 37%–48%,¹⁰⁻¹² probably as a result of intensive myeloablative conditioning regimens being used.

Most previous studies of outcomes in patients with tMNs and factors affecting survival have predominantly focused on adults; pediatric-specific studies have been limited to small, single-center analyses.^{2,13-17} It is unknown whether outcomes in pediatric patients with tMNs differ based on the antecedent diagnosis or whether the conditioning

regimen intensity affects the prognosis. Herein we report the results of a multi-institutional international retrospective collaborative study focusing exclusively on pediatric patients undergoing HCT for tMNs.

Methods

Study design and participants

Pediatric transplant centers in the United States, Mexico, Europe, and Australia were invited to participate in this collaborative study. Centers were asked to report patients with therapy-related myelodysplastic syndrome (tMDS) or tAML who were aged 21 years or younger at the time of HCT and who received transplants at the centers between 1995 and 2017 (both years included). Therapy related myeloid neoplasms were defined according to the 2017 World Health Organization (WHO) criteria.¹⁸ tAML and tMDS were differentiated based on blast count >20% or <20% respectively, although the current version of the WHO classification does not differentiate between them based on blast count or degree of dysplasia.¹⁸ Patients with known inherited genetic predisposition disorders (like Fanconi anemia, or Li-Fraumeni syndrome) were not included in this study. De-identified patient, disease, and transplant-related characteristics were collected using a secured REDCap database after obtaining approvals from the respective institutional review boards.

Definitions

Therapy-related myeloid neoplasms were defined as those occurring after previous cytotoxic therapy exposure, with tAML being differentiated from tMDS based on a blast

count of >20% in the peripheral blood or bone marrow.¹⁹ Myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) regimens were defined by the respective centers. Conditioning regimens were considered as MAC if they included cumulative doses of >8 Gy of total body irradiation (TBI) and >8 mg/kg of busulfan or >140 mg/m² of melphalan administered intravenously. RIC regimens comprised sub-myeloablative doses of these conditioning agents.

Cytogenetic abnormalities were classified as follows: a structurally complex karyotype was defined as having at least three chromosomal aberrations, involving at least one structural aberration defined as a deletion, duplication, translocation, insertion, inversion, ring chromosome, or isochromosome. The trisomy 8 group could include up to two additional aberrations other than monosomy 7 and structurally complex mutations. Monosomy 7 included the complete or partial loss of chromosome 7 along with additional aneuploidies or deletions, because the clinical outcomes are similar in primary MDS.

Overall survival (OS) was defined as the time from HCT until death from any cause, censoring those patients who remained alive at last follow-up. Event-free survival (EFS) was defined as the time from HCT until first relapse or death from any cause, censoring those patients who had experienced no such event at the last follow-up. Relapse was defined as relapse of tMDS/AML, considering deaths from any cause as competing events. NRM was defined as death without relapse, considering death due to relapse as a competing event.

Statistical analysis

Overall survival and EFS curves/functions were estimated by the Kaplan–Meier method and compared by the log-rank test. Single-factor and multiple-factor analysis of OS and EFS were performed by fitting Cox regression models. To assess the relation between the conditioning regimen and transplant outcomes (OS, EFS, relapse, and NRM), conditioning regimen and an independent covariate with a univariate *P* value of ≤ 0.25 were included in the multivariate Cox proportional hazards models and Fine–Gray regression models. Race, Lansky/Karnofsky performance status, maximum chronic graft vs. host disease (GVHD) grade, cytomegalovirus serostatus, and degree of HLA match (N/6) were not included because of the large proportion of missing data (for $>35\%$ patients). The cumulative incidence curve/function was estimated by the Kalbfleisch–Prentice method, accounting for competing risks, and compared by Gray's test. Single-factor and multiple-factor analysis of the cumulative relapse risk was performed by fitting Fine–Gray regression models.

