Singapore Med J 1998; Vol 39(9):388-389

Issues in Peripheral Blood Stem Cell Transplantation

H L Lim, S H Lee

Peripheral blood stem cell (PBSC) or progenitor cell transplants are increasingly used to treat cancer. These are mostly autologous transplants but there is growing interest in allogeneic transplants using this approach, as well as the use of PBSC transplants to treat non-malignant disorders.

The use of PBSC transplantation (PBSCT) is based on extensive experimental data *in vitro* and in animals. The term "blood stem cell" was first used in 1962 by Goodman and Hodgson who showed that circulating stem cells were capable of restoring haematopoiesis in irradiation-myeloblated mice[1]. At the same time, the studies of Till and McCulloch defined our present day concept of the haematopoietic stem cell as one that is capable of regenerating the myeloid, erythroid and lymphoid cell lineages and that has the capacity for self-renewal[2]. Investigations in dogs showed that circulating or cryopreserved PBSCs could reconstitute the marrow[3] and subsequently, circulating stem cells were described and collected from humans[4]. An important advance was the finding that the number of circulating progenitors is dramatically increased during recovery from cytopenia after chemotherapy[5].

Successful PBSCT was reported in chronic myeloid leukaemia by 1981[6], but there were few reports of autologous PBSCT until 1986, when successful attempts were reported by investigators from several centres around the world. Following this, it was shown that single high doses of cyclophosphamide[7] and the use of colony-stimulating factors (CSFs) such as granulocyte colony-stimulating factor (G-CSF) stimulated an increase in the yield of circulating PBSCs[8]. Either chemotherapy followed by CSFs or CSFs alone are presently used to mobilise PBSCs for transplantation. After mobilisation, PBSCs are collected by leukapheresis using continuous flow cell separators, which return most of the processed blood components to the patient. PBSC harvests can be cryopreserved for long periods until transplantation, when the patient receives a conditioning regimen consisting of high dose chemotherapy and/or radiotherapy followed by infusion of the thawed PBSCs. Several studies have confirmed the durability of haematopoietic reconstitution using only PBSCs for engraftment.

An important problem in PBSCT has been to ensure that sufficient PBSCs for haematopoietic reconstitution can be collected in a single mobilisation episode followed by one or more leukapheresis procedures. Therefore, the optimal timing of PBSC harvesting after mobilisation has been a critical issue. Progenitor cells can be enumerated in PBSC collections by *in vitro* colony assays in semi-solid media or more readily by labelling with a monoclonal antibody against the CD34 antigen. The CD34 antigen is expressed by 1% – 2% of the mononuclear cell population in bone marrow that gives rise to virtually all haematopoietic colonies and their precursors[9]. We have recently completed a study at the National University Hospital to determine whether the peripheral blood CD34+ cell count could be used to predict the timing of leukapheresis following PBSC mobilisation. In 20 patients who underwent 22 mobilisation episodes and 48 leukaphereses, we found that if harvesting was commenced when the peripheral blood CD34+ cell count exceeded 10/μL, the majority of mobilisation episodes (80%) resulted in the collection of sufficient PBSCs ($>$ 2 x 10^6/kg body weight) for transplantation. These data agree with figures obtained by other workers[10]. Monitoring of the peripheral blood CD34+ cell count is now routinely used at the National University Hospital to guide the timing of PBSC harvests after mobilisation.

Many clinical applications of PBSCT have emerged in the last decade. Some of the diseases that have been successfully treated in this way include Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, breast cancer, ovarian cancer, chronic granulocytic leukaemia and acute myeloid leukaemia. Compared to bone marrow transplantation, the main advantage of PBSCT is that it gives earlier haematopoietic reconstitution and granulocyte and platelet recovery, thereby reducing the risks of infection and haemorrhage. The increased margin of safety allows higher doses of chemotherapy to be given. In general, leukapheresis procedures are also better-tolerated by patients than bone marrow harvests, which require a general anaesthetic. By 1993, PBSCs had overtaken marrow as the predominant source of stem cells for autotransplantation[11], and at a recent International Consensus Meeting on Blood Stem Cell Transplantation[12], it was concluded that PBSCs had become the appropriate source of haematopoietic support after intensive chemotherapy or radiotherapy for many conditions.

An increasing number of allogeneic PBSC transplants have been performed in recent years, usually with G-CSF to mobilise PBSCs in the stem

Department of Oncology
National University Hospital
5 Lower Kent Ridge Road
Singapore 119074

H L Lim, MBBS,
M Med (Int Med), FAMS
Consultant

Division of Haematology
Department of Laboratory Medicine
National University Hospital

S H Lee, FRCP (Edin),
FRCPath, PhD
Associate Professor

Correspondence to:
A/Prof S H Lee

cell donor[13]. Early fears of an increased risk of graft-versus-host disease (GVHD) due to the higher T-cell content of PBSC harvests appear to have been unfounded. On the contrary, a promising approach is the use of CD34+ selection to reduce GVHD in allogeneic PBSCT.

An issue of concern has been the possibility that the patient may suffer a relapse post-transplant from the re-infusion of small numbers of tumour cells that may have been present in the PBSC harvest. Whether tumour cells may also be mobilised by chemotherapy or CSFs is still unclear and requires further investigation. PBSC harvests can be processed to deplete any tumour cells present by enrichment or selection of the CD34+ cell population using monoclonal antibodies. Although this strategy can significantly reduce tumour cell contamination in harvests, post-transplant relapse can still originate from residual malignant cells in the patient. However, ensuring tumour cell-free PBSC harvests would be an important step towards controlled evaluation of improved pre-transplant conditioning protocols that can eradicate tumour cells in the patient.

