

## Role of Transfusion Medicine Specialist in Stem Cell Transplant: Experience in Bangladesh

Tamanna Afroz<sup>1</sup>, Abu Jafar Mohammed Saleh<sup>2</sup>

1. Senior Specialist, Transfusion Medicine, Evercare Hospital Dhaka.
2. Senior Consultant and Coordinator, Hematology and Stem Cell Transplant, Evercare Hospital Dhaka.

### Address for Correspondence:

Dr. Tamanna Afroz  
Senior Specialist,  
Transfusion Medicine,  
Evercare Hospital Dhaka,  
tamanna.afroz@evercarebd.com

### ABSTRACT

Over the years, the field that was once known as blood banking has evolved into the discipline of Transfusion Medicine. Transfusion Medicine has become a broad, multidisciplinary field which include various facets of clinical medicine. Transfusion medicine specialist plays a vital role in the supportive care of patients undergoing stem cell transplantation, with a spectrum of applications including peripheral blood stem cell collection, graft manipulation, cryopreservation, donor lymphocyte infusions and evaluation of immunohematological issues in ABO and RhD mismatched and other transplant situations.

**Key words:** *Transfusion Medicine, Stem Cell Transplant, Bangladesh*

### INTRODUCTION

Stem cell transplant (SCT) is the therapeutic option for many malignant and nonmalignant hematologic disorders and its use has expanded significantly over the last 20 years. SCT proved to be effective for multiple myeloma, lymphoma, acute myeloid leukemia, acute lymphoid leukemia, sickle cell anemia, thalassemia and inherited immunodeficiencies. In allogeneic transplants, stem cells are taken from a healthy HLA-matched donor and for autologous they are collected from patient's own bone marrow or peripheral blood. Transfusion medicine (TM) specialist plays a vital role in the supportive care of patients undergoing SCT including peripheral blood stem cell (PBSC) collection, graft manipulation, cryopreservation, evaluation of complex immunohematological issues and substantial transfusion support.

### BASIC PRINCIPLE OF SCT

The basic principle of SCT is to give high doses of chemotherapy and/or radiotherapy and then infuse hematopoietic stem cells (HSC) to rebuild the bone marrow and immune system. In allogeneic SCT HLA matched donor is preferred over ABO matching. A sufficient collection of HSC is mandatory as it circulates in a very few numbers in the peripheral blood (PB). So mobilization from bone marrow (BM) to PB is essential which is done by recommended cytokines i.e., G-CSF. Since HSCs express CD34 on their surface,  $\geq 20/\mu\text{l}$  CD34+ cells in PB are considered adequate

before collection<sup>1</sup>. Depending on age, CD34 count, advanced disease stage and prior treatment, some patients in autologous SCT may have mobilization failure. With the use of CXCR4 antagonist (Plerixafor) this predicted failure can be overcome. After successful mobilization, HSCs are collected and infused in the patient after proper conditioning. The kinetics of neutrophil and platelet engraftment is determined by the dose of transplanted CD34+ cells per kg body weight. The main role of a TM specialist starts after mobilization.

### ROLE IN STEM CELL COLLECTION

There are two ways to collect HSC, bone marrow harvest and leukapheresis. The latter is considered standard due to being less stressful for the patient, can be done on out-patient basis and leads to faster engraftment. TM specialist is responsible for the collection of PBSC by apheresis. Various continuous and intermittent flow apheresis machines are available in the market. The prospective patient or donor should have a central or peripheral catheter to maintain adequate flow (60-120 ml/min) to and from the machine. For younger children, the flow needs to be lower. The available apheresis systems have large extracorporeal volumes and it should not exceed 10-15% of the patient's total blood volume (TBV). So expected blood loss in the tube set needs to be calculated in each procedure to decide whether a priming of the set is needed. The function of

a custom prime is to displace the prime saline in the tubing set with donor RBC, plasma or albumin prior to connecting a patient so that the patient remains isovolemic throughout the procedure. If priming is performed full rinse back can result in a positive fluid balance. Plasma pump flow rate needs to be adjusted which affects the concentration of cells that flow through the collect port. Usually in autologous SCT 2-3 times TBV can be processed while in allogeneic it could be 1.5-2 times. Possible sufficient platelet loss can warrant platelet transfusion. The number of leukapheresis should not exceed 3 procedures with each 4-6 hours duration. Collection from pediatric patients is challenging due to small body weight, difficulties in venous access and psychological concern. Citrate-induced hypocalcemia is the most common adverse event which can be managed by giving oral or intravenous calcium preparation or by increasing inlet and anti-coagulant ratio. Other possible side effects can be vasovagal reactions, hypovolemia, hypotension etc.

