Allogeneic hematopoietic cell transplantation outcomes for children and young adults with treatment-related myelodysplastic syndrome or acute myeloid leukaemia

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Abstract

Objective: Therapy-related myeloid malignancies (tMDS or tAML) are well-known complications of cancer therapy for which outcomes are poor. Whether clinical characteristics can predict disease outcome in children and young adults, as they do in older adults, is not well known.

Method: Twenty-five children with tMDS/tAML underwent allogeneic hematopoietic stem cell transplantation (allo-HCT) at the University of Minnesota between 1990 and 2010. Twenty-one patients received myeloablative conditioning. Graft sources included umbilical cord blood in fourteen patients [single (n=9), double (n=5)] and bone marrow in 11. Prior to transplant twenty-one patients received AML-directed chemotherapy and 19 were in complete remission at the time of allo-HCT. Twelve patients had high-risk cytogenetic abnormalities involving 11q23 (n=6), chromosome 5 (n=4) and/or chromosome 7 (n=5).

Result: The 5-year OS and DFS was 23% (CI 95%: 9-41%) and 17% (CI 95%: 5-35%) respectively. Transplant related mortality (TRM) and relapse at 1-year were 39% (CI 95%: 19-59%) and 22% (CI 95%: 5-38%). We found no significant differences in survival based on remission status, pre-transplant cytogenetics or conditioning regimen.

Conclusion: Outcomes of children and young adults with tMDS/tAML continue to be poor with TRM and relapse remaining the major obstacles to cure.

Key words

Pediatric, Acute myeloid leukemia, Myelodysplastic syndrome, Transplantation
Introduction

Although most cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) occur as de novo diseases, less commonly these malignancies result as the consequence of prior cancer therapy. These two therapy-related myeloid malignancies (tMDS or tAML) are well-known complications of alkylating agents, epipodophyllotoxins, and/or irradiation [1]. With the increase in the number of children surviving cancer, therapy-related neoplasms are on the rise [2,3]. Outcomes for patients with tMDS or tAML are generally poor despite intensive chemotherapy regimens or allogeneic hematopoietic cell transplantation (allo-HCT) [4-8]. Studies in adults have shown lower disease-free survival (DFS) and higher rates of relapse in patients with tAML compared to de novo AML [4]. DFS after transplantation for adults typically remains <35% [4,9-11], with relapse being the greatest barrier to cure [9-11]. Relatively few studies have reported outcomes in children and adolescents with tMDS/tAML whose survival appear as poor as those in adults [6,9,11-13]. In adults with tMDS/tAML, increasing age, high-risk cytogenetics and remission status at time of transplantation, have all been associated with inferior outcomes post allogeneic hematopoietic cell transplantation (allo-HCT) [9-11], but there are limited data on how these same characteristics may influence outcomes in pediatric patients [5,6,8]. As the literature is limited surrounding these associations for children and young adults with tMDS/tAML, we reviewed the outcomes of 25 consecutive patients who received allo-HCT at the University of Minnesota.

Materials/patients and methods

Outcomes were evaluated in 25 consecutive children and young adults with tMDS or tAML who underwent allo-HCT at the University of Minnesota between 1990 and 2010. The median age at allo-HCT was 19 (range, 5-29) years. All patients and/or guardians underwent informed consent prior to allo-HCT on University of Minnesota IRB approved treatment protocols. This analysis was approved by the University of Minnesota institutional review board.

