Stem Cell Transplantation for Children with Acute Leukemia

LALIT KUMAR, K. GANESSAN, MANJU SENGAR & N. KHATRI

INTRODUCTION

High dose chemotherapy (HDCT)± radiotherapy followed by haemopoietic stem cell transplantation (HSCT) is now an established treatment for a number of non-malignant and malignant diseases. HSCT refers to intravenous infusion of haemopoietic progenitor (stem cells) to re-establish haemopoiesis in a patient with defective or damaged bone marrow (BM).[1] For this purpose stem cells can be obtained either from an HLA-identical matched sibling (allogeneic) or genetically identical twin (syngeneic, available to 1%) or patient's own (autologous) BM or peripheral blood (PB). For patients who lack an HLA – identical sibling, stem cells can be obtained from alternative donors, either family members other than HLA–identical siblings or matched voluntary unrelated donors (MUD).[2] Probability of finding a match in the family is 25 to 30%, in another 5 to 10%, other family member could be a donor. Another 30 to 35% of patients may be candidates for MUD transplant. For the latter, donor search can be made through bone marrow donor registries established in North America, Canada, Europe and Australia. It is generally difficult to find a match for Asians in these registries due to small no of voluntary BM donors of Asian origin. In India, facilities for allogeneic (sibling) and autologous BM/ PBSC transplantation are available at few centres, MUD transplant programme is yet to be started.

Accurate HLA typing is essential for patients receiving allogeneic SCT. Currently, in addition to standard serologic methods using alloantisera for Class 1 (HLA-A,B,C) and Class II (HLA-DR,DQ and DP) antigens, DNA based techniques such as PCR-with sequence specific oligonucleotide probes (PCR-SSOP) for class II regions are employed.[2]

Correspondence to : Dr. LALIT KUMAR
Additional Professor of Medical Oncology, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi -11 00 29

STEM CELL SOURCE

Traditionally , BM has been used as a source of stem cells for allogeneic transplantation. Use of G-CSF mobilized PBSCs has become more frequent in the adults during past five years, almost 60% received PBSCT in the year 2000[3]. Data on the use of PBSCT is still limited in paediatric patients < 20 years. This is possibly due to difficulty in harvesting PB stem cells in very small children. For autologous transplantation, PB stem cells are virtually always used as a source of stem cells rather than BM.[4]

Umbilical cord (UC) blood is a rich source of most primitive (stem) cells that are able to produce 'in vivo' long term repopulating haemopoietic stem cells compared to adult stem cells. Therefore, these are able to expand rapidly and reconstitute haemopoiesis after myeloablative chemotherapy. Other advantage of UC blood stem cells include-relative immaturity of the immune system at birth, resulting in significantly lower risk of acute GVHD compared to adult BM/Blood stem cells. Since, the total yield of stem cells from a single cord blood is limited , presently, UC blood is being used for children weighing up to 25 Kg. Because of ease of procurement, absence of risks to donors, reduced risk of transmitting infection and the prompt availability of cryopreserved samples to transplantation centres, a number of UC blood banks have been set up in North America and Europe. More than 2000 transplants have been performed worldwide, mainly in children using allogeneic HLA matched sibling or matched unrelated UC blood for both non malignant and malignant conditions.[5-7]

BONE MARROW HARVEST

Marrow is usually harvested under general anaesthesia by repeated aspiration from the posterior iliac crest. If there is difficulty in removing adequate number of stem cells from posterior iliac crest, BM can also be removed from anterior iliac crest or sternum. In practice, approximately $3x10^8$ nucleated cells/kg of the recipient's body weight (or $5x10^6$/kg CD34+ cells) are harvested. The harvesting of BM is generally well tolerated. In allogeneic BMT with major ABO incompatibility between donor and recipient, it is necessary to remove mature erythrocytes from graft to avoid a haemolytic transfusion reaction .