Results

Patient characteristics

Fifty-four centers (19 in the USA, 24 in France, seven in the UK, two in Australia, one in Mexico, and one in the Netherlands) contributed data on 401 patients. Demographic details of these patients, initial diagnoses, HCT status, and final outcomes are provided in **Table 1**. Primary diagnoses included solid tumors (including brain tumors) in 39% and malignant hematologic neoplasm (ALL, AML, MDS, or lymphoma) in 33% of the

patients. Primary diagnosis was not available (not recorded) for 28% patients. Most patients (65%) later developed tMDS; only 30% had tAML. Median age at HCT was 12.9 years (range, 1.2–21 years), and median time from tMN diagnosis to HCT was 3.9 months (range, 0.3–67.2 months). Sixty-eight percent of patients underwent HCT with a MAC regimen, whereas 30.7% received an RIC regimen before HCT. The MAC and RIC cohorts were comparable except as noted below. RIC recipients were more likely to receive a graft from a mismatched related donor (usually a haploidentical parent) (22.8% vs. 7.7%), less likely to receive a cord blood transplant (14.6% vs. 20.2%, $P < 0.001$), and more likely to receive a peripheral blood–derived stem-cell graft (35.8% vs. 20.5%, $P = 0.006$) when compared to MAC recipients. RIC recipients were also more likely to experience grade II–IV acute GVHD (40.7% vs 27.5%, $P = 0.006$). Median follow-up for the entire cohort and for the MAC and RIC cohorts separately was 18.3 months, 21.5 months and 16.7 months, respectively.

Overall survival

There was no significant difference in the survival probability of the two cohorts based on the HCT conditioning intensity ($P = 0.171$). The estimated OS at 1, 5, and 10 years was 65.3%, 34.6% and 32.4%, respectively, for the RIC cohort and 62.8%, 49.9%, and 47.8%, respectively, for the MAC cohort (**Fig. 1A**). Overall, 235 deaths were reported in the entire cohort, a rate of 58.6%. The fraction of patients in the RIC and MAC cohorts who died as a result of disease relapse, persistence, or progression was similar at 46%. Among the MAC recipients, 151 (55.3%) died, of whom 58 (38.4% of the recipients) died of treatment-related causes. Among the RIC recipients, 81 (65.9%) died, with only

17 deaths (representing 20.9% of the recipients) being attributable to treatment-related toxicity (**Table 2**). In a univariate analysis, performance status <90 (hazard ratio [HR] 1.8, 95% CI 1.2–2.8, $P=0.006$), exposure to TBI during conditioning (HR 1.9, 95% CI 1.4–2.6, $P<0.001$), experiencing grade III/IV acute GVHD (HR 2.5, 95% CI 1.6–4.1 for grade III and HR 2.4, 95% CI 1.1–5.2 for grade IV, $P=0.001$), and receiving a transplant from a mismatched donor (HR 1.5, 95% CI 1.0–2.1, $P=0.029$) were all associated with a higher HR (**Supplementary Table 1**). Only TBI exposure (HR 1.8, 95% CI 1.1–2.8, $P=0.018$) and experiencing grade III/IV acute GVHD (HR 2.2, 95% CI 1.2–4.2 for grade III and HR 3.0, 95% CI 1.2–7.9, for grade IV, $P=0.007$) remained significantly associated with survival in the multivariable analysis (**Fig. 2**).

Relapse

The estimated EFS at 1, 5, and 10 years was 52.5%, 29.5%, and 27.6%, respectively, for the RIC cohort and 51.9%, 41.2%, and 40.2%, respectively, for the MAC cohort ($P=0.20$) (**Fig. 1B**). The cumulative incidence of relapse at 1, 5, and 10 years was 33.6%, 42.0%, and 42.0%, respectively, for the RIC cohort and 27.5%, 34.2%, and 35.2%, respectively, for the MAC cohort ($P=0.176$) (**Fig. 1C**). In a univariate analysis for EFS, performance status <90 (HR 1.6, 95% CI 1.1–2.5, $P=0.015$), having a structurally complex karyotype at tMN diagnosis (HR 1.9, 95% CI 1.0–3.5, $P=0.017$), a tMDS diagnosis (HR 1.4, 95% CI 1.0–1.9, $P=0.039$), receiving TBI during conditioning (HR 1.8, 95% CI 1.4–2.4, $P<0.001$) and experiencing grade III/IV acute GVHD (HR 2.1, 95% CI 1.3–3.2 for grade III and HR 2.0, 95% CI 1.0–3.9 for grade IV, $P=0.008$) were all associated with a higher HR (**Supplementary Table 1**). Of these, monosomy 7 or a

complex karyotype at tMN diagnosis (HR 1.6, 95% CI 0.7–3.4 for monosomy 7 and HR 2.0, 95% CI 0.9–4.6, for structurally complex karyotype, $P=0.001$) were the only variables associated with a higher HR for relapse in the univariate model