The majority of patients (n=14) were transplanted after 2001. Myeloablative (MA) allo-HCT was performed in 21 (84%) patients and reduced intensity conditioning (RIC) was used in 4 (16%) patients according to University of Minnesota Blood and Marrow Transplantation protocols. Myeloablative conditioning for most patients (n=20) was cyclophosphamide (120 mg/kg) and 1320 cGy total body irradiation (TBI), with the addition of fludarabine (200mg/m²) in nine patients, and a single patient received cyclophosphamide and busulfan. The decision to receive RIC was determined by the transplant center. The median performance status based on Lansky/Karnofsky scores for patients receiving MA and RIC were the same (median 90; range 70-100). RIC conditioned patients received fludarabine (200mg/m²), busulfan (8-12 mg/kg) and TBI (200 cGy) (n=2) or cyclophosphamide (50mg/kg), fludarabine (200mg/m²) and TBI (200 cGy) (n=2). Graft-versus-host disease (GVHD) prophylaxis was cyclosporine-based in all patients. Graft source for the RIC patients included HLA partially matched unrelated umbilical cord blood (n=2) and HLA matched unrelated bone marrow (n=2). For MA patients donor hematopoietic cell sources were HLA matched related bone marrow (BM) (n=7), HLA matched unrelated bone marrow (BM) (n=4) or HLA partially matched unrelated umbilical cord blood (UCB) (n=14). All matched related donors had antigen level typing at HLA-A, -B and DRB1. Unrelated BM recipients and donors were matched by high resolution typing at HLA-A, -B, and DRB1, with allele level typing for HLA-C beginning in June 2004. Among the UCB transplant recipients, 9 received single UCB and 5 double UCB units. For the UCB units, patients and donors were typed for HLA-A and -B at the antigen level and for DRB1 at the allele level using a previously described selection algorithm [14,15]. Seven were mismatched at 1 HLA locus and 6 were mismatched at 2 HLA loci. Cytogenetic risk classification was performed in all patients via routine chromosome analysis and FISH/G-Banding in the diagnostic bone marrow of tMDS/tAML to determine the presence of 11q23 abnormalities and/or deletions/monosomy of chromosome 5 and/or 7. Routine testing for other molecular mutations such as FLT3/ITD, RUNX1, NPM1, or RAS were not performed and therefore not known in this cohort.
Patients were hospitalized in single rooms ventilated with high-efficiency particulate air filtration systems. Patients at high risk for recurrence of herpes simplex virus (HSV) (titer > 1:8) or cytomegalovirus (CMV) reactivation (recipient or donor with a titer > 1:8) received high-dose acyclovir until day 100. CMV reactivation was treated with ganciclovir as previously described.16 Broad-spectrum antibiotics were administered for fever during aplasia, and antifungals were added for persistent fever unresponsive to antibiotic therapy. Granulocyte-colony stimulating factor (G-CSF) (5 mg/kg/day) was administered daily until neutrophil engraftment in all 25 patients. Following engraftment, all patients received yeast prophylaxis for 100 days and Pneumocystis (carinii) jiroveci prophylaxis for 12 months after transplantation.

Statistical methods

Data on patient characteristics and outcomes were prospectively collected by the Biostatistical Support Group at the University of Minnesota using standardized collection procedures. Study endpoints included neutrophil engraftment (defined as two consecutive days with an ANC > 500/µl), acute graft-versus-host disease (aGVHD) grades II-IV and III-IV, chronic graft-versus-host disease (cGVHD), Transplant related mortality (TRM), relapse, disease-free survival (DFS) and overall survival (OS). Primary graft failure was defined as failure to achieve an ANC > 0.5 × 10^9/L by day + 42. Secondary graft failure was defined as primary engraftment followed by a decrease in the ANC to < 0.5 × 10^9/L without recovery until a new stem cell infusion is required or the patient died. Acute GVHD and cGVHD were graded according to previously published criteria, with histopathologic confirmation when possible [17,18]. All patients with engraftment were considered evaluable for GVHD. Relapse was defined as a recurrence of MDS/AML after allo-HCT, by morphologic and/or cytogenetic criteria. TRM was defined as death in the first year after allo-HCT for any reason other than relapse. Death from GVHD was defined as death by any cause in the presence of GVHD. DFS was defined as the time from transplant (day 0) until disease recurrence, death, or last patient contact, whichever came first. OS was defined as the time from transplant day 0 until death or last contact. Patients and disease characteristics, including remission status at time of allo-HCT (CR vs. not), conditioning regimen (MA vs. RIC) and cytogenetics (high-risk vs. other), were summarized using descriptive statistics. Pearson’s chi-square test was completed for all categorical factors.

