## *EDITORIAL*

# Hemopoietic Stem Cell Transplantation (HSCT) in Bangladesh- Needs Sustained Program and Policy

**HSCT and its evolution:**

Hemopoietic stem cell transplantation(HSCT) is a life saving curative modality of treatment procedure for many hematological malignancies, bone marrow failure syndromes, thalassemias and inborn errors. Since 1960's HSCT has evolved from a clinical concept to an amazing clinical result for several blood diseases with the tremendous development and progress in this field[1]. The principle of HSCT is simple: marrow ablation by high dose chemotherapy and/or radiation and enough immunosuppression of patient so to allow to receive new donor graft without rejection, and within few weeks recipient starts to produce new blood cells from donated stem cells. Intensive supportive management are crucial in this period to ensure the outcome. Continued research efforts on complicated procedure of HSCT and adoption of newer technologies become the blessings for the fatal blood diseases and reflects the better outcome for these patients. Now HSCT is an essential part in many treatment concept and protocols for hematological malignancies.

**First HSCT and Bangladesh perspective: Effect of an international collaboration.**

Bangladesh is increasingly burdened with hematological diseases. Both malignant and non-malignant diseases are being diagnosed more in number than in previous few decades due to improved diagnostic facilities and institutional development. Untill 2014 there was no facilities of HSCT in Bangladesh. Patients with acute leukemia, aplastic anemia and thalassemia need allogeneic HSCT as curative option whereas relapsed lymphoma and myeloma patients need autologous transplant as standard of care . Patients with serious blood diseases had to go abroad for curative and very expansive treatment bone marrow transplantation (HSCT) .

Bangladesh, a middle income country with 18 million population has many limitations in health sectors. In spite of many hurdles the world class, state of art treatment modality Bone marrow transplant or Hemopoietic stem cell transplantation was first introduced in Bangladesh in 2014 with relatively low cost compared with abroad[2]. The journey behind starting stem cell transplant was not smooth. Long dreamt transplant program was first inspired at an international meeting with WBMT and APBMT at Vietnam in 2011. Later on with the intense support from ministry of health and collaborative partnership between DMCH and Massachusetts General Hospital (MGH) it was able to develop a world class transplant centre in largest and oldest government hospital of country, Dhaka Medical College hospital under department of Hematology. The initial goal of the collaboration was to build a comprehensive program and a centre of excellence for hematologic malignancies. Twining between an emerging centres with a well established centre is desired to achieve a safe and comfortable expertise of starting stem cell transplant activity. Although India has very few twinning program on transplant, a successful twinning was seen in Rajasthan and Cure2children, a non profit organization of United States that helped the centre to establish allogeneic transplant program and later on to run that program independantly[3].

The first autologous stem cell transplant of Bangladesh was completed successfully for a myeloma patient on March 10, 2014 in Dhaka medical college hospital. That patient is still enjoying remission with a good quality of life.

The most crucial steps for establishing an HSCT centre in a government hospital was appropriate infrastructure development, human resource capacity building, making a core clinical team and running a sustainable transplant program. Financial constrain and consideration was a key factor. Initially all the funding was provided by the Government of Bangladesh. Each aspect of construction, progress, and development was critically observed by a respective team with the objective to ensure the best care for sick patients. Critical components of a

functioning transplantation program include basic infrastructure and sanitation as well as standard protocols for stem cell mobilization, transplant processes, transfusion medicine, and diagnostics that all were taken care by respective team. Nursing care is the back bone of transplant program and all nurses of DMCH were appropriately trained by nurse faculties of MGH( Massachusetts General Hospital). As a part of twinning program several nurses came to Bangladesh from MGH to train and educate them.

**Expansion of BMT centres in Bangladesh and starting allogeneic transplant:**

After successful establishment of BMT centre in DMCH , two more centres were developed in the country. The private Evercare Hospital Dhaka (previous named as Apollo Hospitals Dhaka) and the Combined Military Hospital(CMH) Dhaka developed autologous stem cell transplant programs in March, 2016 and November, 2016 respectively.

