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Outcomes of blood and marrow transplantation in children less than 2-years of age: 23 years of experience at a single center

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ABSTRACT

Objectives: Allogeneic hematopoietic cell transplantation (Allo-HCT) is a curative option for children with various malignant and non-malignant diseases. Most reports studied all age groups amongst children. Herein we analyzed our data in children transplanted at or less than 2-years of age.

Patients and methods: We reviewed medical charts of 618 patients who underwent 666 transplantation at our center between 1993 and 2015. There were 340 boys and 278 girls. Median age was 0.7 years (range 0.04–2). Stem cell source was bone marrow (BM) in 492 (73.9%), unrelated umbilical cord blood (UCB) in 161 (24.2%) followed by peripheral blood stem cell (PBSC) in 13 (2%) patients. Matched siblings were the most common donors (n = 356, 53.5%), followed by unrelated (n = 161, 24.2%) with haploidentical family member donors in 29 (4.4%) transplants. Disease groups were categorized as benign hematology (Thalassemia, Fanconi, Aplastic anemia etc.), benign neoplasm (Langerhans cell histiocytosis, Hemophagocytic Lymphohistiocytosis etc.), non-neoplasms (metabolic disorders, immunodeficiency disorders etc.) and Leukemia/lymphomas (myeloid and lymphoid malignancies etc.)

Results: Cumulative incidence of acute GvHD (I-IV) was 31.5% (n = 210) and grade III-IV GvHD was 8.7% (n = 58). At median follow-up of 115.1 months, the cumulative probability of overall survival (OS) at 5 years was 70.0% ± 1.9%. Our mortality rate was 31.2% (n = 193). The five-year OS was significantly better in patients transplanted for benign hematological disorders ($P = .001$). Patients transplanted using BM/PBSC as source of stem cells fared significantly better compared to those in which CB was used ($P<.001$). Post-transplant graft failure remains the leading cause requiring further transplants in this age group. In conclusion, the cumulative probability of OS at 5 years was about 70.0% for all with an OS of 61% in our haploidentical recipients.

Conclusion: Analyzing our institutional data over time has enabled us to develop tentative strategies to minimize transplant related toxicities in very young children who are candidates for allo-HCT.

1. Introduction

Allogeneic hematopoietic cell transplant (Allo-HCT) is an established and widely performed curative therapy for a various malignant and nonmalignant disorders in children. These include but are not limited to hematologic malignancies, inherited bone marrow failures syndromes (IBMFS), primary immune deficiencies (PID) and some inborn errors of metabolism (IEM) [1–6]. Indications for various diagnoses, comorbidities, conditioning regimens and graft source are different from adults and have also varied between pediatric groups [6].

Our clinical practice has evolved over the past decades giving us better insight into various aspects such as decreasing cytoreductive toxicity, optimizing graft source, adjusting graft versus host disease (GvHD) medications and improving supportive management of patients [7,8]. Establishing and studying trends in transplant activities is crucial for enhanced patient care. Such studies have helped us recognize effective clinical practices, disparities between disease outcomes and conditions that need more focused research.

Children in the first few years of life are at a higher risk of

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therapy related acute and chronic complications affecting their survival and outcomes [9,10]. There are few studies on survival and transplant related morbidity in children who are less than 3 years of age [11–13]. We conducted a retrospective study of the pediatric Allo-HCT activity in our center over two decades in children who were younger than or equal to two years of age at the time of transplant.

2. Patients and method

2.1. Study design

This is a descriptive account of all patient who were given an allo-HCT at our institution between January 1993 to December 2015 and were younger than or equal to two years of age at transplant. Clinical, laboratory and transplant related data was collected prospectively at an institutional database. All patients' guardians signed consent before transplant. International Classification of Diseases for Oncology (ICD-O, Version 3.0), International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM) and Online Mendelian Inheritance in Man (OMIM) were used to record the primary diagnoses for relevant diagnostic related groups.

2.2. Patients

Six hundred and eighteen (618) patients underwent 666 blood and marrow transplantation at our center. Patients' demographics and related data is shown in Table 1. For most patients the primary indication for transplant were non-neoplastic diseases (primary immunodeficiency and metabolic disorders), followed by 'benign neoplasms except benign hematological disorders' (histiocytic disorders), benign hematological disorders, and leukemias and lymphomas, combined.