### **ROLE IN GRAFT MANIPULATION**

Graft manipulation is performed in allogeneic SCT to optimize the volume and cellular composition of collected PBSC. During leukapheresis the final product can contain approximately 8-15ml donor red blood cells and in bone marrow harvest it can be 200-450 ml<sup>2</sup>. In major ABO incompatibility this can lead to pure red cell aplasia or delayed or failed engraftment. This can be prevented by pre-transplant transfusion of donor group type secretor plasma or therapeutic plasma exchange of recipient to decrease IgM/IgG titer or by red cell depletion in case of bone marrow harvest. Plasma reduction by simple centrifugation can reduce the risk of acute hemolysis in minor ABO incompatibility.

### **ROLE IN CRYOPRESERVATION**

Collected PBSCs are stored for maximum of 72 hours at 2-6°C. In certain situations, fresh PBSCs are infused or else it is cryopreserved within 48 hours or less. To maintain the significant survival of cells during cryopreservation specialized solutions known as cryoprotectants are used in a fixed proportion. These solutions inhibit the formation of intra and extracellular crystals and thus protect the cells from damaging effects. One of these solutions is Dimethyl sulfoxide (DMSO) which prevents freezing damage to living cells<sup>3</sup>. After preparing

the cryobags, they are further frozen down to a target temperature of -90°C using a controlled rate freezing process. Then they are stored in liquid nitrogen at -196°C. 3 reference samples are prepared in parallel and stored under the same cryocondition for the proof of the quality of cells. The composition of cryoprotectant solution, cell concentration, freezing rate and storage temperature plays important roles in cryopreservation.

### **ROLE IN THAWING AND INFUSION**

The total cell dose is calculated and a decision is taken for the volume to be infused. Thawing is done at the patient's bed side in a water bath at 37°C until all ice crystals disappear. Cells should be infused within a maximum time span of 10-20 minutes of thawing. Pre-medications should be given half an hour before infusion to avoid any adverse events. The desired units are then infused over recommended time under proper monitoring.

### **IMMUNOHEMATOLOGICAL SUPPORT**

Many immunohematological complexes are solved by a TM specialist in allogeneic SCT like antibody screening and identification and managing compatible blood units. Some allogeneic donor work up is done in TM department which includes ABO and RhD blood grouping, major and minor cross-matching, and viral markers like hepatitis B, hepatitis C and HIV testing. Isoagglutinin titers give a guideline for graft manipulation in case ABO incompatible SCTs. Secretor study is also done if necessary.

### **TRANSFUSION SUPPORT**

SCT patients need transfusion support for their cytopenias and allogeneic SCT patients present distinct challenges for transfusion services. Due to the fact that the human leukocyte antigen system is inherited independently of blood group system, approximately 50% of allogeneic SCTs are performed across the ABO blood group barrier<sup>4</sup>. Three groups of ABO mismatch can be defined. Minor ABO mismatch (20-25% of transplants) is characterized by the ability of donor B lymphocytes to produce anti-recipient antibodies. In major ABO mismatch cases, anti donor ABO antibodies are present in the recipient. Bidirectional (up to 5% of transplants) occurs if both donor and recipient have

isohemagglutinins (IHAs) directed against ABO blood group antigens of each other. When D antigen status differs between donor and recipient, the allogeneic SCT is D antigen mismatch. When considering transfusion for these patients, one has to consider not only complexities associated with the patient's underlying condition but also potential problems associated with recipient allo antibodies, donor passenger lymphocytes and different blood group systems. TM specialist guides the clinician for transfusion of compatible units in these situations according to institutional protocol and also keeps track of these patients to switch blood group.

### **ROLE IN CELLULAR THERAPY**

Donor lymphocyte infusion (DLI) has been used in allogeneic SCT if there is evidence of disease progression or resistance or if there is a mixed chimera. Its use has shown promising results in haploidentical SCT. Unmanipulated DLI is a form of immunotherapy that can eradicate minimal residual disease by enhancing the graft-versus-tumor (GvT) effect. The donor will be reviewed and individual patient dosing should be carefully considered. TM specialists collect it from donor through normal or large-volume leukapheresis with satisfactory lymphocyte-enriched yields<sup>5</sup>.

