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Outcome and factors affecting survival of childhood myelodysplastic syndrome; single centre experience

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ABSTRACT

Introduction: Although many therapeutic options have been attempted for pediatric myelodysplastic syndrome (MDS), still hematopoietic stem cell transplant (HSCT) is the only curative therapy. We described the outcome of these patients and the factors affecting the overall survival (OS) and event free survival (EFS).
Methods: This is a retrospective descriptive study included 44 patients with MDS who presented to Children Cancer Hospital Egypt (CCHE-57357), between July 2007 and December 2015. HSCT was offered to patients who had HLA matched family donors.
Results: Eighteen patients (40.9%) had refractory cytopenia of childhood (RCC), 19 (43.2%) had refractory anemia with excess blasts (RAEB), and 7 (15.9%) had refractory anemia with excess blasts in transformation/myelodysplastic related acute myeloid leukemia (RAEB-T/MDR-AML). Cytogenetic abnormalities were observed in 54.8% of evaluable patients, in which monosomy 7 was the commonest abnormality observed (26.1%). Allogeneic HSCT from HLA matched donors was performed in 9/44 patients. The Average $CD34^+$ count was 3.57×10^6/Kg recipient weight. The 2-year OS and EFS for the whole cohort were 43.3% and 33.8%, respectively, and for the transplanted patients were 75% and 60%, respectively. Univariate analysis showed improved 2 years-OS and EFS in patients who underwent HSCT as compared to those who didn't (75% versus 35.4% for OS, $P = 0.088$ and 60% versus 27.5%, for EFS, $P = 0.074$).
Conclusion: Allografts from either matched related or unrelated or even haplo-identical donors should be offered for pediatric MDS patients, as HSCT is the only curative option for those patients. Further collaborative efforts, a more precise molecular diagnosis, as well as large-scale prospective therapeutic trials are required to develop standard diagnostic and therapeutic guidelines for such rare disease.

1. Introduction

Pediatric myelodysplastic syndrome (MDS) is an uncommon disorder accounting for less than 5% of hematopoietic neoplasia in childhood. The genetic changes predisposing children to MDS remain unclear. Secondary MDS refers to MDS following chemo- or radiation therapy, congenital bone marrow failure disorders, or acquired aplastic anemia and that in familial disease. Primary MDS refers to all remaining cases [1].

The most common cytogenetic abnormality associated with childhood MDS is monosomy 7. Complex cytogenetic abnormalities, trisomy 8 and trisomy 21 are also occasionally observed. Most cases of refractory cytopenia of childhood (RCC) show a normal karyotype [2].

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Compared with adult MDS, loss of chromosome 5 or a del(5q) is rare in childhood MDS, and when observed generally occurs in the context of complex aberrations. The unique del(5) syndrome is literally absent in pediatric MDS [3].

The new World Health Organization (WHO) classification identified several subtypes of MDS in children, detailed in Table 1 [4].

Hematopoietic stem cell transplant (HSCT) is the only curative option for pediatric patients with MDS. However, other modalities of treatment have been attempted such as immunosuppressive agents, epigenetic modifying agents, and hematopoietic growth factors [5].

The international prognostic scoring system (IPSS), which has effectively correlated disease factors at presentation to outcomes in adults, has been applied to the pediatric population; however, results are of limited value as only BM blasts <5% and platelet count $>100 \times 10^9$/L were found to successfully predict survival [6].

This study aimed at evaluating the clinical characteristics and outcome of pediatric patients newly diagnosed with MDS who presented to Children Cancer Hospital Egypt (CCHE-57357), between July 2007 and December 2015, also to assess different patients and disease factors related to the prognosis of those patients.

2. Materials and METHODS

2.1. Study design

This is a retrospective descriptive study included newly diagnosed patients with MDS who presented to Children Cancer Hospital Egypt (CCHE-57357), between July 2007 and December 2015, and followed till June 2017.

Patients who had congenital (inherited) bone marrow failure syndromes were excluded. All patients were reviewed for the diagnostic criteria according to the pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases [4].

Predisposition syndromes such as those caused by mutations in *GATA2*, *RUNX1*, *CEBPA*, and *SRP72* genes were not evaluated as these molecular tests are still not available to be done initially.