2.3. Graft and donor source

Bone marrow (BM) was the major source of stem cells in 492 (73.9%) transplants. . Matched siblings were the most commonly used donors (n = 356, 53.5%) whereas in 29 (4.4%) transplants we used a haplotype identical family member for donor as well. Median $CD34^+$ cell dose was 8.1×10^6/kg of recipient's weight (range, 0.03–124.0) for BM/PBSC and 0.3×10^6/kg of recipient's weight (range, 0.03–14.9) for UCB transplants. Majority of the patients (n = 576, 86.5%) received GvHD prophylaxis as per institutional guidelines.

2.4. Transplant procedure

All patients were admitted to private rooms and received disease specific cytoreductive regimen followed by an infusion of graft cells. Every patient remained hospitalized till hematopoietic count recovery with no ongoing clinical concerns. Total body irradiation (TBI) combined with cyclophosphamide (Cy) was frequently used in patients undergoing allo-HCT for Acute Lymphoblastic Leukemia (ALL). Busulfan combined with cyclophosphamide was the most regularly used conditioning regimen for Acute Myeloid Leukemia (AML). A regimen was considered 'reduced intensity' if the dose of busulfan was ≤8 mg/kg orally or ≤6.4 mg/kg intravenously, dose of melphalan was 150 mg/m^2, and if the TBI dose was between 200 and 400 cGy. GvHD prophylaxis was mostly cyclosporine. Cyclosporine was either used alone or with methotrexate, mycophenolate mofetil (MMF) and or methylprednisone., All blood products were, irradiated and leukoreduced. Acyclovir, trimethoprim-sulfamethazole and an antifungal agent (usually fluconazole) was used as prophylaxis. In patients with neutropenia, empiric broad-spectrum antibiotics were started for a body temperature 38 °C and/or clinical signs of infection.

Table 1
Patient and transplant related parameters (618 patients with 666 transplants).

	Female	Male	Total	*P* Value
Number of patients transplanted	278 (45%)	340 (55%)	618	–
Total transplant episodes	300 (45%)	366 (55%)	666	–
Single transplant	258 (45.1%)	314 (54.9%)	572 (85.9%)	
Multiple transplants	42 (44.7%)	52 (55.3%)	94 (14.1%)	
First transplant	278	340	618	
Second transplant	20	26	46	
Third transplant	2	0	2	
Age at first transplant, years, median (range)	0.7 (0.04–2.0)	0.7 (0.05–2.0)	0.7 (0.04–2.0)	.250
Primary DRG (all patients, n = 618)				.005
Benign Hematological Disorders	23 (31.9%	49 (68.1%)	72 (11.7%)	
Benign Neoplasms[a]	29 (34.9%)	54 (65.1%)	83 (13.4%)	
Leukemias and Lymphomas	24 (40.7%)	35 (59.3%)	59 (9.5%)	
Non-Neoplasms	202 (50.0%)	202 (50.0%)	404 (65.4%)	
Source of stem cells (all transplants, n = 666)				.637
Cord blood	67 (41.6%)	94 (58.4%)	161 (24.2%)	
PBSC	6 (46.2%)	7 (53.8%)	13 (2.0%)	
Bone marrow	227 (46.1%)	265 (53.9%)	492 (73.9%)	
Donor HLA Type for all transplants (n = 666)				–
Matched sibling donor	–	–	356 (53.5%)	
Matched related donor	–	–	120 (18.0%)	
Haploidentical family member	–	–	29 (4.4%)	
Unrelated	–	–	161 (24.2%)	
Use of TBI in conditioning regimen				1.0
TBI (−)	293 (45.1%)	357 (54.9%)	650 (97.6%)	
TBI (+)	7 (43.8%)	9 (56.2%)	16 (2.4%)	
Era of first transplant (n = 618)				.326
1993–2004	86 (48.3%)	92 (51.7%)	178 (28.8%)	
2005–2015	192 (43.6%)	248 (56.4%)	440 (71.2%)	

[a] Except benign and pre-malignant hematological disorders.