### **THE SCOPE AND FUTURE AHEAD**

The journey of TM began as a simpler entity (blood bank) in 1938.<sup>6</sup> Over the last few years, the field has gradually developed into a broad discipline of TM globally. In Bangladesh blood transfusion service started in 1950 in a few centers which confined to only basic serology. There is a severe dearth of TM specialists in the country. Still in various territories specially in the government sector, they are holding the image of 'storekeeper' of blood, and TM is practiced traditionally. The field is mainly supported by the blood donation system. Given this reality improvement is needed in both background knowledge and practical application. Over the years it progressed to include clinical patient services such as different apheresis technology.

SCT is a new thigh for Bangladesh which was started in 2014. Every year a good number of patients are going abroad for SCT. Currently, the country needs around 10,000 SCTs per year and some centers are already doing both autologous and allogeneic SCTs and a few other centers are preparing to start<sup>7</sup>. This new development

can provide fertile soil for the seeds of TM to grow. The future holds many opportunities for a TM specialist to work in the SCT unit as discussed. TM specialists nowadays are more interested in therapeutic procedures. We need to work on every 'nuts and bolts'.

Currently different postgraduate curriculums like MD, and diploma are offered in five centers. SCT poses unique challenges for TM but the curriculum does not have technical or clinical aspects of transplants. We should revamp our post-graduate curriculum so that we remain relevant with time. We need to diversify our focus more on this for that's the future. This will encourage young fellows to robust their careers in the field of TM. In this manner, we will move forward to a promising future. For example, cardiac surgeries were not common a few years back in our country and people used to go abroad for this. But now it is well established here and many centers are involved in new cardiac surgeries. So that day is not too far when SCT will be well established in our country and TM specialists would play an overtly visible role in serving the medical community. For young and budding TM specialists, identification of antibodies, HLA typing, extracorporeal photopheresis for GVHD, and chimerism study can bring a bright future. It is for TM fraternity to think it over and to adopt creative strategies to overcome this 'pipeline' problem.

### **CONCLUSION**

The quiet days of TM are over. Therefore, educational programs and preparation of the proper curriculum according to the most recent advances are needed. It is high time we need to rethink, change our archaic insight and engage ourselves more to protect this vanishing breed!

### **REFERENCES**

1. Mohty M, Hübel K, Kröger N, Aljurf M, Apperley J, Basak GW, Bazarbachi A, Douglas K, Gabriel I, Garderet L, Gerasimides C, Jaksic O, Kattan MW, Koristek Z, Lanza F, Lemoli RM, Mendeleeva L, Mikala G, Mikhailova N, Nagler A, Schouten HC, Selleslag D, Suciu S, Sureda A, Worel N, Wuchter P, Chabannon C, Duarte RF. Autologous haematopoietic stem cell mobilisation in multiple myeloma and lymphoma patients: a position statement from the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2014 Jul;49(7):865-72. doi: 10.1038/bmt.2014.39. Epub 2014 Mar 31. PMID: 24686988

2. Worel N. ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation. *Transfus Med Hemother* 2016;43:3–12. DOI: 10.1159/000441507.
3. Berz D, McCormack E, Winer E, Colvin G, and Quesenberry P. Cryopreservation of Hematopoietic Stem Cells ; *Am J Hematol*. 2007 June ; 82(6): 463–472.
4. Kopko P. Transfusion Support for ABO-Incompatible Progenitor Cell Transplantation. *Transfus Med Hemother* 2016;43:13–18. DOI: 10.1159/000441612.
5. Castagna L, Sarina B, Bramanti S, Perseghin P, Mariotti J, Morabito L. Donor lymphocyte infusion after allogeneic stem cell transplantation. *Transfusion and Apheresis Science* 54 (2016) 345–355. doi.org/10.1016/j.transci.2016.05.011.
6. Choate J , Snyder E. The rise of cellular therapy. *Transfusion and Apheresis Sci*. doi: 10.1016/j.transci.2011.06.008. Epub 2011 Jul 13.
7. Niederwieser D, Baldomero H, Szer J, Gratwohl M, Aljurf M, Atsuta Y, Bouzas LF, Confer D, Greinix H, Horowitz M, Iida M. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. *Bone marrow transplantation*. 2016 Jun;51(6):778-785.