Initial patients' data included sex, age at initial presentation, modified WHO classification, cytogenetic abnormalities, revised IPSS risk stratification, systemic therapy given, and availability of a matched family donor. For the transplanted group, patients' data included time to transplant (since diagnosis), stem cell dose, and stem cell source.

Wait and see approach was adopted for patients with RCC who had normal karyotype and were transfusion independent. Systemic chemotherapy (acute myeloid leukemia "AML"-like) was given before transplant for those with refractory anemia with excess blasts (RAEB) and refractory anemia with excess blasts in transformation (RAEB-T)/myelodysplastic related AML (MDR-AML) using Children Oncology Group (COG) AAML1031 protocol [Arm A – high risk] (Supplementary Table 1). Hematopoietic stem cell transplantation (HSCT) was offered to patients who had available matched related donor (matched unrelated donor transplantations are still not done in our country due to unavailable registries). They received myeloablative conditioning therapy; IV busulfan from day −10 to day −7 and cyclophosphamide (50 mg/kg/day) from day −5 to day −2, followed by stem cell infusion. Daily busulfan dose is weight-dependent; < 9 kg: 1 mg/kg/6 h, from 9 to <16 kg: 1.2 mg/kg/6 h, from 16 to <23 kg: 1.1 mg/kg/6 h, from 23 to <34 kg: 0.95 mg/kg/6 h, 34 kg or more: 0.8 mg/kg/6 h. Graft versus host disease (GvHD) prophylaxis consisted of Cyclosporine A (CsA) and short course methotrexate at days +1, +3 and + 6 (bone marrow stem cells), with an additional MTX at day + 11 (peripheral blood stem cells).

Patients were treated on institutional review board approved treatment protocols, and all patients' guardians provided signed informed consent.

Table 1
Diagnostic categories of myelodysplastic and myeloproliferative diseases in children.

1. Myelodysplastic/Myeloproliferative disease
- Juvenile myelomonocytic leukemia (JMML)
- BCR-ABL-negative chronic myeloid leukemia (Ph− CML)

2. Down syndrome (DS) disease
- Transient abnormal myelopoiesis (TAM)
- Myeloid leukemia of DS

3. Myelodysplastic Syndrome (MDS)
- Refractory cytopenia of childhood (RCC) (PB blasts <2% and BM blast <5%)
- Refractory anemia with excess blasts (RAEB) (PB blasts 2−19% or BM blasts 5 −19%)
- RAEB in transformation (RAEB-T) (PB or BM blasts 20−29%)
- Myelodysplastic related AML (MDR-AML) (PB or BM blasts ≥30%)

2.2. End points and statistical methods

Study end points included overall survival (OS), event free survival (EFS) and relapse. OS was defined as the time from diagnosis until death or lost contact. EFS was defined as the time from diagnosis until disease recurrence, death, or last patient contact, whichever came first. Relapse was defined as a morphologic and/or cytogenetic recurrence of MDS after therapy (whether chemotherapy or HSCT). Patients' characteristics were presented as frequencies and percentages for categorical variables; means and standard deviations for quantitative variables. Survival analysis was computed using Kaplan Meier curves. The follow up duration was one year post end of treatment. The censored cases were the patients who did not encounter the event till their dates of last contact and lost to follow up.

3. Results

3.1. Patients and disease characteristics

The study cohort analyzed 44 patients with median age at diagnosis of 6.5 years (range from 0.39 to 17.38 years) and male to female ratio was 1.93:1. Primary MDS was encountered in 40 patients (91%), 2 patients were Down syndrome (4.5%), while the remaining 2 patients (4.5%) were secondary (therapy-related) MDS (one patient was Ewing's sarcoma and one was high risk neuroblastoma post autologous HSCT). Eighteen patients (40.9%) had RCC, 19 (43.2%) had RAEB, and 7 patients (15.9%) had RAEB-T/MDR-AML.

Initial cytogenetic analysis was done in 42 patients. Twenty three patients (54.8%) had abnormal karyotype and monosomy 7 was the most common observed abnormality, seen in 26.1% of the tested cases. According to the revised IPSS risk stratification, we found that 5 patients (11.9%) were low-risk, 7 (16.7%) were intermediate-risk, 21 (50%) were high-risk, and 9 patients (21.4%) were very high-risk. Patients' characteristics are summarized in Table 2.