(Supplementary Table 1). In a multivariable model, a tMDS diagnosis (HR 1.6, 95% CI 1.0–2.4, $P=0.034$), having a structurally complex karyotype at tMN diagnosis (HR 2.3, 95% CI 1.0–5.0, $P=0.006$), receiving TBI during conditioning (HR 1.7, 95% CI 1.1–2.6, $P=0.026$), and experiencing grade III/IV acute GVHD (HR 2.1, 95% CI 1.1–4.0 for grade III and HR 2.5, 95% CI 1.0–6.3 for grade IV acute GVHD, $P=0.005$) remained significantly associated with EFS, whereas a tMDS diagnosis (HR 1.8, 95% CI 1.1–2.9, $P=0.028$) and having a structurally complex karyotype (HR 2.7, 95% CI 1.1–6.7, $P=0.001$) were associated with a higher HR for relapse **(Figs. 3 and 4)**.

Non-relapse mortality

The cumulative incidence of NRM at 1, 5, and 10 years was 14.5%, 29.2%, and 31.4%, respectively, for the RIC cohort and 21.0%, 24.3%, and 24.3%, respectively, for the MAC cohort ($P=0.63$) **(Fig. 1D)**. **Table 2** lists the primary causes of death. In a univariate analysis for NRM, year of transplant before 2014 (the HR was higher for earlier years, $P=0.012$), a primary diagnosis of AML (HR 3.4, 95% CI 1.9–5.9, $P<0.001$), receiving TBI during conditioning (HR 1.8, 95% CI 1.8–2.8, $P=0.005$), and experiencing grade III/IV acute GVHD (HR 3.1, 95% CI 1.7–5.5 for grade III and HR 4.5, 95% CI 1.9–10.6 for grade IV, $P<0.001$) were all associated with a higher HR **(Supplementary Table 1)**. Year of transplant before 2014 (the HR was higher for earlier years, $P=0.001$) and experiencing grade III/IV acute GVHD (HR 3.1, 95% CI

1.5–6.1 for grade III and HR 4.7, 95% CI 1.9–11.6 for grade IV, $P=0.001$) remained significant predictors of worse NRM in a multivariable model (**Fig. 5**).

Discussion

Therapy-related myeloid neoplasms are a challenging late complication of cancer therapy and are associated with dismal outcomes with conventional chemotherapy.^{5, 7} Allogeneic HCT is currently the only curative option;^{8, 10, 11} however, given the rarity of this diagnosis, outcomes data for pediatric patients are limited to small, single-center analyses.^{2, 13-17} Furthermore, the factors affecting the prognosis in pediatric patients with tMN are unknown. This retrospective analysis features the largest pediatric cohort of patients with tMN undergoing HCT to date, and we have evaluated various prognostic factors associated with disease relapse and survival, particularly focusing on HCT conditioning intensity.

Although we found no significant difference in long-term survival or relapse related to conditioning intensity, some differences were noted. Survival in the first year after HCT appeared to be almost identical in the two cohorts (65.3% for RIC vs 62.8% for MAC). However, survival fell precipitously in the RIC cohort during years 2–5 after HCT (48.5% at 2 years and 34.6% at 5 years after HCT). In contrast, although survival declined in the MAC recipients, the fall was more gradual (to 55.1% at 2 years and 49.9% at 5 years after HCT). Exposure to TBI and developing grade III/IV acute GVHD were associated with worse OS in the multivariate model. Additionally, non-TBI-based regimens were associated with better EFS. Therefore, less toxic (but not less intense) alkylator-based regimens might be preferred based on superior EFS.