Using recombinant haematopoietic growth factors and cytokines, it is now feasible to expand haematopoietic progenitors *in vitro* to supplement the standard PBSC autograft. Possible applications are the expansion of small harvests, the use of multiple cycles of PBSCT and a further reduction in the duration of post-transplant neutropenia[14]. Another exciting prospect is the graft engineering of CD34+ enriched cells as a form of gene therapy for cancer or for the treatment of single-gene defects in haematopoietic cells. Other non-malignant diseases that may be potentially treatable by PBSCT include various autoimmune disorders, paroxysmal nocturnal haemoglobinuria and multiple sclerosis[14]. Following the success of PBSCT, there has been increasing interest in the use of cord blood as a source of PBSCs for transplantation, especially in children[15]. These recent advances in PBSCT are likely to modify our perspectives of therapeutic options in various malignant and non-malignant disorders in the future.

REFERENCES

1. Goodman JW, Hodgson GS. Evidence for stem cells in the peripheral blood of mice. Blood 1962; 19:702-4.
2. Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow. Radiat Res 1961; 4:213-22.
3. Storb R, Epstein RB, Ragde H, Bryant J, Thomas ED. Marrow engraftment by allogeneic leukocytes in lethally irradiated dogs. Blood 1967; 30:805-11.
4. McCredie KB. Hersh EM, Freireich EJ. C.ells capable of colony formation in the peripheral blood of man. Science 1971; 171:293-4.
5. Richman CM, Weiner RS, Yankee RA. Increase in circulating stem cells followmg chemotherapy in man. Blood 1976; 47:1031-9.
6. Korbling M, Burke P, Braine H, Elfenbein G, Santos G, Kaizer H. Successful engraftment of blood derived normal haematopoietic stem cells in chronic myelogenous leukaemia. Exp Hematol 1981; 9:684-90.
7. To LB, Shepperd KM, Haylock DN, Dyson PG, Charles P, Thorp DL, et al. Single high doses of cyclophosphamide enable the collection of high numbers of hemopoietic stem cells from the peripheral blood. Exp Hematol 1990; 18:442-7.
8. Socinski MA, Cannistra SA, Elias A, Antman KH, Schnipper L, Griffin JD. Granulocyte-macrophage colony-stimulating factor expands the circulating hematopoietic progenitor cell compartment in man. Lancet 1988; 1194-8.
9. Civin CU, Strauss LC, Brovall C, Fackler MJ, Schwartz F, Shaper JH. Antigenic analysis of haematopoiesis. III. A haematopoietic progenitor cell surface antigen defined by a monoclonal antibody raised against KG-la cells. J Immunol 1984; 133:157-65.
10. Knudsen LM, Gaarsdal E, Jensen L, Nikolaisen K, Johnsen HE. Evaluation of mobilized CD34+ cells counts to guide timing and yield of large-scale collection by leukapheresis. J Hematother 1998; 7:45-52.
11. IBMTR Newsletter. 1995; Vol 2 (1).
12. Juttner CA, Fibbe WE, Nemunaitis J, Kanz L, Gianni AM. Blood cell transplantation: report from an International Consensus Meeting. Bone Marrow Transplant 1994; 14:689-93.
13. Korbling M. Peripheral blood stem cells: A novel source for allogeneic transplantation. The Oncologist 1997; 2:104-13.
14. Lie AKW, To LB. Peripheral blood stem cells: Transplantation and beyond. The Oncologist 1997; 2:40-9.
15. Broxmeyer HE. Cord blood as an alternative source for stem and progenitor cell transplantation. Curr Opin Paediatr 1995; 7:47-55.

Cover Photo

Tan Tock Seng Hospital – A Legacy of Caring

Tan Tock Seng Hospital (TTSH) was founded in 1844 as the first and only local hospital for the sick poor. Today, TTSH is an acute care general hospital with 19 medical and surgical disciplines. Much effort has been put into the development of TTSH's special strengths:

• Geriatric Medicine • Infectious Disease • Neurosciences • Rehabilitation Medicine • Rheumatology and Immunology

Having stood at its current premises for close to a century, groundbreaking for the new TTSH took place in September 1993 and topping out was achieved in May 1997. Almost six years later, we look forward to the completion of the new building at the end of 1998. The new 14-storey hospital complex has a gross floor area of 171,000 m^2 and will accommodate 1,211 beds and an ambulatory medical centre. It is designed with our patients in mind, adopting the "one-stop" service concept where inpatient and outpatient facilities are consolidated under one roof. Patients benefit from the cost-effectiveness and convenience of numerous one-stop multidisciplinary programmes, many of which are pioneering programmes in Singapore. The new hospital will also upgrade its current Information Technology system to improve the overall information delivery and communications network.

TTSH values her dedicated staff as the greatest asset, and we will continue to harness on our strong spirit of teamwork to build on our traditional strengths as well as new areas of service. While striving to practise cutting-edge medicine, we will not forget our objective to deliver affordable and cost-effective healthcare to our patients.

Ms Lena Wan
Dr Loh Keh Chuan