Allogeneic HSCT from HLA matched donors was performed in 9/44 patients (20.5%), with median time to transplant of 8.6 months (ranging from 6 months to 15 months). Six patients (66.7%) were diagnosed initially with RAEB, 2 (22.2%) were RCC and one patient (11.1%) was MDR-AML. All patients received myeloablative conditioning regimen in the form of Busulfan/Cyclophosphamide followed by stem cell infusion. Bone marrow harvest was used for 7

Table 2
Characteristics of the whole cohort of patients.

Characteristic	N (%)
Total patients	44 (100)
Sex	
Male	29 (65.9)
Female	15 (34.1)
Age groups	
≤10 years	33 (75.0)
>10 years	11 (25.0)
Median age (years)	6.5
Range (min – max)	0.39–17.38
Modified WHO classification	
RCC	18 (40.9)
RAEB	19 (43.2)
RAEB-T/MDR-AML	7 (15.9)
Cytogenetics[a]	
Normal karyotype	19 (45.2)
Abnormal karyotype:	23 (54.8)
Monosomy 7	11 (26.1)
Trisomy 21	3 (7.1)
del 7q	2 (4.8)
del 5q	2 (4.8)
Complex karyotype	2 (4.8)
Trisomy 8	1 (2.4)
Others[b]	2 (4.8)
Revised IPSS risk stratification[a]	
Low risk	5 (11.9)
Intermediate risk	7 (16.7)
High risk	21 (50)
Very high risk	9 (21.4)
HLA matched donor	
Yes	13 (29.5)
No	24 (54.5)
Not available	7 (16.0)
Systemic therapy	
Yes	26 (59.1)
No	18 (40.9)
Allogeneic HSCT	
Yes[c]	9 (20.5)
No	35 (79.5)

[a] Initial cytogenetic testing was not done for 2 patients.
[b] Other chromosome abnormalities included: t(12; 17) (n = 1) and isochromosome 17q (n = 1).
[c] Nine/13 patients who had HLA matched family donors underwent HSCT; 2 patients died during induction chemotherapy and 2 were lost to follow up before proceeding to HSCT.

Table 3
Characteristics of the patients who underwent HSCT.

Characteristic	N (%)
Total patients	9 (100)
Time to transplant (days)	Mean = 8.3
Range	183–449
Median	260
Modified WHO classification	
RCC	2 (22.2)
RAEB	6 (66.7)
MDR-AML	1 (11.1)
CD34 $^{+}$ count (× 106/kg recipient weight)	
Range	1.70–9.02
Median	3.57
Stem cell source	
BM	7 (77.8)
PB	2 (22.2)
Donor	
Matched sibling	8 (88.9)
Matched parent	1 (11.1)

patients while 2 patients received peripheral blood stem cells and the median CD34 dose was 3.57 × 10^6/Kg recipient weight (ranging from 1.70 to 9.02) as shown in Table 3. GvHD was encountered in 3 patients (33.3%); 2 of them were acute and one was de-novo chronic form. Three of the 9 patients experienced disease relapse post allogeneic HSCT, all were dead. Transplant related mortality (TRM) was not encountered.

3.2. Survival analysis

With median duration of follow up of 14 months, the 2-year OS and EFS of the whole study cohort were 43.3% (±15.68) and 33.8% (±14.896), respectively.

Univariate analysis revealed improved 2 years-OS and EFS in patients who underwent HSCT (n = 9) as compared to those who didn't (n = 35); yet it was not statistically significant mostly due to small number of patients (75% vs 35.4% for OS, P = 0.088 and 60% vs 27.5%, for EFS P = 0.074) as shown in (Fig. 1).

Patients with RCC had EFS of 45.5%, compared to 26.1% for patients with RAEB and 38.1% for patients with MDR-AML (P = 0.196) as shown in (Fig. 2).