2.5. End point definition

Time to neutrophil recovery was defined as the first of three consecutive days of absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L. Primary graft failure was labeled when there was failure to achieve ANC of 0.5×10^9/L by day 28 for BM or PBSC and day 42 for UCB. Patients who have already achieved an ANC of $\geq 0.5 \times 10^9$/L followed by a decline in counts with no recovery or 0% donor chimerism by PCR were categorized as secondary graft failure. Platelet engraftment was defined as the first of three consecutive days on which platelet count is $> 20 \times 10^9$/L without transfusions for seven days.. We defined survival as time from transplant to death from any cause.

2.6. Statistical consideration

Continuous data is presented as median with minimum and maximum points and mean (±SD) wherever appropriate, while discrete data is provided as n(%). Kaplan-Meier curves are used for survival analysis Breslow (Generalized Wilcoxon) test was used to test for the significance of the difference between the groups. Independent sample Mann-Whitney *U* test was used to test for the significance of difference between two groups of non-normal continuous variables. Chi-square test or Fisher's exact test has been used for testing the significance of independence between categorical variables.

3. Results

3.1. Engraftment

ANC engraftment by clinical definition was seen in 494 (74.2%) transplants at a median time to recovery of 15 days (range, 8–93). In 409 (61.4%) transplants we saw platelet transfusion independence at a median of 33 days (range, 3–171). ANC engraftment and platelets recovery were found to be significantly associated with source of stem cells and primary diagnostic related groups (DRG) with those transplanted for non-neoplasms having the highest failure rate ($P < .001$, Table 2).

3.2. GvHD

Cumulative incidence of all grades acute GvHD was 31.5% (n = 210) with grade III-IV GvHD at 8.7% (n = 58). Incidence of severe acute GvHD (grade ≥ III) was significantly higher in patients transplanted with UCB compared to BM (13.0% vs. 7.3%, $P = .036$) and was not associated with the primary DRG. For 562 evaluable transplants, chronic GvHD was seen in 72 (12.8%) transplants; significantly higher in patients transplanted with UCB (21.9%, n = 25, $P = .002$, **Table 2**).

3.3. Graft failure, transplant related toxicity and survival

Of 666 transplants 49 could not be followed for evaluation due to early death and for one patient graft assessment by short tandem repeat analysis was not available. Thus out of the 616 evaluable transplants at day +100 primary graft failure was recorded in 42 (6.8%) and secondary graft failure occurred in 40 (6.5%). Engraftment rate was significantly better for patients transplanted with BM/PBSC (88.9%) than those transplanted with UCB (79%, *P<.001*), and was not associated with primary DRG (Table 2). Though, infectious toxicity recorded during the first day +100 was not associated with primary indication for transplants, episodes of bacterial and viral infections were noted to be significantly higher in patients transplanted using UCB ($P < .001$ and .003 respectively). Incidence of veno-occlusive disease (VOD) measured at day +100 was 7.7% (n = 51 transplants).

At a median follow-up of 115.1 months (95% CI, 111.2–118.8, range, 1.4–314.9 months), cumulative probability of OS at 5 years was 70.0% (1.9%). Our mortality rate was 31.2% (n = 193). Five-year OS was significantly better in patients transplanted for benign hematological disorders ($P = .001$, Fig. 1, Table 2). Patients transplanted using BM/PBSC as source of stem cells fared significantly better compared to those in which UCB was used ($P < .001$, Fig. 2, Table 2).

Upon dividing our data set according to the chronology of first transplant into two era; 1993–2004 and 2005–2015, there was more than two folds increase in the number of transplants (Table 1). The cumulative probability of OS at 5 years was 72.2% ± 3.4% for early recipients compared to 69.1% (2.2%) ($P = .370$). The same was also not statistically significantly different when analyzed separately for malignant (50.0% [10.7%], n = 22, events = 11 vs. 62.3% [8.0%], n = 38, events = 14, $P = .678$) and for non-malignant disorders (75.4% [3.5%], n = 156, events = 43 vs. 69.7% [2.3%], n = 402, events = 125, $P = .201$).