The cumulative incidence of relapse continued to increase for up to 5 years in both cohorts, and the rate of relapse appeared to be higher in RIC recipients in the 1 to 3–years range than in other patients. In a multivariate analysis, the only factors associated with an increased incidence of relapse were a diagnosis of tMDS and the presence of a structurally complex karyotype. Several studies have shown disease status at HCT^{10, 11, 20, 21} and high-risk cytogenetic features^{7, 10, 12, 21} to be associated with increased relapse rate and poor survival. A diagnosis of tMDS, as compared to tAML, at HCT was associated with worse EFS; the higher risk of relapse is probably explained by patients with MDS proceeding to HCT without receiving prior disease-directed/debulking therapy.^{22, 23} These patients might have had low-level smoldering disease at the time of HCT that resulted in relapse. Although this hypothesis cannot be tested in our cohort, previous reports are certainly suggestive of this explanation²² hence, patients with tMDS might benefit from induction chemotherapy before receiving consolidation HCT, even though the quantifiable disease burden is low.

Disappointingly, the cumulative incidence of NRM was comparable in the RIC and the MAC cohorts, even though the causes of death in the patients were quite different. Death from treatment-related causes, especially acute GVHD and end organ failure, was more common in the MAC cohort than in the RIC cohort. These two causes appear to be responsible for the higher incidence of early mortality in our MAC cohort and in many previous studies.^{7, 9, 11, 14, 17} Accordingly, multivariate analysis also suggested that grade III/IV acute GVHD and receiving a transplant before 2014 (versus after 2014)

were both associated with increased NRM. Presumably, better supportive care measures have reduced transplant-related morbidity and mortality in recent years.²⁴

Even though the differences in survival are not statistically significant, RIC appeared to offer no survival advantage in heavily pretreated pediatric patients with tMNs. This finding offers some insight into the pattern of mortality and morbidity in patients with tMNs, who are likely to have accumulated significant end organ damage from previous therapy when compared to peers with *de novo* leukemia. These data suggest that non-TBI-based MAC should be prioritized for pediatric patients with tMNs, if they are suitably healthy, to achieve durable long-term remission. In a randomized trial comparing MAC with RIC in adult patients with *de novo* AML or MDS, RIC was associated with lower treatment-related mortality but higher relapse rates, resulting in OS being better with MAC.²⁵ However, in contrast to the present study, this earlier study did not evaluate outcomes specifically in a highly vulnerable population of pediatric patients with tAML/tMDS. Our findings are consistent with previous reports concerning a cohort of adults with tAML and a prior history of a solid tumor or MDS/MPN.^{20, 21} Interestingly, another analysis from the same European registry showed that patients with tAML had superior survival with RIC if they had had a previous diagnosis of a lymphoid malignancy.²² In our cohort, antecedent disease diagnosis was associated only with NRM (not with OS, EFS, or relapse) in the univariate analysis; it was not significantly associated with any outcome in the multivariable analysis.

There is increasing evidence that second malignant neoplasms of the myeloid lineage may occur due to an underlying genetic predisposition and that exposure to chemotherapy may not be the sole driver.^{26, 27} Indeed, in one study of adult patients with tMN, around 13% patients harbored deleterious pathogenic germline variants (most commonly in TP53).²⁶ These mutations were even found in the early hematopoietic stem cells (HSC) and these HSCs bearing (pre-)tMN mutations were present years before disease onset or chemotherapy exposure.^{26, 28, 29} However, in a recent analysis of 84 pediatric patients with tMN, which included many patients also included in this study, investigators found that contrary to adults with tMN, in pediatric patients with tMN there was no evidence of pre-existing minor clones with germline mutations.³⁰ KMT2Ar and Ras/MAPK pathway mutations were the most common driver alterations in pediatric patients with tMN, and while TP53 mutations were identified, these were not present in the germline like in the adult tMN patients.³⁰ However, recent studies have shown that some pediatric tMN patients may have a genetic mutational signature similar to relapsed mismatch repair-deficient ALL,^{30, 31} which could imply a poor tolerance to genotoxic conditioning. Short telomere length, due to inherited genetic syndromes or acquired exposures, may also lead to impaired cellular recovery after myeloablative conditioning and therefore increased toxicity from transplantation. In a study of adult MDS patients undergoing HCT, short pretransplant recipient telomeres were independently associated with inferior survival due to high NRM.³² This association was highly significant in patients who developed severe acute GVHD.³² In our study as well, developing severe acute GVHD was associated with a worse OS suggesting that perhaps telomere shortening induced by prior chemotherapy exposure pretransplant