For autologous SCT, PBSCs are harvested with the help of a cell separator following mobilization with G-CSF. A minimum of $5x10^8$ per Kg mononuclear cells (or $5x10^6$ /Kg CD34+ cells) are harvested. These are then cryopreserved at -80C using 7.5% DMSO or in liquid nitrogen.[8] Following this, patient is administered chemotherapy. Depending upon the half life of chemotherapy drugs used, PBSC can be re-infused either after 24 hours (melphalan) or after longer interval (5-7 days). The primary concern with autologous SCT is relapse due to re-infusion of malignant cells along with progenitor cells . Various methods including 'in vitro' treatment with chemotherapy drugs, monoclonal antibodies have been developed to remove the contaminating tumour cells (a process called as purging). Retrospective analyses have suggested that purging leads to a reduced rates of relapse in patients with AML and non-Hodgkin's lymphoma.[9]

PREPARATORY REGIMEN

Prior to stem cell transplantation, patient's own BM is destroyed by giving HD-CT with or without total body irradiation (TBI). This is done for cytoreduction, to eradicate the malignant cells, and to provide immunosuppression so to prevent rejection and possibly, for creation of space within the BM microenvironment to allow engraftment of the donor stem cells. For autologous transplantation immuno-supression is not required and the preparative regimen is meant to provide maximum dose intensity with a goal of eradicating the malignancy .

For acute and chronic leukemias , most patients have earlier received cyclophosphamide and TBI (Cyclo-TBI) as the preparative regimen. Fractionation of TBI (total dose 1200 to 1500 cGys) is generally used to reduce toxicity to normal tissues. Combination of busulphan (4mg/kg/day x 4 days=16 mg/kg) and cyclophosphamide (60 mg/kg/day x 2=120 mg/kg) (Bu-Cy2) is an effective regimen for allogeneic and autologous SCT and has gained popularity in past 2 decades.[10 11] One of the recent development has been availability of intravenous busulfan.[12] Oral busulfan has erratic absorption , particularly in children. Recent studies in children with acute lymphoblastic leukemia (ALL) have supported the superiority of TBI over busulfan.[13 14]

In general Cyclo-TBI as preparatory regimen is preferred by many centres for patients with acute leukemia, while for CML, Bu-Cy is commonly used. The toxicity profile of two regimens is given below in Table-1.

TABLE-1 TOXICITY PROFILE OF CONDITIONING REGIMENS

	TBI	Chemotherapy Alone	Non myeloablative
Mucositis	+	++	+/-
Veno-occlusive disease	+	++	-
Growth retardation	++	+/-	-
Secondary malignancies	++	+/-	?
Cataracts	++	+/-	-
Sterility	++	+	?

COMPLICATIONS

In addition to severe, prolonged myclosupression with attendent risk of infection , regime related toxicity, graft versus host disease (GVHD), CMV pneumonitis and relapse are main complications seen after SCT (Table-2-3).

CLINICAL RESULTS IN ACUTE MYELOBLASTIC LEUKEMIA (AML)

The prognosis of children with AML has improved considerably during the last two decades ; 80 to 90% children achieve remission (CR) following standard 3:7 (daunomycin and cytosine arabinoside) induction chemotherapy . Currently, post remission chemotherapy includes - 3 to 4 cycles of high dose cytosine arabinoside (15 to 18g/ m^2) ; about 50% are long-term survivors . Cytogenetics is the most important determinant of prognosis in the management of AML . Based on cytogenetics, patients can be subdivided in 3 subgroups . Favourable cytogenetic findings include-(t(15;17), t(8;21), and inv 16 or del 16. Among patients <60 years of age, a number of randomized trials have studied role of allogeneic, autologous stem cell transplantation versus chemotherapy as post remission intensive therapy. None of the randomized trials [15 21] have demonstrated benefit of allogeneic BMT in this group of patients. Data regarding role of autologous transplantation in patients with favourable cytogenetics is controversial and therefore cannot be recommended as a standard treatment at present in these patients.

For patients with intermediate risk cytogenetics (+8, -Y, +6, del 12p, normal karyotype) , allogeneic stem cell transplantation may be considered if an HLA identical match is available. The MRC trial reported 3 year survival rate of 65% with relapse risk of 18% at 3 years.[19] However, advantage for allogeneic transplant was not demonstrated in the US Intergroup study.[20] Data regarding autologous transplantation in this subgroup is controversial.