3.4. New malignancy

Overall, new malignancy developed in three patients (0.005%) out of the 616 observed. There were two children with familial hemophagocytic lymphohistiocytosis (HLH). One developed AML that was refractory to treatment and expired after receiving 2nd line chemotherapy. The second child was diagnosed with Hodgkin's lymphoma about a year post-HCT. His lymphoma was resistant to therapy and succumbed to disease after two-lines of chemotherapy. The third child had SCID and developed non-metastatic rhabdomyosarcoma a few years after HCT. He responded to therapy and is currently disease free as per his last clinic visit.

3.5. Recipients transplanted using haploidentical family donor

In 29 transplants haploidentical family donor was used for 24 patients. Severe combined immune deficiency (SCID) was the primary indication of transplant in 13 (54.2%), Omenn Syndrome in 10 (41.7%) and Osteopetrosis in the remaining one case. Overall mortality rate was 37.5% (9 out of 24) with a median follow-up of 150.9 months (range, 0.7–252.5, 95% confidence interval, 106.4–195.4 months). Cumulative probability of ten year overall survival for this subgroup of patients was 61.1% ± 10.2%. Six (46.2%) patients transplanted for SCID and three (30%) patients transplanted for Omenn Syndrome died from this sub-group of recipients transplanted from haploidentical family donors. Details on nine patients who underwent multiple transplants where haploidentical family donor was used in first, second or the both, are presented in Table 3.

4. Discussion

HCT is an essential therapeutic modality in infants as well as young children with both malignant and non-malignant diseases. This study is a large single center analysis of allo-HCT outcomes in 618 children who were less than 2-years of age at transplant. Here we see that the number of allogeneic transplants increased over the time studied between the two era's. Reasons for this can be the availability of varied graft sources, establishment and access to donor registries as well as improvement in modalities for treating GvHD when using unrelated donors as resources improved [14,15].

The median age for these young children transplanted in the first era (1993–2004) was about 9-months (range, 0.7–24 months) which was higher than those transplanted in the second era (2005–2015) with a median of 8-months (range, 0.5–24 months).

Table 2
Transplants outcome (618 patients with 666 transplants).

