Background: Acquired aplastic anemia (AA) is a haematological emergency in children and we have gained enormous knowledge about the pathogenesis and immune mediated self-destruction of stem cells and immunosuppressive therapy. Due to its rarity, we have limited data of this entity, especially, its course and outcome in resource limited countries.
Patients and methods: The case records of children who had been diagnosed to have AA since 2002 at our centre were reviewed. The diagnosis of AA was made in children with pancytopenia without organomegaly and confirmed by hypocellular bone marrow showing decreased expression of all three hematopoietic lineages. Clinical findings including dysmorphism, thumb abnormalities, congenital malformations and skin hyperpigmentation were noted down. Mitomycin C induced chromosomal instability to rule out Fanconi anaemia, Ham's test to look for paroxysmal nocturnal haemoglobinuria and chromosomal analysis to look for complex karyotypic abnormalities seen in myelodysplastic syndrome were documented in all patients.
After initial stabilization, the option of haematopoietic stem cell transplantation (HSCT) was offered to all those who had matched related donors. If not, immunosuppressive therapy was delivered within two months from diagnosis after the child was infection free. A combination of 40mg/kg/day of Horse derived antithymocyte globulin (ATGAM) and methylprednisolone at 2 mg/kg/day were started for the first 4 days through a central venous catheter. Oral cyclosporine and G-CSF were started on the fifth day and since 2015 Eltrombopag was added to the IST regimen. Revolade and GCSF were continued for about 8 to 12 weeks and cyclosporine from 6 to 12 months. All patient received Voriconazole and Acyclovir prophylaxis till neutrophil recovery to 1000.
Results: A total of 109 children had been diagnosed as AA, of whom, 42 had acquired AA. The mean age of children with acquired AA was 8.16 years (2-15 yrs). Boys were twice more commonly affected (ratio M: F = 2:1). Details are listed in table 1.
Of the 41, 21 underwent HSCT as they had fully matched related donor and 20 children received IST. Of the 20 children who received ATG, 10 children (70%) had complete remission in a median duration of 78 days. Two of the three non responders were treated with second IST and all three succumbed to the illness. One child developed acute myeloid leukaemia after achieving partial remission and was salvaged with HSCT, and 1 more non responder had an unrelated HSCT and is doing well. One child has suffered a relapse after a durable remission of over 18 months off immunosuppression. The 21 children who have been transplanted have an overall survival rate of 77 %.
Conclusion: Immunosuppressive regimen including Horse ATGAM, Methyl prednisolone, Cyclosporine, GCSF and Eltrombopag along with adequate and meticulous supportive care including neutropenic care, prompt infection management and the use of irradiated and leukodepleted blood products results in a 70% response rate and should be offered to all children with aplastic anaemia with no matched family donor. The addition of Elthrombopag has resulted in early recovery of all three cell lines and must be added to the IST protocol in children.

Table 1
Clinical features & treatment outcome in Pediatric Aplastic anemia, n=41

S. No	Parameter	Results
1.	Mean age at presentation	8.16 year
2.	Severity at presentation	
	Severe	41%
	Very severe	54%
3.	Children required >20 transfusions prior to presentation	31.7%
4.	Karyotypic abnormalities	
	Partial trisomy 10,14 & Trisomy 7	1
	Mitomycin-C rest	Equivocal in 1 Negative in others
	Ham's test	Negative in all
5.	Treatment	
	1. ATG group	20
	Survival	16
	Complete Response	14
	Second IST	2 (expired)
	Salvage BMT	2
	2. BMT group	21
	Survival	16
	Chronic GVHD	3

RBC-1_V1.7
IS SERUM FERRITIN A RELIABLE MARKER FOR EVALUATION OF CARDIAC AND HEPATIC IRON OVERLOAD IN PATIENTS WITH β-THALASSEMIA MAJOR?