All patients were followed longitudinally until death or last follow up. Kaplan-Meier 19 was used to estimate neutrophil recovery, OS and DFS. Cumulative incidence20 was used to estimate relapse, TRM, aGVHD, and cGVHD. Statistical comparison of neutrophil, overall survival and disease free survival between groups was completed by the Log-Rank test. The proportional hazards model of Fine and Gray21 was used to assess the independent factors on relapse, TRM, aGVHD, and cGVHD. Factors included in multivariate analysis were disease status [complete remission (CR) ≤ 5% blasts vs. > 5% blasts], high-risk cytogenetics group (11q23/ch5/7 vs. other) and conditioning group (MA vs. RIC) Analysis was performed with Statistical Analysis System software version 9.2 (SAS Institute). Groups with value of \( p \leq 0.05 \) were considered to be statistically different.

Results

Patient characteristics

Table 1 shows the disease characteristics for the 25 patients. Thirteen patients (52%) were male. Four patients (16%) had tMDS and 21 (84%) tAML. The median ages at time of primary cancer diagnosis and diagnosis of tMDS/tAML were 13 (range, 1-27) and 17 (range, 4-29) years, respectively. The median time from the primary cancer diagnosis to tMDS/tAML was 3.2 (range, 0.89-12.58) years and the median time from diagnosis of tMDS/tAML to allo-HCT was 4 months (range, 2-42). The initial cancer diagnoses included B or T-Cell acute lymphoblastic leukemia/ Non-Hodgkin’s lymphoma in 15 patients and sarcoma of bone in 9, with most (92%) patients receiving alkylating agents and/or epipodophyllotoxins prior to developing tMDS/tAML. The median follow-up was 4.7 (range, 0.9-6.0) years from transplantation.
Twelve patients (48%) had high-risk cytogenetics with abnormalities involving 11q23 (n=6), chromosome 5 deletions (n=4), and/or chromosome 7 deletions/monosomy (n=5). Nineteen patients (76%) were in complete remission (CR) at the time of transplantation (< 5% blasts in the bone marrow). The decision to treat patients with chemotherapy prior to allo-HCT was made by the referring physician. All 21 patients with tAML received anthracycline and cytarabine-based chemotherapy prior to allo-HCT with a median of 1 cycle of therapy (range, 1-4). At diagnosis tAML patients had a median bone marrow blast count of 40% (range, 1-90%), compared to 3.2% (range, 1-10%) for the 4 patients with tMDS who did not receive chemotherapy ($p=0.01$). Prior to transplant, the median bone marrow blast count for tAML patients was 1% (range, 0-62%), compared to 2.5% (range, 0-13%) for those with tMDS ($p=0.87$). All 8 patients with tAML and high-risk cytogenetics were in morphologic remission prior to allo-HCT compared to 8 of 13 (62%) for patients not harboring 11q23, chromosome 5 and/or 7 mutations. Patient characteristics for the 25 patients evaluating age, gender, conditioning, conditioning agents, recipient CMV status, donor source, aGVHD (Grade II-IV), aGVHD (Grade III-IV), cGVHD, HLA-typing, and year of allo-HCT are reported in Table 2.

### Table 1. Disease Characteristics

<table>
<thead>
<tr>
<th>Primary cancer diagnosis</th>
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<tbody>
<tr>
<td>ALL</td>
<td>8 (32)</td>
</tr>
<tr>
<td>NHL*</td>
<td>6 (24)</td>
</tr>
<tr>
<td>EFT</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>4 (16)</td>
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<tr>
<td>MFH</td>
<td>1 (4)</td>
</tr>
<tr>
<td>CMMD</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Medulloblastoma*</td>
<td>1 (4)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Disease status at time of HCT</th>
<th>N (%)</th>
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<tr>
<td>CR</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Refractory</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Untreated</td>
<td>3 (12)</td>
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<table>
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<tr>
<th>WHO classification (MDS)</th>
<th>N (%)</th>
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<tr>
<td>RC</td>
<td>3 (75)</td>
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<tr>
<td>RAEB</td>
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<thead>
<tr>
<th>Cytogenetics</th>
<th>N (%)</th>
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<tr>
<td>11q23</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Monosomy 7</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Deletion 7</td>
<td>2 (8)</td>
</tr>
<tr>
<td>5q deletion</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (32)</td>
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</table>