	DRG				*P* value	Source		*P*-value
	A (73 in 72 pts)	B (89 in 83 pts)	C (62 in 59 pts)	D (442 in 404 pts)		CB (161 in 151 pts)	BM/PBSC (505 in 467 pts)	
ANC engraftment					<.001			.006
No engraftment	1 (1.4%)	8 (9.0%)	4 (6.5%)	159 (36.0%)		28 (17.4%)	144 (28.5%)	
Engrafted within time[a]	70 (95.9%)	78 (87.6%)	52 (83.9%)	268 (60.0%)		123 (76.4%)	345 (68.3%)	
Engrafted beyond time	2 (2.7%)	3 (3.4%)	6 (9.7%)	15 (3.4%)		10 (6.2%)	16 (3.2%)	
Platelets recovery					<.001			<.001
Never Recovered	8 (11.0%)	25 (28.1%)	11 (17.7%)	213 (48.2%)		60 (37.3%)	197 (39.0%)	
Recovered within 40 days	43 (58.9%)	47 (52.8%)	38 (61.3%)	141 (31.9%)		49 (30.4%)	220 (43.6%)	
Recovered 41–60 days	15 (20.5%)	9 (10.1%)	9 (14.5%)	55 (12.4%)		29 (18.0%)	59 (11.7%)	
Recovered 61–100 days	4 (5.5%)	6 (6.7%)	4 (6.5%)	29 (6.6%)		19 (11.8%)	24 (4.8%)	
Recovered >100 days	3 (4.1%)	2 (2.2%)	0 (0.0%)	4 (0.9%)		4 (2.5%)	5 (1.0%)	
D+100 Engraftment (n = 616 evaluable)[b]					.169			<.001
Engrafted	66 (94.3%)	66 (80.5%)	53 (93.0%)	349 (85.7%)		109 (79.0%)	425 (88.9%)	
Primary Graft Failure	2 (2.9%)	9 (11.0%)	1 (1.8%)	30 (7.4%)		21 (15.2%)	21 (4.4%)	
Secondary Graft Failure	2 (2.9%)	7 (8.5%)	3 (5.3%)	28 (6.9%)		8 (5.8%)	32 (6.7%)	
Cumulative incidence of GvHD								
aGvHD (all grade, n = 210)	24 (32.9%)	23 (25.8%)	22 (35.5%)	141 (32.0%)	.591	62 (38.5%)	148 (29.4%)	.032
aGvHD (grade III-IV, n = 58)	9 (12.3%)	8 (9.0%)	3 (4.8%)	38 (8.6%)	.510	21 (13.0%)	37 (7.3%)	.036
cGvHD (72 of 562 evaluable)	8 (11.8%)	9 (13.0%)	7 (13.0%)	48 (12.9%)	.996	25 (21.9%)	47 (10.5%)	.002
SOS/VOD (~day+100, n = 51)	8 (11.0%)	15 (16.9%)	4 (6.5%)	24 (5.4%)	.003	11 (6.8%)	40 (7.9%)	.736
	DRG				*P* value	Source		*P* value
	A (73 in 72)	B (89 in 83)	C (62 in 59)	D (442 in 404)		CB (161 in 151)	BM/PBSC (505 in 467)	
Infections (~day+100)								
Bacterial (n = 173)	18 (24.7%)	31 (34.8%)	10 (16.1%)	114 (25.8%)	.078	63 (39.1%)	110 (21.8%)	<.001
Viral (n = 87)	10 (13.7%)	13 (14.6%)	6 (9.7%)	58 (13.1%)	.842	32 (19.9%)	55 (10.9%)	.005
Fungal (n = 35)	3 (4.1%)	5 (5.6%)	3 (4.8%)	24 (5.4%)	.980	13 (8.1%)	22 (4.4%)	.071
5-year OS (n = 618)	83.2% (4.4%)	56.3% (5.5%)	56.8% (6.5%)	72.3% (2.2%)	.001	53.6%(4.1)	75.2%(2.0%)	<.001
Mortality (expired = 193)	12/72 (16.7%)	37/83 (44.6%)	25/59 (42.4%)	119/404 (29.5%)	<.001	70/151 (46.4%)	123/467 (26.3%)	<.001
Era 1993–2004 (n = 178)	27/72	14/83	21/59	116/404		–	–	
5-year OS	88.7%(6.1%)	50.0%(13.4%)	47.6% (10.9%)	75.7% (4.0%)	.007	–	–	
Mortality (expired = 54)	3 (11.1%)	8 (57.1%)	11 (52.4%)	32 (27.6%)		–	–	
Era 1993–2004 (n = 440)	45/72	69/83	38/59	288/404	.056	–	–	
5-year OS	80.0%(6.0%)	57.6% (6.0%)	62.3% (8.0)	71.0% (2.7%)		–	–	
Mortality (expired = 139)	9 (20.0%)	29 (42.0%)	14 (36.8%)	87 (30.2%)		–	–	

[a] Recovery within day +28 for BM and within day +42 for CB.
[b] Based on chimeric studies. Early deaths were 49, and STR values were not available for 1 transplant, A, Benign Hematological Disorders, B, Benign Neoplasms except Benign and Pre-Malignant Hematological Disorders, C, Leukemia and Lymphoma, D, Non-Neoplasms. Values are provided as n (%) and cumulative proportion of subjects surviving at the specified time with ±standard error.

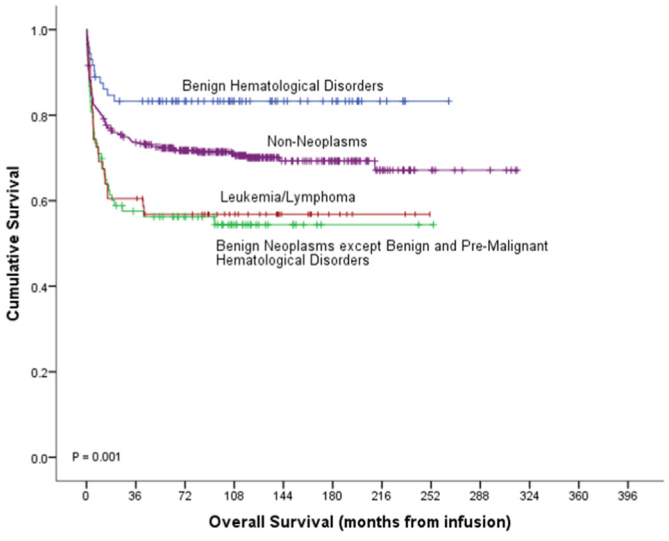

Fig. 1. OS by primary DRG.

