EDITORIAL

HAPLOIDENTICAL HAEMOPOIETIC STEM CELL TRANSPLANTATION - PAKISTANI PERSPECTIVE

The process of transferring stem cells from the donor to the recipient with an intention to achieve haematological as well as immune reconstitution is called Allogeneic Haemopoietic Stem Cell Transplantation (Allo-HSCT)[1].

Allo-HSCT is the only curative option for the patients with various benign as well as malignant haematological disorders e.g very severe aplastic anaemia (VSAA), other bone marrow failure syndromes, beta thalassaemia major (BTM), severe combined immunodeficiency (SCID) and poor risk leukaemias[2]. More than 50% of the patients are not fortunate enough to have a fully HLA-matched donor and as smaller family size is in vogue all over the world this probability is decreasing day by day[3]. For the patients who do not have 8/8 HLA matched sibling, matched unrelated donor (MUD)[4] or haploidentical donor is preferred. Since MUD can be searched only when matched unrelated donors registry is either available or approachable, bone marrow transplantation from related haploidentical donor is gaining popularity. The chance of finding a MUD is less than one in a million individuals[5]. Furthermore, despite inclusion of more than 20 million volunteer donors in these registries, it is very difficult for few ethnicities to find a fully matched unrelated donor.

Blood relative of the patient who shares one human leucocyte antigen (HLA) haplotype but has different HLA genes on unshared haplotype is called haploidentical donor (HID)[6]. Every individual has one haplotype similar to each of the parent and each offspring. Every sibling also has 50% chance of having matched haplotype for the patient. So HID can be searched by HLA typing of the parents, siblings, offsprings and close blood relatives. According to an estimate 95% of the patients have at least one HID and on average there are 2.7 donors available for each recipient[7].

Haploidentical stem cell transplantation (Haplo-HSCT)[8] has become need of the day due to immediate donor availability especially in resource constraint countries where MUD registries and cord blood banks (CBB) are neither available nor planned in near future due to extremely high involved costs. Historically Haplo-HSCT was associated with compromised outcome due to graft versus host disease (GVHD) and graft failure but after the discovery of post-transplant high dose Cyclophosphamide (PT/Cy) causing selective T-cells depletion, the bidirectional T-cell allo-reactivity has been adequately addressed. However PT/Cy results in delayed immune reconstitution and higher rates of life threatening infections.

Pakistan's Perspective

Pakistan is the sixth most populous country with more than 200 million inhabitants. The country is facing many challenges including population explosion, illiteracy, lack of nationwide health infra structure, economic crises and last but not the least war on terrorism.

The incidence of aplastic anaemia (AA) in Asia is two to three folds as compared to the incidence in any other part of the world[9]. In Pakistan more than 50% patients in any haematology clinic have diagnosis of aplastic anaemia[10]. Etiology of increased incidence of AA includes both genetic as well as acquired factors[11]. Host genetic factors especially short telomere length has been recognized to be the culprit. Environmental factors responsible for increased incidence of AA include pesticides, benzene, arsenic and many viruses. In Pakistan rural population is at a greater risk of AA as compared to urban population because being an agricultural country, people living in villages have increased exposure to pesticides[12].

Pesticides have been reported to be associated with haematological malignancies as well. Exposure to excessive radiations also

increases the risk of acute as well as chronic leukaemias.

Among genetic disorders the most frequently encountered haemoglobinopathy is β-thalassaemia major. There are more than 100000 thalassaemics in the country and despite increasing awareness about prevention 5000 annual births are still being reported[13].

Bone marrow transplantation is the only curative option for aplastic anaemia, β-thalassaemia major and poor risk leukaemias. In Pakistan only five well established centers are carrying out haemopoietic stem cell transplantation (HSCT) and few smaller centers are also coming up. Less than 10% of the potential candidates requiring HSCT can actually undergo the procedure basically because of the following reasons:

1. Lack of specialized centers.
2. Lack of trained human resources including doctors, nurses, pharmacists, technologists and paramedics. Very low BMT team density as there are just five BMT teams for a population of 200 million i.e 0.025 team/million as compared to Europe where the ratio is 14.43/million and Eastern Mediterranean countries having the ratio of 1.55/million population[14].
3. Limited availability of specialized instruments.
4. High cost involved in the procedure.
5. Limited availability of fully HLA matched donors.
6. Non-availability of MUDs registry and cord blood bank.
7. Extremely high cost required for approaching International MUDs registries /Cord blood banks.
8. Lack of infrastructure and Government support for National Bone Marrow Transplantation Programs.

So Haploidentical HSCT is the only ray of hope in the presence of above mentioned constraints and limitations. Among all the different strategies of carrying out haploidentical transplants, PT/Cy is the most preferred and cost effective alternate. Haploidentical HSCT is the realistic approach in present scenerio not only for Pakistan but for the whole developing world.

