Stem Cell Transplantation in Malaysia and Future Directions

S A W Fadilah*,**, C F Leong**,****, S K Cheong***,****

*Department of Medicine, **Department of Pathology, UKM Medical Centre, ***Department of Medicine, International Medical University, ****Cell Therapy Centre, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia

There is a website named EDGE (www.edge.org) which explores unconventional ideas in this rapidly changing world. In 2006, this site had invited many eminent scientists and thinkers to write about "What is your dangerous idea?" An idea considered dangerous now may in future turn out to be beneficial to mankind. In the early seventies, Dr ED Thomas not only toyed with such a dangerous idea, but also was able to convince his colleagues to carry out the first clinical trial in allogeneic (donor-recipient) bone marrow transplantation in humans[1]. This study showed a plateau in the survival curve suggesting that a cure is possible in endstage acute leukemia. It became a major milestone in clinical transplantation research and therapy. In the mid seventies, Dr NC Gorin performed the first autologous (patient's own) bone marrow transplantation (BMT) for patients who had no family donor for allogeneic transplant[2]. Since then, BMT has progressed considerably and benefited patients with not only blood disorders but also other systemic diseases such as solid tumours and autoimmune disorders.

In Malaysia, BMT took a rather slow course in development despite the excitement then about a major breakthrough for blood cancer treatment. Patients who qualified for support of the Government or were able to afford the high cost of the procedure continued to receive this treatment overseas. The first BMT was performed in University Malaya in a child in 1987 and in an adult in 1993. The article on a single centre experience with hematopoietic stem cell transplantation (HSCT) in this issue of the Journal is a result of this endeavour[3]. HSCT was established in the Institute of Paediatrics in 1994 and in Subang Jaya Medical Center, Hospital Kuala Lumpur and Hospital Universiti Kebangsaan Malaysia in 1999. To date, 1382 patients were transplanted nationwide and registered with the Malaysian Blood and Marrow Transplant Registry with cumulative results that are as good as any well-known centers in the West[4]. The numbers of patients treated with HSCT continue to rise over the past 20 years except in patients with chronic myeloid leukemia where the indication of HSCT has declined after 2006[4] due to the introduction of imatinib mesylate.

Transplantation began with the use of bone marrow (BM), which is a rich source of haemopoietic stem cells (HSC). BM harvesting can result in considerable morbidity due to soft tissue and bone trauma as well as the potential risks of general anesthesia. The discovery that HSC are found in significant numbers in the peripheral blood for several days after chemotherapy or a course of growth factors enabled peripheral blood stem cell transplantation (PBSCT) to be established in 1986[5]. Since then transplant physicians have not looked back except in difficult cases where patients fail to be mobilized for HSC. The trend towards the use of peripheral blood stem cells for transplant is highlighted in the article in this issue of the Journal[3]. The procedure is preferred by the donor and recipient as it is technically easier and is associated with faster haematopoietic recovery and no increase in the incidence of acute graft versus host disease (GvHD)[6]. However, there is some increase in chronic GvHD which transplantation investigators try to overcome such as the concomitant use of mesenchymal stromal cells during allogeneic transplant[7]. Additional studies with long-term follow-up are required to determine whether BMT or PSCT will produce improved disease free or overall survival.

Initially allogeneic HSCT is limited to the use of stem cells from HLA-matched sibling donor. As nuclear family is getting smaller, such match may have to be searched beyond family members and this have stimulated the formation of blood and marrow donor registries to facilitate donor search and manage delivery of donor stem cells to transplant centers. With the help from the National Cancer Council (MAKNA), a BM donor registry was established in the Institute for Medical Research Kuala Lumpur in 1999 and to date, over 13,000 volunteer donors have been typed. This development coupled with the advances in HLA typing, will hopefully boost the relatively low activity of Matched Unrelated Donor (MUD) HSCT in this part of the world. MUD, however, is still associated with higher complication rates than in HLA-identical sibling donor transplants. Improvements in prevention and treatment of GvHD and opportunistic infections, new preparative regimens and better donor selection will likely expand the indications of unrelated donor HSCT in the next decade[8].

Until mid 90's, highly toxic myeloablative regimens were considered mandatory for the eradication of undesirable cells of host origin. Recent data suggest that high-dose chemoradiotherapy can be successively replaced by non-myeloablative stem cell transplantation (NST) that involves the induction of host-versus-graft transplantation tolerance. In NST, the curative potential relies on the ability of the donor cells to elicit a graft-versus tumor effect. This transplant strategy has extended the use of allogeneic HSCT to older patients and also patients who, owing to the malignant disease or to comorbidities, are unable to tolerate myeloablative conditioning with promising results[9].