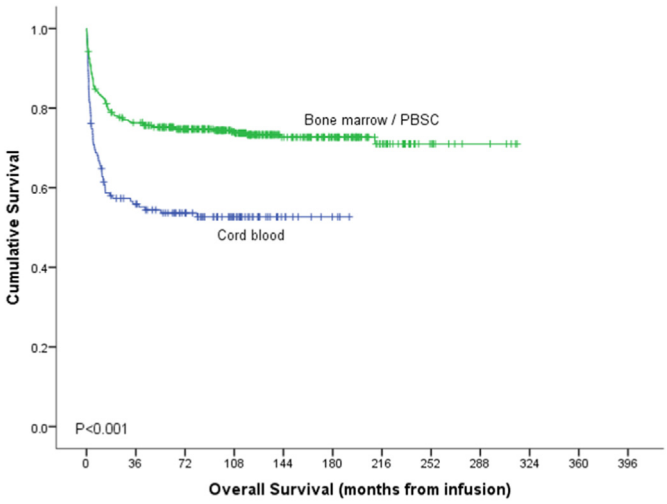

Fig. 2. OS by source of stem cells.

With our continuing understanding, experience of transplant in younger children along with managing comorbidities during transplant course, led us to lay down more defined criteria for

Table 3
Details on patients transplanted from Haplo-type identical donors.

Primary disease	1st Transplant							2nd Transplant						Survival status	Causes of death
	Age (months)	Cell Source	Donor	HLA type	$CD34^+$ cells (10 [6])	Acute GvHD	Graft Failure	Cell Source	Donor	HLA type	$CD34^+$ cells (10 [6])	Acute GvHD	Graft status		
Omenn Synd.	6.5	BM	Mother	Haplo	8.15	-ve	SGF	BM	Mother	Haplo	5.71	-ve	Engrafted	Alive	–
Omenn Synd.	2.8	BM	Mother	Haplo	7.73	-ve	SGF	BM	Mother	Haplo	5.3	-ve	SGF	Alive	–
Omenn Synd.	1.9	BM	Sister	Haplo	14.78	-ve	PGF	BM	Sister	Haplo	10.67	-ve	PGF	NS	Multi-organ failure secondary to MDR sepsis
SCID	3.5	BM	Sister	Haplo	8.73	-ve	SGF	BM	Sister	Haplo	10.7	-ve	Engrafted	Alive	–
SCID	6.4	PBSC	Mother	Haplo	15.12	-ve	PGF	PBSC	Mother	Haplo	6.05	-ve	SGF	NS	Sepsis with ARDS
Omenn Synd.	8.4	UCB	Unrel	2-AGm	0.56	-ve	SGF	BM	Mother	Haplo	14.44	-ve	SGF	LTFU	–
Osteopetrosis	9.7	UCB	Unrel	1-AGm	0.19	-ve	PGF	BM	Father	Haplo	5.84	Skin, II	Engrafted	Alive	–
Omenn Synd.	2.0	BM	Mother	Haplo	14.00	-ve	SGF	BM	Aunt	HLA Id	13.40	-ve	Engrafted	LTFU	–
Omenn Synd.	2.3	PBSC	Father	Haplo	13.91	-ve	SGF	UCB	Unrel	2-AG	1.10	-ve	Engrafted	Alive	–

BM, Bone marrow; PGF, Primary Graft Failure; SGF, Secondary Graft Failure; NS, Non-survivor; MDR, Multi-drug resistant; ARDS, Acute respiratory distress syndrome.

disease categories going forward. With the given improvement in transplant related approaches the tendency for upfront transplant in younger children gained momentum in our practice.

Among our cohort the most common indication for an allo-HCT were non-neoplastic disorders, primarily comprising of immunodeficiencies and inborn errors of metabolism. Despite continued monitoring of infectious parameters, prophylaxis and treatment of invasive infections and interval checks for organ toxicities we did not see an increase in OS across all disease categories. The reason might be the inherent nature of the underlying diseases in such young children. Though, an improved trend in five year OS was observed in two DRG's (Table 2). There can be multiple reasons for this improvement including but not limited to the advancement in supportive care, development of care pathways, awareness amongst families and early referrals over time [16]. Over the years, number of patients getting allogeneic HCT for hematologic malignancies increased despite improvement in chemotherapeutic regimens. We did not see good outcomes with infantile acute lymphoblastic leukemias as expected [17–19].