<table>
<thead>
<tr>
<th>Latency period to tMDS/tAML (Mean)</th>
<th>Years</th>
<th>Range</th>
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<tbody>
<tr>
<td>ALL</td>
<td>3.25</td>
<td>2.2-6.0</td>
</tr>
<tr>
<td>NHL</td>
<td>4.16</td>
<td>0.9-10.6</td>
</tr>
<tr>
<td>EFT</td>
<td>3.3</td>
<td>1.2-6.4</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>2.8</td>
<td>1.0-5.3</td>
</tr>
<tr>
<td>MFH</td>
<td>1.1</td>
<td>NA</td>
</tr>
<tr>
<td>CMMD</td>
<td>3.0</td>
<td>NA</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>5.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

*patient developed medulloblastoma and 4 years later NHL, prior to development of MDS

Abbreviations. ALL=Acute Lymphoblastic Leukemia; NHL=Non-Hodgkin’s Lymphoma; EFT=Ewing Family of Tumors; MFH=Malignant Fibro-Histiocytosis; CMMD=Chronic Mono-myeloproliferative Disease; CR=Complete Remission; RC=Refractory Cytopenia; RAEB=Refractory Anemia with Excess Blasts
Table 2. Patient Characteristics

<table>
<thead>
<tr>
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<th>tMDS/tAML</th>
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<tr>
<td>Group</td>
<td>25</td>
</tr>
<tr>
<td>Age Median (range)</td>
<td>19 (5-29)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Donor Source</td>
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<tr>
<td>BM</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>UCB</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Single</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Double</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Single Cords HLA</td>
<td></td>
</tr>
<tr>
<td>4/6</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>5/6</td>
<td>4 (44%)</td>
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<tr>
<td>6/6</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Double Cords HLA</td>
<td></td>
</tr>
<tr>
<td>4/6</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>5/6</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>6/6</td>
<td>0</td>
</tr>
<tr>
<td>Conditioning</td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>RIC</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Conditioning agents</td>
<td></td>
</tr>
<tr>
<td>Cy/Flu/TBI (1320cGy)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Cy/TBI (1320cGy)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Bu/Cy</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Bu/Flu/TBI (200cGy)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Recipient CMV</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Positive</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Acute GVHD (II-IV)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>No</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Acute GVHD (III-IV)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>No</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>No</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Year of Allo-HCT</td>
<td></td>
</tr>
<tr>
<td>1990-2000</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>2001-2010</td>
<td>14 (56%)</td>
</tr>
</tbody>
</table>

Abbreviations: BM=Bone Marrow; UCB=Umbilical Cord Blood; Cy=Cyclophosphamide; Flu=Fludarabine; Bu=Busulfan; TBI=Total body irradiation; MA=Myeloablative; RIC=Reduced intensity conditioning; Allo-HCT=Allogeneic hematopoietic cell transplantation

Neutrophil engraftment

Overall, 20 patients (81%) achieved donor neutrophil engraftment by day 42, with 75% (n=3) of tMDS and 86% (n=18) of tAML patients engrafting (p=0.78). Patients who received RIC allo-HCT were more likely to have neutrophil recovery by day 42 compared to MA conditioned patients [RR 3.16 (1.02-9.79); p=0.05]. There were no significant differences in engraftment based on year of allo-HCT (p=0.71), presence of high-risk cytogenetics (p=0.63) or CR status at time of allo-HCT (p=0.81).
GVHD