Transplantation using cord blood (CBT) represents the most recent strategy to expand the potential donor pool as it permits a higher degree of HLA disparity. The increasing use

Corresponding Author: S Fadilah Abdul Wahid, Head, Department of Medicine, Coordinator, Cell Therapy Centre, UKM Medical Centre, Jalan Yaacob Latiff Cheras, 56000 Kuala Lumpur Email: sfadilah@mail.hukm.ukm.my

of CB is driven by the fact that more than 50% of patients in need of HSCT lack a fully HLA-matched related and unrelated BM or PB stem cell donor. Though CBT takes longer time to engraft, it has the advantage of lower incidence and severity of GvHD[10]. The first cord blood transplantation (CBT) in Malaysia was performed for a child with thalassemia in 1997, ten years after it was first introduced by Dr. E Gluckman[11]. CBT is now available to not only children, but also adults especially with the development of double CBT. In fact, CBT is now accepted as the treatment of choice if there is no HLA matched blood or marrow donor or the patient's condition requires prompt allogeneic transplantation. Thus it is timely that the Ministry of Health of Malaysia has invested a vast sum of money to establish and operate a public cord blood bank in Malaysia in 2008.

Haematology patients are the first to benefit from stem cell research and therapy. The scene is now set to benefit other patients as stem cell research and therapy rapidly reaches out to other disciplines. Basic and clinical research accomplished during the last few years on embryonic, fetal, amniotic, umbilical cord blood and adult stem cells has constituted a revolution in regenerative medicine and cancer therapies by providing the possibility of generating multiple therapeutically useful cell types. Among the disorders that might benefit from stem cell-based therapy are Parkinson's, Alzeimer's, diabetes mellitus, heart and liver failures, skin and eye disorders as well as aggressive and recurrent cancer[12].

Stem cell research and therapy suffers a major set back when the methods generating embryonic stem cells created many controversies from social, religious and ethical viewpoints as these methods are capable of human cloning. This may soon be over as scientists have found an alternative method to create induced pluripotent stem cells that have the properties of human embryonic stem cells in 2007[13]. The recent identification of multipotent adult stem cells (ASC) within specific niches in most human tissues/organs scientists have caused great interest and enthusiasm for their use in cellular therapies[14]. Mesenchymal stem cells, endothelial progenitor cells and neural stem cells are among the well characterized ASC that have already been demonstrated to be useful in cardiovascular and degenerative disorders in humans[14].

The widening scope of application of stem cells in therapy also drives medical institutions to strategise for the provision of these new services. Universiti Kebangsaan Malaysia (UKM) has taken the lead to establish a Cell Therapy Centre in UKM Medical Centre for these purposes in 2007. The Centre not only has scientific goals, but also strives to be a coordinating center for the research and development of new therapeutic procedures employing cell therapy, a center for career development in the field of stem cell biology and cell therapy and a place for intensive international collaboration.

Recognizing the enormous potentials and significant impact of stem cell research and therapy to the country's health and economic development, the Ministry of Health of Malaysia in 2007 formulated the National Policy for Organ, Tissue and Cell Transplantation. In the following year, the National Standards for Cord Blood Banking and Transplantation, the National Guidelines for Haemopoietic Stem Cell Therapy and the National Guidelines for Stem Cell Research and Therapy have been drafted to promote, guide and regulate the practice of transplantation in Malaysia. A Stem Cell Oversight Committee will soon be established to ensure that stem cell research and therapy is reviewed at the national level and conforms to the highest ethical and scientific standards. The Committee shall include representatives from the general public and religious bodies, as well as those with expertise in stem cell biology and therapeutics, ethics, law, and social sciences.

We were all brought up in pathology that once a stem cell is committed to differentiation, the cell is destined to carry out a specific function and disintegrates by apoptosis once the job is done. Limited regeneration is found only in certain tissues such as gut lining or the skin. There is no replacement for cardiac tissues or neurons other than fibrosis or gliosis after tissue damage or unnatural death (necrosis). This dogma is now being challenged. Regeneration appears possible with the right ingredients and microenvironment. Even a fibrotic bone marrow can be rejuvenated to become an active bone marrow again after allogeneic stem cell transplantation. Research in stem cells would unfold many of our buried potentials that could have been lost during our climb in the evolutionary ladder. It is astonishing to observe that many of things we practise today were unpredicted or even ruled as impossible years ago. We look forward to the days when "off-the-shelf" human spare parts or organ regeneration programmes are no longer in the realm of science fiction.