may have limited tissue recovery after myeloablative conditioning in these patients and hence led to increased organ-toxicity and treatment-related mortality, especially in the patients exposed to TBI containing regimens. These observations strengthen the argument that not only are tMNs a diverse group of myeloid malignancies with variable outcomes, but pediatric patients may have had very different antecedent exposures and origins of tMN which must be taken into account when determining the best conditioning regimen. Furthermore, outcomes in studies involving predominantly adult patients might not be applicable to pediatric patients because the treatment intensity and associated comorbidities after prior diagnoses are very different.

This study has several limitations. Given its retrospective nature, some data is incomplete or missing, and information about treatment regimens for antecedent malignant neoplasms was unavailable. Accordingly, we excluded several variables with a large proportion of missing data (for >35% patients) from the multivariate analysis. The choice of a particular conditioning regimen is based on multiple factors, and there might have been selection bias with regard to conditioning intensity. It appears, however, that many RIC recipients also received grafts from mismatched unrelated donors (MMRDs) or peripheral blood stem cell (PBSC) grafts. Therefore, it is likely, although this cannot be confirmed, that the choice of conditioning regimen was indeed intentional, perhaps with the aim of leveraging a strong graft-versus-leukemia effect.³³ There was also substantial heterogeneity in the conditioning regimens across multiple centers, but this facilitated a more pragmatic study evaluating the true impact of conditioning intensity rather than a particular drug combination or regimen. Lastly, we

acknowledge the importance of comorbid conditions,³⁴ disease risk index,³⁵ and hematopoietic cell transplant comorbidity index (HCT-CI)³⁶ in determining outcomes after HCT, but we could use only the cytogenetic classification and performance score for studying associations with outcomes because comprehensive co-morbidity data was lacking. Also, the HCT-CI might not, in fact, be very predictive of outcomes in pediatric patients.³⁷ We recognize that some patients included in our cohort might have been included in previous single-center reports.^{14, 16, 17} However, previous studies lacked the statistical power necessary for the analyses performed in our combined cohort.

Conclusion

In conclusion, in this multi-center, large cohort of pediatric patients with tMNs undergoing HCT, RIC-based HCT showed no survival advantage over MAC-based HCT for pediatric patients with tMNs. Although outcomes have improved, the prognosis remains suboptimal, with a modest long-term survival rate of around 50%. As treatment-related causes remain the predominant reason for post-HCT mortality, novel reduced-toxicity treatment regimens using immunotherapy, augmented cell-based therapeutics, and targeted agents might prove to be the key to improving long-term survival.

Author Contributions

AS, SH, CC and BMT designed the study. AS, YL, IA, HBA, PA, AB, NSB, MBB, JB, CB, JEB, AD, J-HD, HE, MF, AG, NJG, WSG, ESG, KH, RH, MPH, JSH, DJ, KAK, EK, SK, AKK, NAK, YPK, CRL, GL-H, PM, KCM, SN, AO-V, TO, MR, SR, KR, HGR, PAR, MES, PJS, JLS, KS, HJS, MdT, ANU and BV acquired the data and verified it. AS, SH, RJB, CC and BMT analyzed the data. AS and BMT wrote the manuscript, and YL, IA, HBA, PA, AB, NSB, MBB, JB, CB, JEB, AD, J-HD, HE, MF, AG, NJG, WSG, ESG, KH, RH, MPH, JSH, DJ, KAK, EK, SK, AKK, NAK, YPK, CRL, GL-H, PM, KCM, SN, AO-V, TO, MR, SR, KR, HGR, PAR, MES, PJS, JLS, KS, HJS, MdT, ANU and BV critically reviewed the manuscript. All authors agree with and take full responsibility for the content of this manuscript.