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Background: Regular packed red cell transfusions, which is the mainstay of therapy in thalassemia major, leads to iron overload. This requires frequent monitoring, thereby instituting appropriate treatment and preventing its associated complications. Iron overload-induced cardiomyopathy is reversible if intensive chelation therapy is instituted on time. Early detection of myocardial iron deposition is imperative to prevent cardiac complications known with iron overload. Conventionally, serum ferritin has been used to monitor iron overload in these children. But there have been recent studies, which have shown that T2* MRI is a better tool for cardiac and liver iron overload in comparison with serum ferritin. We analyzed our data to verify this correlation in our patients.
Aims and objectives: To study the correlation between serum ferritin and T2*MRI for assessment of cardiac and hepatic iron overload in patients of β-Thalassemia Major.
Materials and methods: It was a retrospective, cross sectional, descriptive study which analyzed records of 52patients with transfusion dependent β-Thalassemia major in the Thalassemia day care centre at our institution.
Inclusion Criteria: Children with transfusion dependent β-thalassemia major above 6 years of age in whomserum ferritin and T2*MRI were performed at least within 3 months of each other.
Exclusion criteria: Any child withHepatitis B, Hepatitis C and HIV infection.
Methodology: Demographic data, serum ferritin during last 3 months and T2*MRI results (which was taken as the gold standard for iron overload) were retrieved from the records.Standard definitions of severity of iron overload for liver and heart on T2* MRI were used for comparisons (Liver: normal > 6.3ms, mild - 2.8-6.3ms, moderate - 1.4-2.7ms, severe <1.4ms, Cardiac: normal >20ms, mild - 14 – 20ms, moderate - 10 – 14ms, severe <10ms.).Statistical analysis was done using Fisher's Exact test and ANOVA test.
Results: A total of 52 patients were enrolled in the study.Their ages ranged from 6 years to 22, with a median of 8.5yrs .31 were males and 21 were females. On the basis of T2* MRI values, patients were divided into none, mild, moderate and severe hepatic and cardiac iron overload. Hepatic iron overload in our patients was as follows: none – 5 (9.6%), mild – 14 (26.9%), moderate – 10 (19.2%), severe – 23 (44.2%) and cardiac iron overload as follows: none – 36 (69.2%), mild – 12 (23.0%), moderate – 3 (5.7%), severe – 1 (1.9%). When correlating serum ferritin below and above 2000 ng/ml with the severity of iron overload on T2* MRI, there was no significant association between serum ferritin levels and degree of iron overload in cardiac as well as liver MRI ($p = 0.92$ for cardiac iron overload and $p = 0.39$ for liver iron overload).Our results also show that there was no significant correlation between serum ferritin and cardiac MRIfindings ($p = 0.725$) or between ferritin and hepatic MRI ($p = 0.910$). Also no significant correlation was observed between cardiac and hepatic MRI values ($p = 0.07$).
Conclusion: The present study concludes that there is no correlation between serum ferritin level and T2*MRI for cardiac as well as liver iron overload. Hence, serum ferritin should not be the sole marker for evaluating iron overload. Also, cardiac and hepatic iron overload on T2* MRI did not correlate with each other. This suggests that individual organ evaluation by T2* MRI may be the way ahead for effective prevention of complications by appropriate chelation.

Stem Cell Transplantation
SCT-1_V1.1
RIC HSCT IN PRIMARY IMMUNODEFICIENCY CHILDREN IN DEVELOPING WORLD – A RAY OF HOPE

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Abstract

Background: Primary immunodeficiency disorders (PIDs) are an important but under-diagnosed cause of childhood morbidity and mortality. HSCT is the curative treatment for PIDs. Finding a matched donor is a stumbling block. Moreover, presence of severe infections at the time of transplants increases the transplant-related mortality (TRM. Poor infrastructure in developing world adds to the Gordian knot. So, RIC HSCT has been reported as a safer modality.

Objectives: To describe the feasibility and outcome of RIC HSCT for PIDs.

Methods: Twelve children with various PIDs, from August 2013 to August 2016 who underwent HSCT under our care were included. Clinical records were analyzed retrospectively.