Graft-versus-host-disease grade II-IV, III-IV and chronic GVHD occurred in 14 (56%), 5 (20%) and 7 (28%) patients respectively. Grafts sources associated with grade II-IV GVHD were UCB (n=7; 50%) and marrow (n=7; 64%); UCB (n=3; 21%) and marrow (n=2; 18%) for grade III-IV aGVHD, and UCB (n=4; 29%) and marrow (n=3; 27%) for cGVHD. In multivariate analysis patients who received RIC allo-HCT had significantly greater risk of grade II-IV aGVHD [RR 2.51 (1.14-5.57); p=0.02] and chronic GVHD [RR 5.36 (1.36-21.1); p=0.02], but less grade III-IV aGVHD (RR 0; <0.01) compared to patients who received MA conditioning.

Survival

The 5-year DFS was 17% (Figure 1A) for the group with an overall survival at 5-years of 23%. When considering clinical characteristics as risk factors, there was no significant difference in 5-year DFS based on remission status [not in CR, RR 2.15 (0.67-6.88); p=0.20], presence of high-risk cytogenetics [RR 1.18 (0.42-3.32); p=0.75] or RIC versus MA conditioning [RR 0.72 (0.20-2.63); p=0.61].

Relapse

Five patients relapsed, all who had tAML and received a MA conditioning, providing a cumulative incidence of 22% at 1-year (Figure 1B). When considering the clinical characteristics of remission status, conditioning regimen, high-risk cytogenetics and year of allo-HCT as risk factors in the univariate analysis, none were significantly associated with relapse. In multivariate analysis relapse was significantly lower in patients who received RIC allo-HCT compared to MA (RR 0; p<0.01), although the small sample size for these patients may account for the findings.

Mortality

A total of 9 patients died of TRM, 1 with tMDS and 8 with tAML, providing a cumulative incidence at 1-year of 39% (Figure 1C). Five of these deaths occurred before day + 100. The causes of TRM were GVHD (n=4), infection (n=5), veno-occlusive disease (n=1) and/or multi-organ failure (n=3). There were no differences in the incidence of TRM at 1-year for patients with tMDS compared to tAML (25% vs. 42%; p=0.47). When considering the clinical characteristics of remission status, conditioning regimen, high-risk cytogenetics and year of allo-HCT as risk factors, none were significantly associated with TRM in univariate or multivariate analysis.

Figure 1A. Disease-free Survival; The cumulative incidence of disease-free survival for the 25 patients with tMDS/tAML at 5-years was 17%

Figure 1B. Relapse; The cumulative incidence of relapse for the 25 patients with tMDS/tAML at 1-year was 22%
**Discussion**

With the current success of large cooperative group studies, more children and adolescents are surviving childhood cancer [22, 23]. As there is now a large number of childhood cancer survivors, the population at risk for secondary MDS/leukemia will likely increase. The management of these patients is difficult and there are few reports detailing outcomes [6,8,12]. In this retrospective analysis of children and young adults with tMDS/tAML undergoing allo-HCT, we found relatively poor outcomes with a 5-year OS < 30%. These findings are consistent with current data for pediatric and adult patients [4,8,24]. We were unable to find an association between transplant outcomes and remission status or high-risk cytogenetics in our cohort of children and young adults with tMDS/tAML. We did identify less relapse in patients who received RIC allo-HCT, however, the very small number of patients in this subgroup prevents establishing a firm risk assessment. In these 4 patients who received RIC, 3 had high-risk cytogenetics (chromosome 5 and/or 7 deletion/monosomy), 3 were in morphologic remission (< 5% marrow blasts) prior to allo-HCT with only 1 of the 4 (a 10 year old with a 5q and 7q deletion) receiving pre-HCT chemotherapy and subsequently was not in morphologic remission prior to allo-HCT. As there was a greater incidence of both acute (Grade II-IV) and chronic GVHD in patients receiving RIC, an underlying graft-versus-leukemia (GVL) effect may be responsible for the lower incidence of relapse. A major factor protecting patients with tMDS/tAML from relapse could be the development of GVHD, particularly chronic GVHD, suggesting a role of GVL effect in long-term disease control. As intensive myeloablative conditioning is not well tolerated in these patients and may not be protective from relapse, further efforts to improve outcomes for these patients should be focused on reliably establishing engraftment with the least amount of toxicity and then augmenting the GVL effect.