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Conflicts of Interest

AS's institution receives support for the conduct of industry sponsored trials from Vertex Pharmaceuticals, CRISPR Therapeutics and Novartis. AS has received consulting fee from Spotlight Therapeutics. HBA reports that she is an employee of BeiGene Ltd and began her employment after the contribution of any clinical data. RJB reports that he currently is an employee of Smith & Nephew, a position that he transitioned to while this project was ongoing. J-HD reports receiving honoraria from blue bird bio, Orchard, Jazz Pharmaceuticals, Novartis, Sanofi Genzyme and Gilead. MPH serves on the advisory board for Mesoblast. HJS reports personal fees from Jazz Pharmaceuticals. HJS has a patent US-2020-0163997-A1 with royalties paid. BMT has received financial support for research and travel from Miltenyi Biotec. Remaining authors do not have any conflicts of interest to disclose.

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Figure Legends

Figure 1. Outcomes following HCT for tMN stratified by conditioning intensity: (A) overall survival, (B) event-free survival, (C) cumulative incidence of relapse and (D) cumulative incidence of non-relapse mortality.

Figure 2. Multivariable analysis of risk factors associated with overall survival after HCT for tMN.

Figure 3. Multivariable analysis of risk factors associated with event-free survival after HCT for tMN.

Figure 4. Multivariable analysis of risk factors associated with relapse after HCT for tMN.

Figure 5. Multivariable analysis of risk factors associated with non-relapse mortality after HCT for tMN.

Tables

Table 1: Patient Characteristics (N = 401)

Characteristic	Total N = 401 (100%)	MAC N = 273 (68.1%)	RIC N = 123 (30.7%)	Unknown N = 5 (1.2%)	P* MAC vs. RIC
Sex					0.391
Male	208 (51.9)	143 (52.4)	63 (51.2)	2 (40.0)	
Female	155 (38.6)	114(41.8)	41 (33.3)	0 (0.0)	
Unknown	38 (9.5)	16 (5.9)	19 (15.5)	3 (60.0)	
Race					0.665
White	178 (44.4)	125 (45.8)	52 (42.3)	1 (20.0)	
Black	23 (5.7)	16 (5.9)	7 (5.7)	0 (0.0)	
Other	40 (10.0)	31 (11.4)	9 (7.3)	0 (0.0)	
Unknown	160 (39.9)	101 (37.0)	55 (44.7)	4 (80.0)	
Primary diagnosis					0.130
ALL	81 (20.2)	62 (22.7)	17 (13.8)	2 (40.0)	
AML	13 (3.2)	8 (2.9)	5 (4.1)	0 (0.0)	
Other malignant heme disorder#	39 (9.7)	23 (8.4)	16 (13.0)	0 (0.0)	
Solid/brain tumor	156 (38.9)	104 (38.1)	50 (40.7)	2 (40.0)	
Unknown	112 (27.9)	76 (27.8)	35 (28.5)	1 (20.0)	
Diagnosis at HCT					0.104
tMDS	261 (65.1)	175 (64.1)	82 (66.7)	4 (80.0)	
tAML	122 (30.4)	93 (34.1)	29 (23.6)	0 (0.0)	
Unknown	18 (4.5)	5 (1.8)	12 (9.8)	1 (20.0)	
Age at HCT in years					0.270
Mean ± SD	12.6 ± 5.0	12.4 ± 5.0	13.0 ± 5.0	10.2 ± 5.0	
Median (range)	12.9 (1.2–21.0)	12.5 (1.2–21.0)	13.5 (2.8–21.0)	10.1 (4.8–15.7)	
Unknown	1 (0.2)	0 (0.0)	0 (0.0)	1 (20.0)	
Time from tMDS/tAML to HCT in months					0.097
Mean ± SD	6.5 ± 8.7	5.9 ± 8.3	7.5 ± 9.4	18.0 ± 9.6	
Median (range)	3.9 (0.3–67.2)	3.8 (0.3–67.2)	4.4 (0.9–60.7)	22.9 (7.0–24.1)	
Unknown	7 (1.7)	3 (1.1)	2 (1.7)	2 (40.0)	
Performance status					0.516
≥90	212 (52.9)	153 (56.0)	59 (48.0)	0 (0.0)	
<90	47 (11.7)	31 (11.4)	15 (12.2)	1 (20.0)	
Unknown	142 (35.4)	89 (32.6)	49 (39.8)	4 (80.0)	
Donor type					<0.001
MSD	103 (25.7)	77 (28.2)	25 (20.3)	1 (20.0)	
MUD	115 (28.7)	78 (28.6)	35 (28.5)	2 (40.0)	