Results: Twelve children (SCID-2, DOCK-8 deficiency-1, Chediak-Higashi Syndrome-1, WAS-3, HLH-2, GATA2 mutation-1 and CVID-1, HO-1 deficiency-1) with mean age 5.72 year underwent HSCT. Male: Female ratio was 11:1. Mean follow-up 419 days (9 to 1209 days). Eight underwent haploidentical HSCT three had matched sibling donor (MSD) HSCT, and one had MUD HSCT. In seven T-cell replete haploidentical and one MUD HSCT the conditioning was with serotherapy (Alemtuzumab-4 or Rabbit Anti-Thymoglobulin-4) along with Fludarabine, Cyclophosphamide, Thiotepa and TBI in 5, Fludarabine and Treosulfan in 2 and Fludarabine and Busulfan in 1. All received post transplant cyclophosphamide 50 mg/kg on day 3 and 4 for GVHD prophylaxis along with tacrolimus and MMF. In one, TCR alpha-beta/CD19 depleted haploidentical HSCT the conditioning was Alemtuzumab, Fludarabine, Treosulfan and Thiotepa with no GVHD prophylaxis. Two MSD were conditioned with Anti-Thymoglobulin, Fludarabine and Cyclophosphamide and GVHD prophylaxis was cyclosporine and methotrexate and one MSD was given Alemtuzumaab, Fludarabine, Cyclophosphamide and TBI with Tacrolimus and MMF for GVHD prophylaxis. Mean $CD34^+$ cell dose was 14.24×10^6/kg for 8 patients with PBSC graft and 32.1×10^6/kg for 4 patients who got bone marrow. Ten patients engrafted and two died prior to engraftment with bacterial sepsis on day +8 and day+14 respectively. Mean neutrophil engraftment was on 16.8 day. One patient died with thrombotic microangiopathy on day+28. Eight survivors are fully donor (>95%) and one had mixed chimerism (85%). Acute GVHD grade I-II developed in 4 children. Chronic GVHD of skin developed in two. CMV reactivation was seen in two and BCG reactivation in two. Overall survival 75% and TRM 25%.

Conclusion: RIC HSCT constitutes a feasible option for PIDs in developing world and gives a ray of hope for these patients.

SCT-1_V1.2

HAPLOIDENTICAL STEM CELL TRANSPLANTS WITH POST TRANSPLANTATION CYCLOPHOSPHAMIDE FOR HEMATOLOGICAL MALIGNANCIES IN CHILDREN

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Abstract

Background/Objectives: Donor availability remains one of the major challenges for performing hematopoetic stem cell transplantation (HSCT) in the treatment of hematologic malignancies. Matched sibling or unrelated donor cannot be identified or mobilized in time for many patients. HLA-haploidentical donor transplantation (HIDT) using T cell replete grafts and post-transplantation cyclophosphamide (PTCY) for control of alloreactivity has emerged as an important option for patients who lack a donor. Post-transplant cyclophosphamide (PTCY) is not toxic to hematopoietic stem cells because of high expression of enzyme aldehyde dehydrogenase but it induces selective allodepletion by killing host and donor T cells proliferating in response to donor and host cells, respectively. Thus, PTCY decreases GvHD but doesnot effect GvL. We report here the feasibility and outcome of HIDT in a developing world setting.

Designs/Methods: Six children with hematological malignancies and no available matched donor underwent HIDT from Dec2013 to Sept2016. The clinical records and investigation sheets were analyzed retrospectively. Patient's follow-up ranged from Day+10 to Day+732 (Mean Day+278)