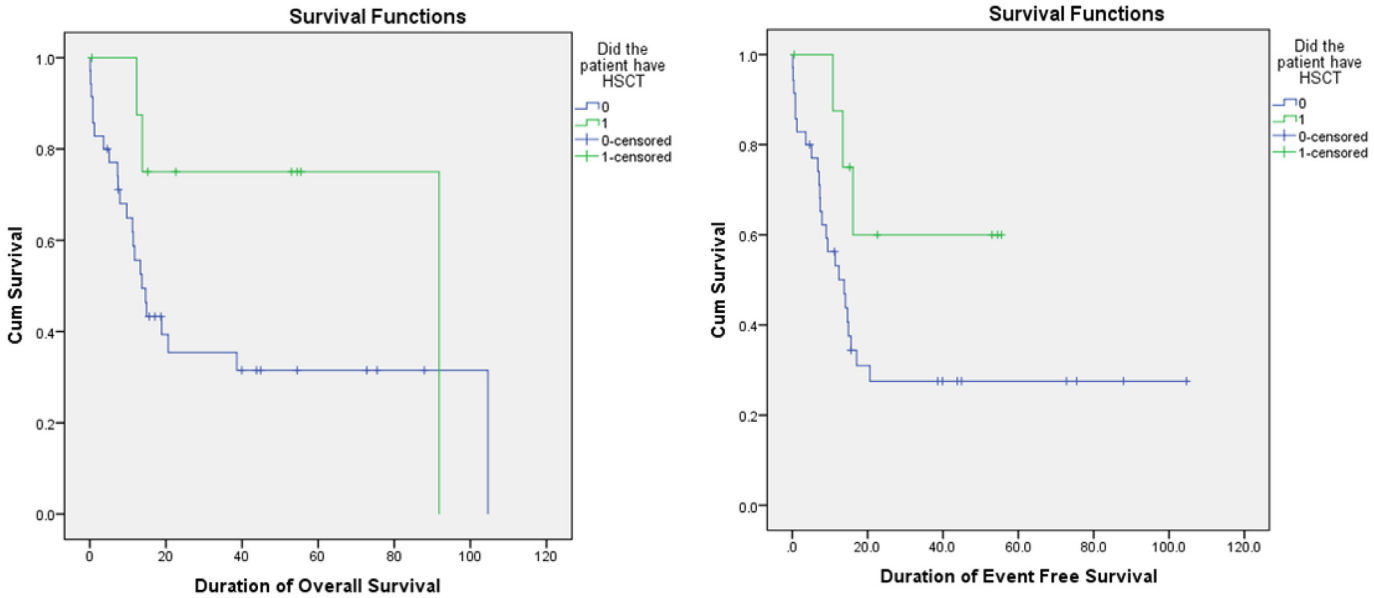

Fig. 1. 2 years Overall survival and Event free survival for patients as regards to HSCT.

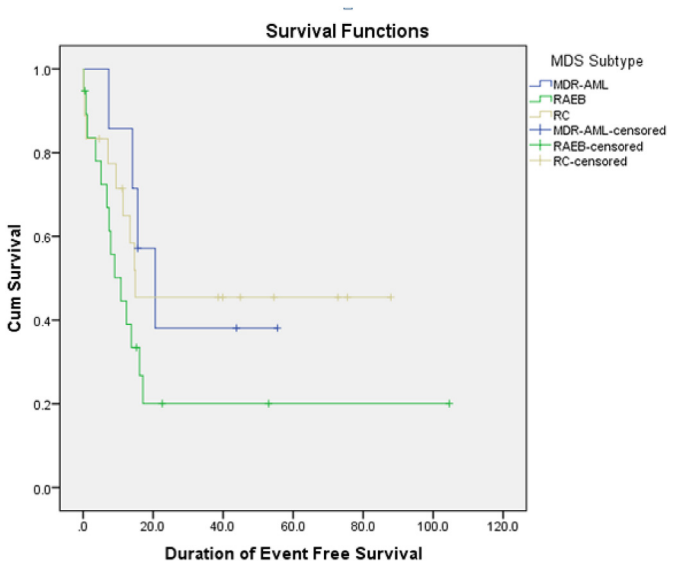

Fig. 2. 2 years Event free survival for patients as regards to MDS subtype.

Other risk factors were studied, but it showed no statistical significance (Table 4).

4. Discussion

Many issues concerning treatment of pediatric MDS like pre-HSCT remission-induction therapy, timing of HSCT, optimal preparative regimen and stem cell source need to be resolved. Also there has been little consensus regarding patient or disease characteristics, or treatment-related factors that may be associated with transplant outcomes for those patients. This study tried to address our experience in treatment of this rare disorder and investigate the impact of different patient related and disease related factors on their outcome.