MMRD	49 (12.2)	21 (7.7)	28 (22.8)	0 (0.0)	
MMUD	28 (7.0)	22 (8.1)	6 (4.9)	0 (0.0)	
Cord	73 (18.2)	55 (20.2)	18 (14.6)	0 (0.0)	
Unknown	33 (8.2)	34 (12.5)	13 (10.6)	2 (40.0)	
Graft source					0.006
BM	223 (55.6)	160 (58.6)	61 (49.6)	2 (40.0)	
PBSC	101 (25.2)	56 (20.5)	44 (35.8)	1 (20.0)	
Cord	73 (18.2)	55 (20.2)	18 (14.6)	0 (0.0)	
Unknown	4 (1.0)	2 (0.7)	0 (0.0)	2 (40.0)	
Cytogenetic category					0.138
MLL rearrangement	69 (17.2)	54 (19.8)	15 (12.2)	0 (0.0)	
Monosomy 7	67 (16.7)	44 (16.1)	23 (18.7)	0 (0.0)	
Normal/trisomy 8	26 (6.5)	18 (6.6)	6 (4.9)	2 (40.0)	
Random aberrations	65 (16.2)	42 (15.4)	23 (18.7)	0 (0.0)	
Structurally complex karyotype	36 (9.0)	20 (7.3)	16 (13.0)	0 (0.0)	
Unknown	138 (34.4)	95 (34.8)	40 (32.5)	3 (60.0)	
Death					0.043
Yes	235 (58.6)	151 (55.3)	81 (65.9)	3 (60.0)	
No	163 (40.7)	121 (44.3)	41 (33.3)	1 (20.0)	
Unknown	3 (0.7)	1 (0.4)	1 (0.8)	1 (20.0)	
Relapse					0.441
Yes	133 (32.9)	87 (31.9)	44 (35.8)	1 (20.0)	
No	265 (66.1)	184 (67.4)	78 (63.4)	3 (60.0)	
Unknown	4 (1.0)	2 (0.7)	1 (0.8)	1 (20.0)	
Year of transplant					<0.001
1995–1999	44 (11.0)	41 (15.0)	3 (2.4)	0 (0.0)	
2000–2004	66 (16.5)	44 (16.1)	19 (15.5)	0 (0.0)	
2005–2009	85 (21.2)	52 (19.1)	32 (26.0)	3 (60.0)	
2010–2014	141 (35.2)	92 (33.7)	49 (39.8)	1 (20.0)	
2015–2017	64 (16.0)	44 (16.1)	20 (16.3)	0 (0.0)	
Unknown	1 (0.2)	0 (0.0)	0 (0.0)	1 (20.0)	
TBI					<0.001
Yes	124 (30.9)	103 (37.7)	21 (17.1)	0 (0.0)	
No	273 (68.1)	169 (61.9)	101 (82.1)	3 (60.0)	
Unknown	4 (1.0)	1 (0.4)	1 (0.8)	2 (40.0)	
Maximum grade of aGVHD					0.006
0	157 (39.2)	122 (44.7)	33 (26.8)	2 (40.0)	
I	58 (14.5)	44 (16.1)	14 (11.4)	0 (0.0)	
II	66 (16.5)	43 (15.8)	23 (18.7)	0 (0.0)	
III	43 (10.7)	24 (8.8)	19 (15.5)	0 (0.0)	
IV	16 (4.0)	8 (2.9)	8 (6.5)	0 (0.0)	
Unknown	61 (15.2)	32 (11.7)	26 (21.1)	3 (60.0)	
Maximum grade of cGVHD					0.661
None	176 (43.9)	123 (45.1)	50 (40.7)	3 (60.0)	