In our cohort, cumulative incidence of grade III-IV acute GvHD was higher in the second era (8.9%, 42 of 474 evaluable transplants) as compared to the first (8.6%, 16 of 185 evaluable transplants), unlike other reports [20,21]. A major reason for this was increased usage of CB grafts in the second era. Despite the improvement in supportive care strategies for infections in children with delayed immune reconstitution the above mentioned patient groups did not do well overall [22].

Sinusoidal obstruction syndrome/Hepatic veno-occlusive disease (SOS/VOD) is a potentially life-threatening complication of HCT conditioning chemotherapy. Lee et al. reported the overall incidence of VOD at 21.1% for children less than 2-years of age [23]. While the overall mean incidence of SOS/VOD has been reported to be 14% in a pooled analysis of 135 studies [24]. Looking at SOS/VOD toxicity in our patients, the highest incidence was seen in children with hemoglobinopathies and histiocytic disorders (14%) followed by those with metabolic disorders (5.4%) [25]. Across all DRGs our incidence was about 10%. It is the lowest amongst those reported in literature to our knowledge. These very young patients likely did better than older children due to the immature and adaptability of their hepatic function despite the myeloablative (MAC) conditioning given in the background of transfusion needs.

Patients undergoing allo-HCT have a higher risk of presenting with severe infections. These can be due to commensal and/or opportunistic microorganisms. In our young patients, the overall rates of bacterial infection (25.4%) are lower than that reported in published literature. Perez et al. in their retrospective review found an overall bacteremia incidence of 41% during the initial 100-days of allo-HCT for all indications in children less than 18-years of age [26]. Others have also reported bacterial infection rates around 20–39% [27]. The lower rates are possibly due to their limited mobility and caution observed while handling these very young children.

In conclusion survival in very young children with malignant diseases improved over the period analyzed. Our outcomes of transplanting children with benign hematological entities are better among other indications for transplant. SOS/VOD as well as infectious complications are lower in very young children thus it is safe to transplant sooner than later for established indications. More graft failure and infection related complications are expected with UCB transplants. Analyzing our institutional trends has enabled us to develop further strategies to minimize transplant related toxicities in these very young children needing allo-HCT.

Ethical statement

This clinical research study was approved by the Institutional Review Board (IRB) the hospitals via approval numbers 2141033, which was to be conducted under the international guidelines for the enrollment of human subjects. The data from patients' medical records were collected and maintained at the Department of Pediatric Hematology/Oncology, in accordance with institutional policy on data confidentiality, security, and safety. As the study was designed as a retrospective review, no consent/assent was taken from patients/parents. A waiver of informed consent/assent was sought from the IRB and was duly granted.

Author statement

1. Saadiya Khan: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - original draft; Writing - review & editing.
2. Khawar Siddiqui: Conceptualization; Methodology; Data processing; Formal analysis; Validation; Writing Results; Writing - review & editing.
3. Hasan ElSolh: Writing - review & editing.
4. Abdullah AlJefri: Writing - review & editing.
5. Ali AlAhmari: Writing - review & editing.
6. Ibrahim Ghemlas: Writing - REVIEW & editing.
7. Hawazen AlSaedi: Writing - review & editing.
8. Awatif AlAnazi: Writing - review & editing.

9. Amal AlSeraihy: Writing - review & editing.
10. Mouhab Ayas: Project administration; Resources; Supervision; Writing - original draft; Writing - review & editing.

Ethical approval

This study was submitted to the Institutional Review Board of King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, before initiation and was approved by the Research Advisory Committee through established procedures with Approval Number 2141033.

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Submission declaration and verification

The work described in this article has not been published previously (except in the form of an abstract, a published lecture or academic thesis), and is not under consideration for publication elsewhere. Its publication is approved by all authors and is explicitly approved by the responsible authorities where the work was carried out. If the work gets accepted in IJPAM, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Data statement

The data used in this work cannot be shared publicly in its raw format due to institutional restrictions.

Declaration of competing interest

None of the authors have any conflicts of interest to declare.

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