REFERENCES

1. Thomas ED, Storb R, Clift RA, *et al*. Bone Marrow Transplantation. N Engl J Med 1975; 292: 895-902.
2. Gorin NC, Najman A and Duhamel G. Autologous bone-marrow transplantation in acute myeloid leukaemia. Lancet 1977; 1: 1050.
3. Gan GG, Zakaria Z, Sangkar JV, Haris AR, Bee PC, Chin E and Teh A. Adult Allogeneic Haematopoietic Stem Cell Transplantation: A Single Centre Experience in Malaysia. Med J Mal 2008; 63: 281-7.
4. Hooi LS and Lela Yasmin Mansor, editors. Third Report of the National Transplant Registry. Kuala Lumpur: Clinical Research Centre, Ministry of Health of Malaysia; 2006.
5. To LB, Haylock DN, Kimber RJ and Juttner CA High levels of circulating haemopoietic stem cells in very early remission from acute non-lymphoblastic leukaemia and their collection and cryopreservation. Br J Haematol 1984; 58: 399-410.
6. Deaver D. Peripheral blood progenitor cell or bone marrow transplantation. Curr Opin Oncol 2008; 20: 220-6.
7. Bacigalupo A. Mesenchymal stem cells and haemopoietic stem cell transplantation. Best Practice & Research Clin Haematol 2004; 17: 387-99.
8. Zuckerman T, Rowe M. Alternative donor transplantation in acute myeloid leukemia: which source and when? Curr Opin Hematol 2007; 14: 152-61.
9. Kato K, Khaled Y, Mineishi S. Reduced-intensity stem cell transplantation for hematological malignancies: current status and the future. Curr Stem Cell Res Ther 2007; 2: 149-62.
10. Brown JA, Boussiotis VA. Umbiliocal cord blood transplantation: basic biology and clinical challenges to immune reconstitution. Clin Immunol 2008; 127: 286-97.
11. Gluckman E, Broxmeyer HE, Auerbach AD *et al*. Haematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical cord blood from an HLA-identical sibling. N Engl J Med 1989; 321: 1174-8.
12. Mimeault M, Hauke R, Batra SK. Stem cells: A revolution in therapeutics – recent advances in stem cell biology and their therapeutic applications in regenerative medicine and cancer therapies. Clin Pharmacol & Therapeutics 2007; 82: 252-64.
13. Yamanaka S. Strategies and developments in the generation of patient-specific pluripotent stem cells. Stem Cell 2007; 1: 39-49.
14. Mimeault M, Batra SK. Recent advances on the significance of stem cells in tissue regeneration and cancer therapies Stem Cells 2006; 24: 2319-45.

Haploidentical stem cell transplantation in adults for the treatment of hematologic diseases: results of a single center (cic725). 2019 / Beynarovich Anastasia V., Babenko Elena V., Moiseev Ivan S., Paina Olesya V., Pirogova Olga V., Rudakova Tatiana A., Gindina Tatyana L., Darskaya Elena I, Morozova Elena V., Bondarenko Sergey N., Zubarovskaya Ludmila S. Zubarovskaya, Afanasyev Boris V.Â Key words: platelet transfusion, hematopoietic stem cell transplantation, haemostasis, thrombin. Introduction. Allogenic platelet transfusions are important in clinical practice as an efficient treatment of persistent thrombocytopenia, which is a common complication after hematopoietic stem cell transplantation (HSCT). Aim. Stem cell transplantation, in combination with traditional treatments, can improve outcomes for patients with multiple myeloma and non-Hodgkin's lymphoma.Â Stem cell transplants have become important weapons in the fight against certain blood cancers, such as multiple myeloma, non-Hodgkin's lymphoma, Hodgkin lymphoma, and leukemia. A stem cell transplant may help you live longer. In some cases, it can even cure blood cancers. About 50,000 transplantations are performed yearly, with the number increasing 10% to 20% each year. More than 20,000 people have now lived five years or longer after having a stem cell transplant. Hematopoietic stem cell transplants, including peripheral blood, bone marrow, and cord blood transplants are used most often to treat cancers affecting the blood or immune system. There are two main types of stem cell transplant: autologous and allogeneic. Autologous stem cells come from the person who will be receiving the transplant and are mainly used to treat leukemias, lymphomas, and multiple myeloma as well as other cancers such as testicular cancer and neuroblastoma. Autologous stem cell transplants are also used to treat certain childhood cancers.Â For example, bone marrow or peripheral blood progenitor cell harvesting is appropriate for patients with multiple myeloma in CR and who might be transplanted in the future. Consult benefit document. However, yields of hematopoietic stem cells vary greatly between patients, and the optimal strategy to mobilize hematopoietic stem cells into peripheral blood for collection has not been defined. Current mobilization strategies consist of cytokines alone or in combination with chemotherapeutic agents. Cytokine-only mobilization regimens are well tolerated, but their utility is limited by suboptimal PBSC yields. When a myelosuppressive chemotherapeutic agent is added to a cytokine mobilization regimen, PBSC collections improve two- to five-fold. This benefit is tempered by increased toxicity, morbidity and resource utilization. Hematopoietic stem cell transplantation is a procedure in which multipotent hematopoietic stem cells sourced from peripheral blood cells, bone marrow, or umbilical cord blood are transplanted into the patient. Hematopoietic stem cell transplantation is commonly used in the treatment of lymphoma (Hodgkin, Non-Hodgkin), leukemia, multiple myeloma, thalassemia, sickle cell anemia, and osteoporosis. It includes two transplantation sources; 1) autologous, that uses stem cells from the patient's own body, 2) and allogeneic that sources stem cells from a donor's body. According to World Health Organization (WHO), over 50,000 hematopoietic stem cell transplantation procedures are carried out globally, every year and this number is expected to increase over the years.