Allogeneic SCT from an HLA – matched sibling must be considered for patients with unfavorable cytogenetics (-5/5q-, t(8;21)with del 9q or complex karyotype, inv(3q), abn 11q23,20q, 21q, del9q,t(6;9),t(9;22), abn 17p, complex karyotypes (>3 abnormalities). In the US Intergroup study, 5-year survival of 44% was reported in the the transplant group compared to 15% in the chemotherapy alone group.[22] Similar results have been reported in a recent study from Japan.[23]

Recently, Woods et al[24] on behalf of the Children's Cancer Study Group have reported results of a randomized study. A total of 652 children and adolescents with AML who achieved remission on 2 induction regimens using identical drugs and doses (standard and intensive timing) were eligible for allocation to allogeneic bone marrow transplantation (BMT) based on matched related donor status (n = 181) or randomization to autologous BMT (n = 177) or to aggressive high-dose cytarabine-based chemotherapy (n = 179). Only 115 patients (18%) refused to participate in the postremission phase of this study. Overall compliance with the 3 allocated regimens was 90%. At 8 years actuarial, 54% +/- 4% of all remission patients remain alive. Survival by assigned regimen ("intent to treat") is : allogeneic BMT, 60% +/- 9%; autologous BMT, 48% +/- 8%; and chemotherapy, 53% +/- 8%. Survival in the allogeneic BMT group is significantly superior to autologous BMT (P =.002) and chemotherapy (P =.05); differences between chemotherapy and autologous BMT are not significant (P =.21). No potential confounding factors affected the results. Patients receiving intensive-timing induction therapy had superior long-term survival irrespective of postremission regimen received (allogeneic BMT, 70% +/- 9%; autologous BMT, 54% +/- 9%; chemotherapy, 57% +/- 10%). Results of this study favour allogeneic BMT for children and adolescents with AML in remission, when a matched related donor is available.

Patients in CR2 or those with an untreated relapse are curable with allogeneic SCT with 3 year leukemia-free survival of 22 -30%. About 10-20% of patients with primary chemo-refractory AML can be salvaged with allogeneic transplant.[2] Allogeneic SCT is not indicated in patients AML with Down's syndrome[25].

ACUTE LYMPHOBLASTIC LEUEKEMIA (ALL)

About 65% of children with good risk ALL are cured with standard chemotherapy. Therefore, allogeneic SCT is generally reserved for (i) children below 15 years with cytogenetic abnormalities such as t (4;11) and Philadelphia (Ph) chromosome, t (9;22) (ii) children in second or third remission and (iii) young adults between 15 and 21 years who have a high leucocyte count at diagnosis and have Ph chromosome. Such patients are considered at high risk for relapse with standard chemotherapy.[26,28] Best results for allogeneic BMT in ALL are reported in children and adults in first remission, leukemia-free survival (LFS) being approximately 55% and 40%, respectively.[3] Allogeneic BMT might also cure a proportion of patients (15%) with ALL in whom remission could not be achieved with conventional chemotherapy .

TABLE-2

Complications Following BM/ Stem cell Transplantation	
Acute Complication	
Infection	
Acute graft versus host disease	
Graft rejection	
Pulmonary	**Regime Related Complication**
Haemorrhagic cystitis	
Veno-occlusive disease	
Late Complications	
Chronic GVHD	
Relapse	
Sterility	
Cataract	
Secondary Leukaemia	

TABLE-3

COMMON CAUSES OF INFECTIONS AFTER BMT

Cause of Infection	Early Period (Day 0-30)	Middle Period (Day 31-120)	Late Period (Day 120[4])
Bacteria	Streptococci Staphylococci Aerobic gram Positive rods	Nocardia	Streptococcus Pneumoniae Haemophilus influenza
Viruses	Herpes simplex Virus	Cytomegalovirus	Varicella- zoster virus
Fungi	Candida Aspergillus	Candida Aspergillus	
Parasites		P. carinii T. gondii	P.carinni T. gondii

LATE EFFECTS OF STEM CELL TRANSPLANTATION IN CHILDHOOD

The late complications seen with HSCT are more pronounced in children when compared to the adults as they have growing tissues which are more susceptible to delayed toxicity. Though the rapidly dividing cells are highly susceptible to chemo/radiotherapy, the damage caused are rarely permanent while in the slowly dividing cells like muscles, nerves and connective tissues, the damage is permanent. There is long list of late effects attributed to SCT,[29 30] common complications are (i) chronic graft-versus-host disease, (ii) immunodeficiency and infections, (iii) impairment of growth and development (iv) infertility (v) post-transplant malignancies (vi) psychosocial effects. The details of these havc been described else where.[29,32]