Mild	26 (6.5)	21 (7.7)	5 (4.1)	0 (0.0)	
Moderate	13 (3.2)	10 (3.7)	3 (2.4)	0 (0.0)	
Severe	15 (3.7)	12 (4.4)	3 (2.4)	0 (0.0)	
Unknown	171 (42.6)	107 (39.2)	62 (50.4)	2 (40.0)	
CMV serostatus					0.996
R+/D+	69 (17.2)	50 (18.3)	19 (15.5)	0 (0.0)	
R+/D-	61 (15.2)	45 (16.5)	16 (13.0)	0 (0.0)	
R-/D+	27 (6.7)	20 (7.3)	7 (5.7)	0 (0.0)	
R-/D-	76 (18.9)	55 (20.2)	21 (17.1)	0 (0.0)	
Unknown	138 (41.9)	103 (37.7)	60 (48.8)	5 (100.0)	
Degree of matching, N/6					0.005
3-5	89 (22.2)	57 (20.9)	32 (26.0)	0 (0.0)	
6	105 (26.2)	86 (31.5)	19 (15.5)	0 (0.0)	
Unknown	207 (51.6)	130 (47.6)	72 (58.5)	5 (100.0)	

*Chi-square test and *t*-test; unknown category was not included.

#Other malignant heme disorders included Burkitt lymphoma, chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), and hemophagocytic lymphohistiocytosis (HLH).

Abbreviations: aGVHD: acute graft versus host disease; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BM: bone marrow-derived graft; cord: cord blood unit; cGVHD: chronic graft-versus-host disease; CMV: cytomegalovirus (R and D indicate recipient and donor serostatus, respectively); HCT: hematopoietic cell transplant; tAML: therapy-related acute myeloid leukemia; tMDS: therapy-related myelodysplastic syndrome; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; MMRD: mismatched related donor; MMUD: mismatched unrelated donor; PBSC: peripheral blood-derived hematopoietic progenitor cells; RIC: reduced-intensity conditioning; SD: standard deviation; TBI: total body irradiation.

Table 2: Primary Cause of Death by Conditioning Intensity

Primary cause of death	Conditioning intensity			
	MAC N (%)	RIC N (%)	Unknown N (%)	Total N (%)
Total number of deaths	151	81	3	235
Treatment related	58 (38.4)	17 (20.9)	1 (33.3)	68 (32.3)
Acute GVHD	7 (4.6)	1 (1.2)	0 (0.0)	8 (3.4)
Chronic GVHD	8 (5.3)	4 (4.9)	0 (0.0)	12 (5.1)
Graft rejection or failure	6 (4.0)	0 (0.0)	0 (0.0)	6 (2.6)
Infection*	11 (7.3)	5 (6.2)	0 (0.0)	16 (6.8)
Organ failure (not due to GVHD or infection)	20 (13.3)	6 (7.4)	0 (0.0)	26 (11.1)
Pulmonary complications	6 (4.0)	1 (1.2)	1 (33.3)	8 (3.4)
Malignancy [#]	3 (2.0)	7 (8.6)	0 (0.0)	10 (4.3)
Relapse / persistence / progression of disease	70 (46.4)	37 (45.7)	1 (33.3)	108 (46.0)
Other	2 (1.3)	1 (1.2)	0 (0.0)	3 (1.3)
Unknown	18 (11.9)	19 (23.5)	1 (33.3)	38 (16.2)

*Infection (isolation of an organism leading to sepsis/organ failure with no other ascertainable cause of death in the previous 7 days)

[#]Malignancy refers to a malignancy unrelated to the therapy-related myeloid neoplasm diagnosis.

Abbreviations: GVHD: graft-versus-host disease; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning.