Indian J Hematol Blood Transfus (Jan-Mar 2019) 35(1):12–16
https://doi.org/10.1007/s12288-018-01067-5

REVIEW ARTICLE

Highlights of Abstracts on Hematopoietic Stem Cell Transplant in Annual Conference of ISHBT 2018

Preethi Jeyaraman[1] · **Rahul Naithani**[1]

Received: 28 November 2018 / Accepted: 17 December 2018 / Published online: 14 January 2019

Abstract Stem cell transplant in India has been seeing a steady progressive growth over the last decade. Thirty abstracts related to various aspects of bone marrow transplant were presented in the annual conference of Indian Society of Hematology and Transfusion medicine in 2018. All abstracts which were published were reviewed. They were categorized into autologous transplants, allogeneic transplants, lab aspects and supportive care. They have been summarized to provide a snapshot of the data presented. These data are likely to encourage to start or enhance transplant activity at other centers.

Keywords HSCT · India · Late effects · DLI

Introduction

Hematopoietic stem cell transplantation (HSCT) has changed from a treatment of last resort into a commonly performed medical procedure with the possibility of curing complex hematologic diseases and replacing dysfunctional hematopoietic stem cells. New transplant centres are increasingly being set up with the absolute number of transplants showing an upward trend [1]. Outcomes have improved by the introduction of better GVHD prophylaxis and improvements in supportive care. This update focuses on the research and data presented in national conference of Indian Society of Hematology and Blood Transfusion, 2018.

Methods

All oral and poster presentations which were published were reviewed. Key findings are being highlighted.

Autologous Stem Cell Transplant

A retrospective study on the addition of Rituximab to BEAM on the outcomes in 20 high risk B cell lymphoma was reported from a tertiary care center in Eastern India [2]. One-hundred-day mortality was 5%. The estimated 3-year event free survival (EFS) and overall survival (OS) was 61% and 69% respectively.

Pai et al. [3], developed a population pharmacokinetic model for melphalan. Serum creatinine and bilirubin were significant covariates that predicted clearance of melphalan. Kulkarni et al. [4] published the results of 245 patients of myeloma who underwent autologous stem cell transplant with non-cryopreserved stem cells. The transplant related mortality was 2.86%. The median follow-up was 40.7 months. The 5-year overall survival and progression-free survival for the entire cohort was 61.6% and 37.2% respectively. Malhotra et al. [5], recently published slightly better results of autologous stem cell transplant in 76 patients of multiple myeloma with OS of 76.7% at 6.5 years. We have earlier documented a low (2%) treatment related mortality (TRM) in our cohort of myeloma transplants [6].

✉ Rahul Naithani
dr_rahul6@hotmail.com

[1] Division of Hematology and Bone Marrow Transplantation, Max Super Speciality Hospital, Saket, New Delhi, India

Allogeneic Stem Cell Transplant

Benign Hematology

Many authors presented single center experience of stem cell transplant in benign hematological diseases like thalassemia, sickle cell anemia, inherited bone marrow failure syndromes (IBMFS) and primary immuno deficiency (PID) syndromes. A single centre experience in thalassemia transplant was published by Kapoor et al. [7]. Forty-two patients [35 matched sibling donor (MSD) and 7 matched unrelated donor (MUD)] had undergone HSCT. Majority (60%) of patients belonged to Lucarelli class III. Graft source was peripheral blood stem cells (PBSC) in 35 patients. About 90% of patients achieved engraftment. Three patients had graft rejection, 9% had venoocclusive disease (VOD). Acute graft versus host disease (GVHD) grade II–IV and chronic GVHD developed in 17 and 7 patients. Four year OS and EFS is 90.5% and 83.1%. Korula et al. [8], evaluated the outcome of 58 thalassemia patients in a tertiary care centre in Southern India. They showed a higher risk of graft rejection when the donor is a non-sibling (OR 4.8; 95% CI 1.3–18.2; $p = 0.02$). This data has already been published. The 2-year thalassemia free survival (TFS) and OS was lesser in non-sibling donors in comparison to sibling donors (TFS—56.8% vs 81.8%; $p = 0.011$, OS—75.4% vs 85.0%; $p = 0.168$, respectively).

Balancing stable graft engraftment and treatment related mortality in sickle cell anemia HSCT is challenging. Nikhila et al. [9] published their results in a retrospective analysis on outcomes of 34 sickle cell anemia patients who underwent HSCT from a matched sibling donor. Patients received conditioning with treosulphan–thiotepa–fludarabine. Mean age at transplant was 9 years. Majority (85%) of patients were Middle Eastern in origin. The source of stem cells was PBSC in 60%. The median time to neutrophil engraftment was 12.2 days and for platelets, 17.8 days. The 100 day mortality was 5.8%. The day-28 donor chimerism varied from 93 to 100% with a durable graft. Five patients had limited chronic GVHD.

However, not so encouraging results were seen in PID and IBMFS. Venkateswaran et al. [10] evaluated the outcomes 55 children with PID treated with treosulphan based conditioning. Allogeneic related PBSC was used in 25%, bone marrow in 27%, unrelated in 4%, cord blood in 17% and haplo-identical bone marrow in 27%. Over 90% of the children had mixed chimerism after 60 days managed with early withdrawal of immunosupression. Acute GvHD was seen in 17%, chronic GvHD in 7% and graft rejection in 5%. The mortality was high at 40%. Uppuluri et al. [11], published a relatively large series of 68 patients undergoing allogeneic stem cell transplant in IBMFS over 15 years. The series had 51 patients of Fanconi anemia, majority of them from a matched related donor (28 patients). Fourteen patients had a haploidentical donor, 7 from cord blood and 2 MUD. Source of stem cells was peripheral blood in 75%. Engraftment by D + 16-21 was achieved in 72%. Overall rate of acute GvHD was 25% and chronic GvHD 11%. Overall mortality rate was 49%. Most common cause of death was GvHD (9 patients). Two patients died of primary graft failure. Secondary malignancies were also seen (AML in 3 and PTLD 3 years post HSCT in 1 patient). Survival rates were better in MRD (54%) and haplo SCT (65%) as compared to UCB (29%) and MUD (nill). Nine patients of pure red cell aplasia were also transplanted with overall survival rate of 68%.

Malignant Hematology

Lahane et al. [12], published a single center retrospective analysis of outcome of 28 transplanted patients of AML. Sixteen patients were in CR1, 2 in CR2 and 10 in active disease. Sixteen patients had full HLA match donor, 10 patients had Haplo match donor and 2 patients had 9/10 match donor. Conditioning regimes included Flu-Bu (n = 12), Flu-Mel (n = 5) and Flag-Ida-Mel (n = 6). Day 28 mortality was 25% and day 100 mortality was 50%. Among patients transplanted with active disease day 100 mortality was 80% highlighting the futile nature of transplant in active disease. Haplo SCT too had a high 60% day 100 mortality. Overall survival at 1 year was only 25%. Poor outcomes in this study could be related to the fact that 1/3rd of patients were transplanted in active disease.

Meanwhile, a study published by Selvarajan et al. [13], showed promising results in 31 lymphoma patients undergoing allogenic stem cell transplant. Eleven patients had Hodgkin lymphoma, 8 had B Cell NHL and 12 had T-cell lymphoproliferative disorder. At the time of allogeneic transplantation, 42% patients were in complete remission—6% in CR1 and 35% in $\geq$ CR2. Of the remaining, 35% were in partial remission and 22% had refractory disease. Twenty-four patients received matched related donor grafts and 6 received haplo-identical donor grafts. The 100-day treatment-related mortality rate was 25%. The 5 years EFS and OS were 46% and 54%, respectively. Patients in CR and PR had better EFS than those in refractory disease (88.9% and 57.1% vs 14.3% respectively).

GVHD and Donor Lymphocyte Infusion

Studies evaluating the role of donor lymphocyte infusions (DLI) in adults and children were presented. Venkateswaran et al. [14] published a retrospective analysis on outcomes of 57 children who received DLI. Majority

(72.4%) were for benign haematological conditions including thalassaemia major, sickle cell anaemia and primary immune deficiency disorders. Indication of DLI was mixed chimerism in less than 95%, to prevent graft rejection in 79% and in 21% children it was used as pre-emptive therapy in high risk malignancies to prevent a molecular relapse. Twenty-one children achieved 100% chimerism, 12 children had mixed chimerism and were clinically stable. Grade I–II aGVHD was seen in 22 children. The mortality rate was 17% due to graft loss, relapse of leukemia and one death attributed to graft versus host disease.

Reba et al. [15], evaluated the impact of DLI in adult patients post HSCT. Of the 99 patients who had received DLI, 38 had non-malignant disease and 61 had malignant disease. In patients with benign diseases, donor chimerism prior to DLI ranged from 14 to 93% donor cells (Median 78% donor cells). Sixteen patients reverted to a full donor chimerism, 8 had a stable mixed chimerism, 14 patients progressed to graft rejection, of whom 3 died and 3 subsequently underwent a second transplant for rejection. GVHD was seen in 15 patients and 1 patient had GVHD related mortality. The 3 years event-free survival was 42.2%. In the 61 patients with malignant disease, indications included a drop in chimerism (n = 9), molecular relapse (n = 3), to induce GVHD (n = 27) and after relapse as a consolidation post-chemotherapy (n = 21). Five out of the 19 patients who developed GVHD died. There was a significant correlation between dose of DLI and development of GVHD. The 3 years event-free survival was 50.5%.

Supportive Care and Other Topics

Nagarajan et al. [16], showed that GSTA1 genotype and formulation affected the pharmacokinetics of busulfan. The first dose busulfan AUC was significantly influenced by the formulation used (Bufatas > Busulfex > Buslera > Bucelon). However, Balasubramanian et al. [17], showed that in the 102 patients studied, formulation and % dose change of Bu did not significantly influence OS and RFS even though busulfan AUC was significantly higher in those patients who were alive compared to those who were dead.

Cytomegalovirus (CMV) reactivation was prospectively evaluated in 97 allogeneic stem cell transplant recipients [18]. Fifty-three patients had CMV reactivation of which 37 patients required pre-emptive therapy. Only one patient had CMV disease. A large Indian series of 475 patients have shown incidence of CMV infection does not seem to be higher despite a high sero-prevalence of CMV. However, patients who developed CMV infection post SCT had inferior outcomes [19]. Suraj et al. [20], did a retrospective chart review of antifungal prophylaxis in163 patients of aGVHD. Sixty-one patients received posaconazole as antifungal prophylaxis, and 36 received once weekly liposomal amphotericin (3 mg/kg). By EORTC criteria, 19.6% patients developed a breakthrough fungal infection, of whom 37.5% received Liposomal ampho and 31.2% had received posaconazole as antifungal prophylaxis. The 2 years EFS was significantly lower in patients who had a documented fungal infection. Posaconazole was more effective antifungal prophylaxis in this series.

Upreti et al. [21], evaluated the outcomes of 53 patients who underwent stem cell transplant in non HEPA filtered rooms in a center in Western India. Ninety-six percentage of patients engrafted with no sepsis related mortality till d + 30. Overall survival was 81% at a median follow up of 16 months, with 6% TRM at d + 100. This is encouraging as majority of centers in India who may not have access to HEPA filters may be encouraged to at least start autologous bone marrow transplant.