CONCLUSIONS / FUTURE DIRECTIONS

Haploidentical HSCT is the only feasible way to rescue those patients requiring Allo geneic BMT who do not have fully HLA matched donor especially in developing countries where lack of resources pose the major challenge. T-cell depletion was associated with very high non relapse mortality (NRM) after haplo HSCT all over the world. So the presence of T-cells in the graft along with better preventive regimens for the prevention of graft versus host disease (GVHD) was recommended. The use of high dose Cyclophosphamide for the removal of allo-reactive T-cells on day +3 and +4 post Haplo-HSCT turned out to be very effective as on one hand it depletes allo reactive T-cells responsible for GVHD and graft rejection and on the other hand it does not harm stem cells in the graft which are resistant to Cyclophosphamide due to high levels of enzyme Aldehyde dehydrogenase in them. Mega doses of stem cells, reduced intensity conditioning and more comprehensive antibiotics cover decrease early complications associated with haploidentical HSCT.

Importance of the benefits of haplo HSCT cannot be undermined. Ongoing studies are required to discuss the challenges associated with haploidentical HSCT and to devise ways for better immune reconstitution and improved survival post haplo HSCT.

Our role is to develop guidelines for:

1. Selection of alternate donors for the patients who do not have fully HLA matched sibling donor.
2. Selection of haploidentical donor among the potential candidates sharing one haplo type with the patient.

3. Development of better and safer conditioning regimens for Haplo HSCT.

4. Choosing more effective GVHD prophylaxis with the preservation of graft versus leukemia (GVL) effect.

REFERENCES

1. Sakaguchi H, Watanabe N, Matsumoto K, Yabe H, Kato S, Ogawa A et al. Comparison of Donor Sources in Hematopoietic Stem Cell Transplantation for Childhood Acute Leukemia: A Nationwide Retrospective Study. Biology of blood and marrow transplantation. Biol Blood Marrow Transplant 2016; 22(12): 308577815.
2. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biology of blood and marrow transplantation. Biol Blood Marrow Transplant 2008; 14(6): 641-50.
3. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. Nature reviews. Clinical oncology 2016; 13(2): 132.
4. Rashidi A, Slade M, DiPersio JF, Westervelt P, Vij R, Romee R. Post-transplant high-dose cyclophosphamide after HLA-matched vs haploidentical hematopoietic cell transplantation for AML. Bone Marrow Transplant 2016; 51(12): 1561-64.
5. Bergstrom TC, Garratt RJ, Sheehan-Connor D. One chance in a million: Altruism and the bone marrow registry. Am Econ Rev 2009; 99(4): 1309-34.
6. Li HH, Li F, Gao CJ, Huang WR, Bo J, Dou LP et al. Similar incidence of severe acute GVHD and less severe chronic GVHD in PBSCT from unmanipulated, haploidentical donors compared with that from matched sibling donors for patients with haematological malignancies. Br J Haematol 2016; 176(1): 92-100.
7. Ruiz-Arguelles GJ, Ruiz-Delgado GJ, Gonzalez-Llano O, Gomez-Almaguer D. Haploidentical Bone Marrow Transplantation in 2015 and Beyond. Current oncology reports 2015; 17(12): 57.
8. Xu T, Chen J, Jin ZM, Miao M, Fu CC, Qiu HY et al. Outcome of haploidentical hematopoietic stem cell transplantation for non-Hodgkin lymphoma. Zhonghua xue ye xue za zhi 2016; 37(8): 656-60.
9. Issaragrisil S, Kaufman DW, Anderson T, Chansung K, Leaverton PE, Shapiro S, et al. The epidemiology of aplastic anemia in Thailand. Blood 2006; 107(4): 1299-07.
10. Shamsi T, Hashmi K, Adil S, Ahmad P, Irfan M, Raza S, et al. The stem cell transplant program in Pakistan - The first decade. Bone marrow transplant 2008; 42(Supp-1): S114-S117.
11. Young NS, Kaufman DW. The epidemiology of acquired aplastic anemia. Haematologica 2008; 93(4): 489-92.
12. Taj M, Shamsi TS, Ansari SH, Farzana T, Nazi A, Nadeem M, et al. Epidemiologic and HLA Antigen Profile in Patients with Aplastic Anemia. J Coll Physicians Surg Pak 2014; 24(8): 549-52.
13. Ali N, Moiz B, Bin Azhar W, Zaidi N, Memon R. Carrier detection for beta-thalassemia trait in general Pakistani population: A way forward. Hematology 2012; 17(4): 237-40.
14. Aljurf M, Zaidi SZ, Hussain F, Ghavamzadeh A, Alimoghaddam K, Jahani M et al. Status of hematopoietic stem cell transplantation in the WHO Eastern Mediterranean Region (EMRO). Transfus Apher Sci 2010; 42(2): 169-75.

Lt Col (Dr) Mehreen Ali Khan
Consultant Haematologist
Armed Forces Bone Marrow Transplant Center
Rawalpindi, Pakistan
0092-3335164941
mehreen35@hotmail.com