Gradually all three institutes started allogeneic transplant program after gaining experience on auto-transplant. First Allogeneic transplant was successfully done for relapsed acute myeloid leukemia(AML) at CMH in 2018. Then Dhaka Medical college hospital did allogeneic transplant for refractory ALL in 2019, and Evercare started in same year too. All institutions initially started with full (100%) HLA matched sibling donor HSCT for allogeneic transplant. Later on Evercare hospital also initiated Haplo-identical transplant successfully for various hematological diseases. So far Evercare hospital did the highest number of allogeneic transplant (22).

Bangabandhu Sheikh Mujib Medical University (BSMMU) and Asgar Ali Hospital also performed one and four auto-transplant respectively since 2018, although no definitive BMT unit established yet there.

**Hemopoietic stem cell Transplant activities of Bangladesh:**

In Bangladesh Total 168 hemopoietic stem cell transplantation have been done since establishment of first BMT centre in DMCH in 2014. Major centres are DMCH(52), Evercare (62) and CMH Dhaka(49). Mean age of all patients is 39.4 years( range 15-69 Y) and sex distribution is M:F 3:1.

As of February 2020, the pioneer centre DMCH performed total 52 cases of HSCT including 5 allogeneic and 47 autologous transplant for various diseases successfully. Major indication for autologous transplant were relapsed non-Hodgkins Lymphoma/NHL (18), relapsed Hodgkins lymphoma/HL(12), Multiple myeloma/MM (13), others (04). Average age was 36 years( range 16-59years). Separate mobilizing and conditioning chemo protocols were used for each disease. Allogeneic transplants were done from full HLA matched sibling donor for acute leukemia( ALL/2, AML/ 3). Five year progression free survival is 61% for all patients, and overall survival is 73% as depicted in analysis from DMCH data. Due to COVID-19 pandemic the transplant program was stopped in March,2020 and yet to start due to renovation works.

Evercare hospital Dhaka is a sustainable private sector centre that is successfully running transplant program since March, 2016. As of June 2022 data of this centre, total 62 stem cell transplant have been done since 2016 including 40 auto and 22 allo-transplant. Major indication of auto-transplant was multiple myeloma (24), non-Hodgkin lymphoma(08), Hodgkin lymphoma(07) and others(01). Allo-transplants were done for acute myeloid leukemia(14), acute lymphoblastic leukemia (04), undifferentiated leukemia (01), relapsed NHL(1), relapsed HL(1) and thalassemia(01). Average age of all patients was 46 years(range 15-69Y). Among allogeneic transplant 7 were haplo-identical donor transplant and rest(15) were full matched sibling donor transplant. Progression free survival is 62% so far for all cases.

CMH Dhaka has started transplant activities in November,2016 and as of June 2022 total 49 cases have been done including 38 auto-transplant and 11 allo-transplant. Major indications of auto transplant were MM(15), NHL(13) , HL (08) and others (02). Eleven (11) allogeneic transplant have been done so far and majority were for acute myeloid leukemia/AML(06) and severe aplastic anemia/ SAA(04). They have also done time demanding allogeneic transplant for an E-Beta thalassemia for the first time in country recently. Average age of all patients was 40 years( range 18-63 Y). Progression free survival is 83% for all patients in CMH Dhaka.

As all centre used almost similar conditioning mean engraftment time in all centres were almost similar. Mean time for neutrophil engraftment was 10-12 days and for platelet engraftment was 12-16 days on average. Each

centre follows specific infection control protocols, conditioning chemo protocols and use of growth factor protocols for the best patient care. Conditioning chemo protocols that usually used are high dose melphalan for MM, BEAM( Carmustine, Etoposide, Ara-C and Melphalan) for lymphoma and Bu-Cy( Busulphan-Cyclophosphamide) based for acute leukemia. All centres use irradiated blood component transfusion products to avoid transfusion associated GVHD.