Preemptive plerixafor has been found to reduce the cost of autologous stem cell transplant for patients of multiple myeloma who had received lenalidomide [22]. The cost of a second day of donor apheresis is far more as compared to the cost of plerixafor especially as many lower cost generic formulations are becoming increasingly available. Kumar et al. [23], performed a pilot study on the use of plerixafor—0.24 mg/kg as rescue strategy for 12 healthy donors who failed to mobilise on D5 with GCSF alone. The circulating CD 34 cells increased by 2.2-fold in peripheral blood and 3.1-fold in harvest bag. There were no major side effects.

Late Effects of Stem Cell Transplant

Allogeneic stem cell transplant affects Quality of Life (QoL) and psychological status of patients due to the long recovery period and recurrent admissions associated with graft versus host disease and infectious complications. Prabha et al. [24], evaluated the prevalence of psychiatric illness in post-transplant patients in a center in southern India. Out of the 72 enrolled patients, 26 (36%) met psychiatric diagnosis criteria. Adjustment disorder (43%) was the most common diagnosis followed by depressive illnesses (24%).

The QoL of patients undergoing allogeneic stem cell transplant was studied [25]. One hundred patients at a tertiary center in southern India were evaluated using the FACT BMT or PedsQL questionnaire for quality of life. Fifty-four percentage of patients had poor quality of life after allogenic hematopoietic stem cell transplantation. There was significant correlation between type of disease, graft versus host disease and quality of life.

Kesavan et al. [26], did a retrospective analysis of growth and sexual development of 36 children who underwent HSCT for thalassemia using treosulphan based conditioning. Median follow up was 5 years. Only 6 out of 36 children showed a dip in their centile chart and all of them had required steroid for chronic GVHD. All of them, however, passed through their puberty without any need for supplementation. This study showed the good growth and developmental patterns in children who receive treosulphan for conditioning.

Laboratory Aspect

Many technical advances have occurred in HLA typing, CD 34 quantification and chimerism analysis. New techniques have been studied to reduce the turnaround time and cost of investigations. Recently our center had published our results comparing single versus dual platform analysis methods for CD 34 enumeration [27]. We found that both methods were comparable. While single platform analysis is easier to perform, in terms of cost reduction dual platform analysis is better.

Mishra et al. [28] compared HPC count from Sysmex XN and CD34 by flow cytometry both in peripheral blood and harvest bag samples. Sixty-seven allogenic and 35 autologous samples were analysed and good correlation was found between the HPC and CD34 count both in peripheral blood and harvest bag (0.887; p value < 0.01 and 0.847; p value < 0.01 respectively). On the other hand, TLC had a poor correlation with the HPC count.

HLA typing traditionally performed by Sanger sequencing, requires a 2-step process. It has increasingly been replaced by Next Generation Sequencing (NGS). In a study done by Vani et al. [29], in a stem cell lab in southern India, 20 cord blood samples were sequenced using both Sanger based sequencing and NGS. While 74.4% of sanger results had ambiguities only 4.38% of NGS results had ambiguities. NGS helped in identifying null and novel alleles by using dynamic phasing algorithm thereby reducing turnaround time and ambiguity.

Srinivasan et al. [30], compared 2 methods of DNA based chimerism analysis-isolating DNA followed by amplification versus direct amplification using whole blood in 16 patients post HSCT. Both methods had comparable results. However, the direct DNA amplification method was associated with less cost and turnaround time (< 12 h vs > 48 h).

Conclusion

More and more presentations are happening on varying aspects of HSCT in India. Studies analyzing the pharmacokinetics of chemotherapeutic agents will be beneficial to individualise therapy and reduce treatment related morbidity and mortality. Good outcomes have been reported by most centers in both benign and malignant hematological diseases. The future of stem cell transplant in India seems promising.

Compliance with Ethical Standards

Conflict of interest The author declares that they have no conflict of interest.