Similar to the findings of Aguilera et al., who reviewed 22 pediatric patients with tMDS/tAML6, the most common primary cancer diagnoses in our analysis was leukemia/lymphoma followed by bone sarcoma. Although Aguilera identified a male predominance (68%) and shorter survival in patients with high/intermediate-risk cytogenetics, we were unable to confirm these findings and found an equal prevalence of tMDS/tAML in males/females (52%/48%) and no difference in survival based on high-risk cytogenetics.

In our study, an increased percentage of bone marrow blasts prior to allo-HCT was not associated with a greater risk of relapse, as reported by Woodard and colleagues [8]. In their report of 38 children with tMDS/tAML, the percentage of pre-transplant bone marrow blasts was positively associated with relapse, while we found no difference in relapse and only a trend toward improved DFS for patients in CR versus those with > 5% marrow blasts prior to HCT. As all the patients who had tAML received chemotherapy in our study, we are unable to analyze whether pre-HCT chemotherapy was beneficial. As the biology of treatment-related leukemia is likely quite different than de novo AML and more resistant to chemotherapy, it is not surprising that we were unable to find a difference in survival between patients with lower blast counts and those not in remission. As to whether or not children and young adults with tMDS and increased blasts benefit from salvage chemotherapies prior to allo-HCT also cannot be determined in our analysis as our numbers were small. Larger studies investigating the role of pre-HCT therapy in children and young adults with tMDS/tAML are necessary to adequately address this question.

TRM in our cohort was 39% at 1-year, which is consistent with current data [6,8,24] and perhaps not surprising given that patients with tMDS/tAML have received significant amounts of prior therapy, which likely is associated with reductions in organ function and/or decreased tolerance to intensive chemotherapy. As well, heavily pre-treated patients may also come to transplant with subclinical infections and/or organ dysfunction. These issues are a significant challenge and constitute a barrier to cure for patients with tMDS/tAML. Since year of transplant did not appear to impact outcomes, it appears that improvements in supportive care (including the introduction of newer antifungal fungal medications) did not
impact outcomes. Whether or not RIC allo-HCT will result in adequate disease control and less TRM is unknown at present, as most published data include patients with tMDS/tAML treated mainly with MA regimens [6,8,24]. In our analysis we report on 4 patients who received RIC, which limits our power to detect differences.

Conclusion
In summary, we present outcome data for 25 pediatric and young adult patients with tMDS/tAML treated at a single center. We found no correlation between remission status, high-risk cytogenetics, or year of transplantation on HCT outcome. We did identify less relapse in patients who received RIC versus MA allo-HCT, although the limited numbers in these two subgroups requires caution in the interpretation and further studies evaluating larger patient cohorts should be pursued. While HCT may be an effective treatment for some children with tMDS/tAML, non-relapse mortality and relapse remain barriers to long-term cure. More data regarding risk factors predicting outcomes of allo-HCT in pediatric patients with tMDS/tAML are needed to help determine which patients might most be at risk for either TRM or relapse. Although RIC allo-HCT appears feasible from our results and beneficial in adults with tMDS/TAML [13], larger prospective studies are needed to determine whether it provides equivalent DFS and can possibly replace current MA approaches for pediatric patients with treatment related MDS/AML.

Conflict of interest
The authors have no conflict of interest to disclose.

Authors’ contributions
MJB: conceived the study, reviewed data and writing of the manuscript; JM: reviewed data and writing of the manuscript; QC: statistical analysis; BT: data collection; MRV: reviewed data and writing of the manuscript.

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