Major early complications following transplant were neutropenic fever (>80%) and bacteraemia (25-30%). Severe sepsis, pneumonia, typhlitis were in few cases. Mucositis, vomiting and diarrhoea were mild to moderate in most patients. Almost all patients need at least 1-2 red cell and platelet transfusion during the time waiting for engraftment. Transplant related mortality was <1% for autologous transplants.

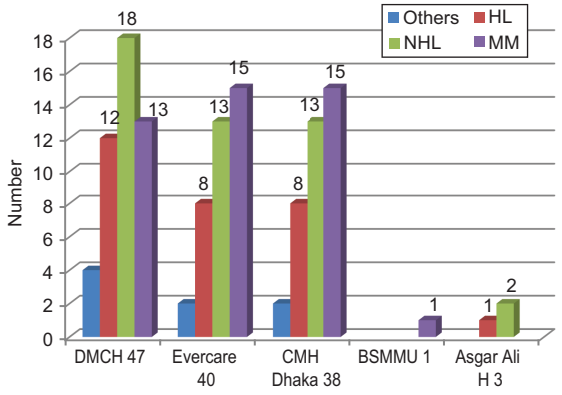


**Fig.-1:** *Number of auto-transplant in all 5 centres of Bangladesh*

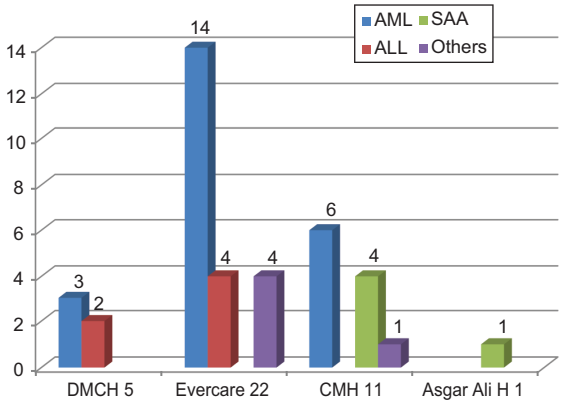


**Fig.-2:** *Number of Allo-transplant in Bangladesh*

**Lack of transplant activity registry and database:**

Each and every transplant patient should be monitored and followed up for a long time and keeping all records are crucial. Monitoring patient's demographics, treatment details and outcomes is an essential requirement for each centre. Each program should keep accurate and detail patient's records and an organized database containing relevant patient information should be established and maintained. But in Bangladesh currently this data management is under looked and each centre is trying to keep the records in their own way. There is no national transplant registry. Few countries eg India, Australia, New Zealand, Korea, Japan and Taiwan have their own transplant registry.[4] They send data through national database to regional and international association eg APBMT (Asia-Pacific Blood and Marrow Transplantation Group) and/or CIBMTR( Centre for international blood and marrow transplant research) which are dedicated to improve survival, treatment, and quality of life for transplant patients through continued research based on data each year. Bangladesh also submits transplant data each year to regional group data centre of APBMT though one registry committee member who collects data from every centre.

Although data manager in each program is highly recommended, in Bangladesh usually transplant physicians are keeping the records in spite of busy work schedule, whereas in developed countries nurses with experience in transplantation are able to maintain database.

**South East Asia and Pacific regional experience in HSCT:**

Among the south east Asian countries Sri Lanka started HSCT program in same year as Bangladesh in 2014 after two and half years of planning and performed 20 auto-transplant for myeloma and lymphoma in first year with almost no mortality but acceptable morbidity[5]. On that contemporary period Myanmar also started transplant program in 2014 overcoming many barriers and did an auto-transplant for a myeloma case and till 2016 they have done 6 cases of auto transplants[6]. In Malaysia the first pediatric HSCT was performed in 1987, followed by an adult HSCT in 1993. Since then it was rapidly evolving and 13 centres are doing HSCT in Malaysia with nearly survival rate 70%[7]. India is clearly ahead in

transplant area as it started with successful first allogeneic transplant in 1983 for an acute myeloid leukemia girl. Later it took long years to achieve a sustainable program. Recent transplant activity of India reported that more than 19000 transplant have been performed for various indications[8].