References

1. Naithani R (2018) Hematopoietic stem cell transplantation in India-2017 annual update. Indian J Hematol Blood Transfus 34(1):5–7
2. Modak K, Radhakrishnan V, Lama M, Kathrotiya M, Bhave JS, Kumar J et al (2018) Outcomes of consolidation with R-BEAM high dose chemoimmunotherapy and autologous hematopoietic cell rescue in high risk B-cell lymphoma: a tertiary care single center experience. Indian J Hematol Blood Transfus. November, S 385
3. Pai AA, Mani S, Panetta CJ, Ezhilpavai M, Stallon I, Balkrishnan B et al (2018) Pharmacokinetics of melphalan in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Indian J Hematol Blood Transfus. November, S 380
4. Kulkarni U, Devasia AJ, Korula A et al (2018) Clinical outcomes in multiple myeloma post-autologous transplantation—a single centre experience. Indian J Hematol Blood Transfus. https://doi.org/10.1007/s12288-018-0989-y
5. Malhotra P, Yanamandra U, Khadwal A et al (2018) Autologous stem cell transplantation for multiple myeloma: single centre experience from North India. Indian J Hematol Blood Transfus 34(2):261–267
6. Naithani R, Dayal N, Rai R, Pathak S, Singh M (2018) Autologous hematopoietic stem cell transplantation for multiple myeloma in India. Indian J Hematol Blood Transfus 34(3):564–565
7. Kapoor J, Soni P, Bhatia N, Agrawal N, Ahmed R, Mehta P et al (2018) Clinical profile and outcomes post allogenic hematopoietic stem cell transplantation in thalassemia patients: A single centre experience. Indian J Hematol Blood Transfus 50–51
8. Korula A, Devasia AJ, Fouzia NA et al (2018) Outcomes following allogeneic stem cell transplantation using non-sibling family donors. Indian J Hematol Blood Transfus. https://doi.org/10.1007/s12288-018-0988-z
9. Nikila R, Patel S, Sankaran M, Venkateswaran VS, Kesavan MR, Ramya U et al (2018) Balancing cure versus toxicity-haematopoietic stem cell transplantation for sickle cell anemia. Indian J Hematol Blood Transfus. November, S 200
10. Venkateswaran VS, Patel S, Sankaran M, Kesavan MR, Nikila R, Ramya U et al (2018) Treosulfan based conditioning regimen—reduced toxicity with excellent outcomes in children with primary immune deficiency. Indian J Hematol Blood Transfus. November, S 53