In our study RCC, RAEB and RAEB-T/MDR-AML were found in 40.9%, 43.2% and 15.9% respectively, which was similar to what was reported by Schwartz et al. [7] who found that 50% of their patients were classified as RCC and 50% as RAEB. However, Smith et al. [5] reported different subtype distribution; among 37 patients who underwent HSCT, RC and RAEB were found in 81% and 19% respectively. In our cohort, the frequency of RCC was lower than other reported literature, might be due to late presentation of patients in developing country as they may present first with advanced disease.

The most frequent cytogenetic abnormality among our patients is monosomy 7 (26.1% of patients). Trisomy 8 was found in 2.4%, while normal karyotype was found in 43.2%. Smith et al. [5] reported that monosomy 7 was found in 57% of their patients, trisomy 8 in 19% while normal karyotype was found in 8.3%. Gabriela et al. [8] reported that karyotype was normal in 33.3% of their children, 48.5% of patients had monosomy 7 and 9.1% had trisomy 8. These variations in frequencies may reflect racial and regional differences among different cohorts of patients.

Because MDS is a rare pediatric disease, the majority of the studies on outcomes are limited by heterogeneous treatment and supportive care regimens. However, of clear value, most investigators agree that HSCT can improve survival for the majority of children with MDS. This study showed an estimated 2- years OS and EFS of 43.3% and 33.8% respectively, and the survival outcome was better for those who did HSCT (75% OS and 60% EFS) compared to those without HSCT (35.4% OS and 27.5% EFS). A single centre study by Smith et al. reported an estimated OS of 53% and DFS of 48% at 3 years [5]. The survival advantage of HSCT in pediatric MDS was reported in other studies [9,10].

Our cohort showed that patients with RCC had an estimated 2-years EFS as low as 45.5%. Patients with RCC in our cohorts had inferior survival than their counterparts in the literature due to 2 reasons. First, just one patient had the favorable criteria of wait & see approach. Second, HSCT which was indicated in the rest of them was not done except for 2 patients who had matched family donors, as we are still not doing matched unrelated donor transplants in our country.

The small number of the transplanted patients among this cohort (due to limitation of available donors) precludes doing sub analysis to assess the impact of pre-transplant cytotoxic

Table 4
Univariate analysis for overall survival and event free survival.

	N	OS at 24-months (%)	P-value	EFS at 24-months (%)	P-value
Whole group	44	43.3		33.8	
Age:			0.276		0.311
≤10 years	33	54.4 (±17.836)		40.3 (±17.836)	
>10 years	11	27.3 (±26.264)		18.2 (±22.736)	
Sex:			0.112		0.595
Male	29	49 (±19.012)		34.7 (±18.228)	
Female	15	31.9 (±25.48)		31.9 (±25.48)	
MDS subtype			0.651		0.196
RCC	18	44.9 (±24.5)		45.5 (±24.304)	
RAEB	19	37.2 (±23.324)		26.1 (±19.404)	
MDR-AML	7	47.6 (±44.1)		38.1 (±39.004)	
Karyotype[a]			0.554		0.456
Normal Karyotype	19	48.2 (±23.716)		33.7 (±23.912)	
Monosomy 7	11	22.7 (±26.656)		18.2 (±22.736)	
Other than monosomy 7	12	54.5 (±29.4)		46.9 (±29.4)	
Revised IPSS risk[b]			0.650		0.337
Low	5	50 (±69.384)		33.3 (±53.312)	
Intermediate	7	57.1 (±36.652)		42.9 (±36.652)	
High	21	41.7 (±21.56)		38.3 (±22.344)	
Very high	9	29.6 (±32.144)		11.1 (±20.58)	
HSCT			0.088		0.074
Yes	9	75 (±29.988)		60 (±35.672)	
No	35	35.4 (±17.052)		27.5 (±15.484)	

[a] Two patients had no initial cytogenetic testing.
[b] Two patients had no initial risk stratification.

chemotherapy and timing of HSCT on the outcome. This analysis was done by Smith et al. and revealed that, in multivariate analysis, higher 3-years DFS was associated with patients who didn't receive pre-HSCT chemotherapy ($P = 0.03$) and with those who were transplanted within 140 days from initial diagnosis ($P = 0.02$). Other studied factors like karyotype, pre-HSCT BM blast percentage and donor source had no significant impact on 3 years DFS [5].