In Asia Pacific region there are 624 transplant centres according to data of 2015, and the rate of transplants are increasing every year. Allogeneic transplants are performed more frequently than autologous in some countries eg Pakistan, whereas Thailand, Malaysia, Australia and New Zealand reported more auto than allotransplant in 2015[4].

**Bone marrow donor registry is a necessity:**

Bone marrow donor registry has been playing an important role in searching suitable unrelated HLA matched donor for transplant. According to WMDA( World Marrow Donor Association) a donor registry is an organization responsible for coordination of search for hemopoietic stem cell from donors unrelated to potential recipient. It plays an important role in communication between transplant physician and healthcare professional contacting the donor at national or international level. Donor centres recruit volunteer donor from 16 to 55 years of age with various other policies. As of January 2018, more than 32 million potential adult unrelated donor and cord blood units are listed in global Search & Match service of WMDA. Every year approximately 2 million new volunteer donors are added to the registry pool. Close to 75% of Caucasians are likely to identify an 8/8 HLA match unrelated donor but this chance is very low for Asian, ethnic minority, and mixed- race patients.

Bangladesh like many other emerging countries does not have bone marrow donor registry as India, Malaysia, Japan, Australia have. DATRI, India's largest Blood Stem Cell Donors Registry, a wide and diverse database has more than 4 lac donors registered[8]. ABMDR( Australian bone marrow donor registry) is responsible for recruitment of Australian volunteers willing to donate blood stem cells for life-saving transplants. Such organizations allow patients to find suitably matched donors anywhere in the world. As family sizes are shrunken demand for MUD(matched unrelated donor) are increasing and searching a MUD is a major challenge and barrier in Asian region due to higher genetic diversity of HLA haplotype in these population.

The alternative option, Haploidentical donor transplantations that have begun in a few countries are increasing due to lack of full matched donor. The safety and success of post-transplant cyclophosphamide (PTCy), pioneered by the Johns Hopkins group, has initiated the scope of haploidentical transplants.

Bangladesh attempted to initiate Bangladesh marrow donor registry (BMDR) in 2019. But still it is not organized. To search a suitable unrelated donor for Bangladeshi patients, it is very important to organize a national donor registry which needs extensive support from government.

**Challenges and barriers of HSCT:**

The main challenges of bone marrow transplant in developing country is financial constrain and lack of health insurance. Other issues include availability of trained physician, technologist, nurses and laboratory facilities and unrelated donors. Lack of trained personnel is a big challenge for running sustainable transplant program. Laboratory facilities are essential for HSCT including high resolution HLA typing for donor and recipient, flowcytometry, chimerism study, antibody screening and other essential support for diagnosis and follow up. Adequate blood and blood product transfusion support is very essential, especially the facility of irradiation of blood product is not readily available in all centres.

Lack of database for transplant activity and lack of data manager are two obstacles for keeping records of patients. Transplant registry is an important step to take next. Another issue is lack of national marrow donor registry for searching suitable unrelated donor for a patient who doesn't have family donor. Quality control, regular audits of various transplant events and upholding the standards of a centre are essential issues. Every procedure and every treatment should have specific and standard operative procedures. Essentially a unique system is required for to detect any adverse event or errors.

**Conclusion:**

Over the decades, the clinicians have greatly acquired knowledge from their experience handling transplant patients and donors. In the field of HSCT, a multi team care is required to maintain the quality and patient care to deliver maximum positive outcome. This is very crucial

to the establishment of HSCT program to have experienced and appropriately trained personnel to lead the program. Formalization of national transplant registry and bone marrow donor registry are two most important policy making issues that needs to be addressed.

Clearly also requires legal, financial, ethical and institutional support as well as governmental policy for doing that continuously. HSCT transformed thousands of life and family who were fighting with deadly diseases and this complex, expansive procedure is encouraging and worthy.

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