11. Uppuluri R, Sivasankaran M, Patel S, Swaminathan VV, Ravichandran N, Ramanan KM et al (2018) Haematopoietic stem cell transplantation for children with inherited bone marrow failure syndromes: a single centre experience over 15 years from India. Indian J Hematol Blood Transfus. November, S 204
12. Lahane CG, Apte S, Subramanian K, Phatale R, Roshan R (2018) Outcome of allogenic stem cell transplant in acute myeloid leukemia patients in a single centre over 7 yrs. Indian J Hematol Blood Transfus. November, S 378
13. Selvarajan S, Korula A, Fouzia NA, Abraham A, Srivastava A, Mathews V et al (2018) Outcomes of allogeneic hematopoietic stem cell transplantation for lymphomas: a single-centre experience. Indian J Hematol Blood Transfus. November, S 54
14. Venkateswaran VS, Meena S, Shivani P, Keasvan MR, Nikila, Ramya U et al (2018) Donor lymphocyte infusion in children—efficacy in preventing graft rejection and relapse— experience from a tertiary referral centre in southern India. Indian J Hematol Blood Transfus. November, S 10
15. Reba H, Korula A, Abraham A, Sindhuvi E, Lakshmi K, George B et al (2018) Impact of donor lymphocyte infusion in malignant and nonmalignant disease post-allogeneic stem cell transplant. Indian J Hematol Blood Transfus. November, S 383
16. Nagarajan R, Pai AA, Ravichandran AJ, Mani S, Mohanan E, Balakrishnan B et al (2018) GSTA1*B genotype influences intravenous busulfan pharmacokinetics and targeted dose adjustment in patients undergoing HSCT with busulfan based conditioning regimen. Indian J Hematol Blood Transfus. November, S 379
17. Balasubramanian P, Pai A, Ezhilpavai M, Nagarajan R, Eunice SE, Kavitha ML et al (2018) Targeted iv busulfan-based conditioning regimen in patients with acute myelogenous leukemia undergoing allogeneic hematopoietic stem cell transplantation—a single centre experience. Indian J Hematol Blood Transfus 34–35
18. Bharath Ram S, Bhat S, Nataraj KS, Badiger S, Kailasnath VP, Mallya P et al (2018) A prospective observational study of incidence of early cytomegalovirus reactivation and factors affecting it following allogeneic stem cell transplantation. Indian J Hematol Blood Transfus 205–206
19. Devasia AJ, Mammen S, Korula A, Abraham A, Fouzia NA et al (2018) A low incidence of cytomegalo virus infection following allogeneic hematopoietic stem cell transplantation despite a high seroprevalence. Indian J Hematol Blood Transfus 34(4):636–642
20. Suraj C, Korula A, Fouzia NA, Kavitha ML, Abraham A, Srivastava A, Mathews V et al (2018) Antifungal prophylaxis in acute GVHD post stem cell transplant—a single centre experience from Southern India. Indian J Hematol Blood Transfus. November, S 206
21. Upreti R, Sharma S, Satyanand K, Kapoor A, Asthana B, Venkatesan S et al (2018) Initial HSCT in non-HEPA filter AHU rooms: a single center experience. Indian J Hematol Blood Transfus. November, S 196
22. Kumar R, Kapoor R, Asthana B et al (2017) Single dose preemptive plerixafor for stem cell mobilization for ASCT after lenalidomide based therapy in multiple myeloma: impact in resource limited setting. Indian J Hematol Blood Transfus 33(4):463–469
23. Kumar K, Chezhian S, Prabhu D, Asokan L, Dharani B et al (2018) On demand plerixafor as a rescue strategy in healthy donors to achieve adequate stem cells—a pilot study. Indian J Hematol Blood Transfus. November, S 201
24. Prabha L, Kumar K, Chezhian S (2018) Psychiatric illness in bone marrow transplantation patients. Indian J Hematol Blood Transfus. November, S 203
25. Sathianathan P, George B (2018) Quality of life among allogenic hematopoietic stem cell transplant patients. Indian J Hematol Blood Transfus. November, S 386
26. Kesavan MR, Patel S, Sivasankaran M, Venkateswaran VS, Nikila R, Uppuluri R et al (2018) Normal growth and development post haematopoietic stem cell transplantation for thalassemia major using treosulfan based conditioning regimen—single centre long term study. Indian J Hematol Blood Transfus. November, S 49
27. Naithani R, Dayal N, Dixit G (2017) Single versus dual platform analysis for hematopoietic stem cell enumeration using ISHAGE protocol. Indian J Hematol Blood Transfus 33(3):370–374
28. Mishra S, Mammen JJ, George B, Nair S, Kulkarni U, Matthews N et al (2018) A study to compare Haematopoietic Progenitor Cell (HPC) determined on the Sysmex XN-9000 with flowcytometric CD34 count in peripheral blood and in the harvested peripheral blood stem cell graft from autologous and allogenic donors. Indian J Hematol Blood Transfus. November, S 9
29. Vani S, Devi AS, Chandramouleeswaran N, Meganathan V, Kumar NM, Yogesh NK et al (2018) Next generation sequencing: an accurate and unambiguous method for HLA whole genome typing. Indian J Hematol Blood Transfus. November, S 195
30. Srinivasan G, Eswari S, Sumithra S, Shaji RV, Edison ES (2018) Comparison of DNA based chimerism analysis with direct amplification using whole blood. Indian J Hematol Blood Transfus. November, S 202