Strahm et al. [10] found that the use of intensive chemotherapy before HSCT did not improve survival, and hence they recommended giving intensive chemotherapy only for children with MDR-AML, rather than those with RAEB or REAB-T.

Klein et al. described similar rates of engraftment, GvHD, and transplant related mortality (TRM) following nonmyeloablative haploBMT with post-transplantation cyclophosphamide (PT/Cy) and HSCT with HLA-matched related (MRD) and HLA-matched unrelated (MUD) donors [11].

Currently we are investigating haplo-identical transplant with bone marrow stem cell source and PT/Cy for those with no available MRD.

As with any single centre report, the main limitation to this series is the small sample size, which limits the applicability of the results without further confirmation in larger groups of patients. Also, being retrospective, the cohort was heterogeneous with regard to diagnostic methods, pre-HSCT chemotherapy, and timing of performing HSCT.

In summary, allografts from either matched related or unrelated or even haplo-identical donors should be offered for pediatric MDS patients, as HSCT is the only curative option for those patients. Further collaborative efforts, a more precise molecular diagnosis, as well as large-scale prospective therapeutic trials are required to develop standard diagnostic and therapeutic guidelines for such rare disease.

Appendix A. Supplementary data

Supplementary data to this article can be found online at ce:https://doi.org/10.1016/j.phoj.2019.03.001.

References

[1] Niemeyer CM, Kratz CP, Hasle H. Pediatric myelodysplastic syndromes. Curr Treat Options Oncol 2005;6(3):209–14.
[2] Chatterjee T, Choudhry VP. Childhood myelodysplastic syndrome. Indian J Pediatr 2013;80(9):764–71.
[3] Niemeyer CM, Kratz CP. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia: molecular classification and treatment options. Br J Haematol 2008;140(6):610–24.
[4] Hasle H, Niemeyer CM, Chessells JM, Baumann I, Bennett JM, Kerndrup G, et al. A pediatric approach to the WHO classification of Myelodysplastic and myeloproliferative diseases. Leukemia 2003;17(2):277–82.
[5] Smith AR, Christiansen EC, Wagner JE, Cao Q, MacMillan ML, Stefanski HE, et al. Early hematopoietic stem cell transplant is associated with favorable outcomes in children with MDS. Pediatr Blood Canc 2013;60(4):705–10.
[6] Hasle H, Baumann I, Bergsträsser E, Fenu S, Fischer A, Kardos G, et al. The International Prognostic Scoring System (IPSS) for childhood myelodysplastic syndrome (MDS) and juvenile myelomonocytic leukemia (JMML). Leukemia 2004;18(12):2008–14.
[7] Schwartz JR, Ma J, Lamprecht T, Walsh M, Wang S, Bryant V, et al. The genomic landscape of pediatric myelodysplastic syndromes. Nat Commun 2017;8(1):1557.
[8] Kardos G, Baumann I, Passmore SJ, Locatelli F, Hasle H, Schultz KR, et al. Refractory anemia in childhood: a retrospective analysis of 67 patients with particular reference to monosomy 7. Blood 2003;102(6):1997–2003.
[9] Woodard P1, Carpenter PA, Davies SM, Gross TG, He W, Zhang MJ, et al. Unrelated donor bone marrow transplantation for myelodysplastic syndrome in children. Biol Blood Marrow Transplant 2011;17(5):723–8.
[10] Strahm B, Nöllke P, Zecca M, Korthof ET, Bierings M, Furlan I, et al. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome in children: results of the EWOG-MDS 98 study. Leukemia 2011;25:455–62.
[11] Klein OR, Buddenbaum J, Tucker N, Chen AR, Gamper CJ, Loeb D, et al. Nonmyeloablative haploidentical bone marrow transplantation with post-transplant cyclophosphamide for pediatric and young adult patients with high-risk hematologic malignancies. Biol Blood Marrow Transplant 2017;23(2):325–32.