Results: Mean age was 4.88 year (1.6-9 years). M:F = 3:3. All had hematological malignancies (High risk Acute myeloid leukemia-2, Relapsed acute lymphoblastic leukemia-4) and all were in complete remission (CR) at the time of transplant. Conditioning was Fludarabine ($40mg/m^2$/day) from Day-8 to day-5, Cyclophosphamide (14.5mg/kg/day) on Day-4 and Day-3, Thiotepa (8mg/kg/day) on Day-2 and TBI (2Gy) on Day-1. All patients received haploidentical peripheral blood stem cells. Mean $CD34^+$ cell dose was 12.7×10^6/kg/recipient weight. PTCY (50 mg/kg/day) was given on Day+3 and Day+4. Tacrolimus and MMF were started from Day+5 for Graft-Vs-Host disease (GvHD) prophylaxis. Supportive care along with Voriconazole and Valacyclovir for antifungal and antiviral prophylaxis was given. Five patients engrafted while one awaits engraftment (short follow-up). Mean neutrophil engraftment was on 18.6 day. Immediate post-transplant period was uneventful. Only one patient had viral reactivation, who had Adenovirus induced hemorrhagic cystitis on Day+44 which was successfully treated with Cidofovir. Chimerism studies showed fully donor in all patients who were post Day+100. One patient of Pre-B ALL relapsed on Day+406 of HIDT. This patient was very difficult to bring in remission even before the transplant and is now being taken up for the next transplant. Acute GVHD was not seen in any patient. Chronic GVHD of skin was seen in two patients which was conservatively managed. All six patients are alive.

Conclusion: In hematological malignancies patients who have no matched donor available, HIDT with PTCY constitutes a feasible and effective option.

SCT-1_V1.3

HALF MATCHED BUT TWICE AS GOOD – HAPLOIDENTICAL STEM CELL TRANSPLANTATION FOR BENIGN DISORDERS IN CHILDREN – CHALLENGES AND OUTCOME FROM A TERTIARY CARE CENTRE IN INDIA

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Background: Haploidentical stem cell transplantation in children with benign haematological disorders offers a unique opportunity to cure a child who has no matched family donor. However, the associated challenges are different to conventional allograft making the options suboptimal so far. Recent advances have made this procedure feasible in very young children and we describe our experience in the use of this technique.

Patients and methods: The study was conducted at the blood and marrow transplantation unit at Apollo Hospital, Chennai. Children aged up to 18 years who underwent haploidentical transplantation from 2002 to 2016 were included in the study.

Results: A total of 23 paediatric haploidentical stem cell transplantations have been performed at our centre so far. Of these 16/23 (69.5%) have been for benign disorders including Fanconi anaemia in 3, Haemophagocytic LymphoHistiocytosis in 2, 1 with severe aplastic anaemia and 10 with primary immunedeficiency disorders namely, severe combined immunedeficiency in 6, 1 each with Wiskott Aldrich syndrome, Hyper IgM syndrome, MSMD and Adrenoleukodystrophy. The sources of stem cells were from sibling and parent and bone marrow and peripheral blood in equal numbers. Techniques of T depletion used were CD 34 selection in 1, Campath in the bag in 1, TCR alpha/beta depletion 2, CD3/19 depletion in 1 and post transplant cyclophosphamide (PTCy) in 11 children.

In transplants where PTCy was used, conditioning included Fludarabine/ Treosulphan in primary immunedeficiency, Fludarabine/ Treosulphan/ single dose TBI 200cGy in HLH, Fludarabine/ Cyclophosphamide/ single dose TBI 200cGy in Fanconi anaemia and severe aplastic anaemia. In the child with ZAP70 mutation where TCR alpha/beta depletion was used, conditioning regimen included Fludarabine/ Treosulphan/ Thiotepa/ ATG. 12/16 (75%) transplants resulted in engraftment by Day 16-21 post HSCT with sustained complete chimerism. Hyper IgM syndrome and MSMD were 2 conditions where primary rejection resulted in autologous reconstitution. Acute skin and gut GVHD of grade 2-3 was noted in 5/16 (31%) which was responsive to steroids. Chronic skin and mouth GVHD has been noted in 1 child. CMV reactivation was noted in 5/16 (31%) children wherein 4 children achieved negative CMV copies on treatment with Valganciclovir.

Mortality among this group of patients was found to be 6/16 (37.5%). In the PTCy group, 3 children died of aspergillosis, severe ARDS and ruptured peliosis hepatis respectively. Campath use resulted in refractory CMV