SUMMARY

About half of children with AML and two third with ALL can be cured today with effective standard chemotherapy. Those who relapse or have high risk features can be considered for stem cell transplantation. The majority of patients who recover from the immediate post-transplant period become healthy long-term survivors and return to a normal life. Some patients, however, develop chronic or delayed problems. Major factors contributing to these problems are pre-transplant therapy, intensive conditioning regimens and chronic GVHD. Thus, managing (and preventing, if possible) post-transplant complications requires careful consideration of transplantation early in course of disease (risk based treatment planning), development of less toxic conditioning regimens and the prevention of GVHD, particularly in its chronic form.

REFERENCES

01. *Gross TG, Egeler RM, Smith FO. Pediatric hematopoietic stem cell transplantation. Hemat/Oncol Clin N Am 2001;15:795-808.*

02. *Kumar I and Goldman JM. Bone Marrow transplantation for patients lacking an HLA-identical sibling donor. Current Opinions in Hematology 1993:234-39.*

03 *International Bone Marrow Transplant Registry/ Autologous Blood & Marrow Transplant Registry (IBMTR/ABMTR) News letter. 2000;7(1):3-10.*

04 *Kumar L and Gulati SC. Peripheral stem cell transplantation. Lancet 1997;S9:346.*

05. *Rubinstein P, carrier C, Scaradavou A et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med 1998;339:1565-.*

06. *Locatelli F, Rocha V, Chastang C et al. factors associated with outcome after cord-blood transplantation in children with acute leukemia. Blood 1999;93:3662-*

07. *Rocha V, Wagner JE, Sobocinki Ka. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA - identical sibling. N Eng J Med 2000;342:1846-51.*

08. *Raju GMK, Kochupillai V, and Kumar L. Storage of haematopoietic stem cells for autologous bone marrow transplantation. Nat Med Jn India. 1995;8:216-221.*

09. *Gulati SC and Duensing S. Evaluating the benefit of purging in stem cell transplantation Cancer Invest. 1994;12: 447-49.*

10. *Ringden O, Ruutu T, Remberger M etal. A randomized trial comparing busulfan with total body irradiationas conditioning in allogeneic bone marrow transplant recipients with leukemia : a report from the Nordic Bone Marrow Transplantation Group. Blood 1994;83:2723-30.*

11. *Blaise D, Maraninchi D, Michallet M, et al. Long term follow up of a randomized trial comparing the combination of cyclophosphamide with total body irradiation or busulfan as conditioning regimen for patients receiving HLA-identical marrow grafts for acute myeloblastic leukemia in first complete remission. Blood 2001;97:3669-3670.*

12. *Schuller US, Renner VD, Kroschinsky F, et al. Intravenous busulphan for conditioning before autologous or allogeneic human blood stem cell transplantation. Brit J Haematology 2001;114:944-950.*

13. *Socie G, Clift RA, Blaise D, Devergie A, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. Blood. 2001;98:3569-74*

14. *Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant. 2003 Sep;32(6):543-8*

15. *Creutzig U. Current controversies: which patients with AML should receive a bone marrow transplantation-a European view. Br J Hematol 2002;118;365-77.*

16. *Creutz U, Zimmerman M, Ritter J. Definition of standard-risk group in children with AML. Br J Hematol 1999;104:630-39.*

17. *Stevens RF, Hann IM, Wheatley K, Gray RG. Marked improvement in outcome with chemotherapy alone in pediatric AML: Results of the United Kingdom-MRC 10 AML trial. Br J Hematol 1998;101:130-40.*

18. *Harousseau JL, Cahn JY, Pignon B, et al. Comparision of autologous bone marrow transplantation and intensive chemotherapy as post remission therapy in adult acute myeloid leukemia. Blood 1997;90:2978-2986.*

19. *Burnett AK, Goldstone AH, Stevens RMF, et al. Randomized comparision of addition of autologous bone marrow transplantation and intensive chemotherapy as post remission therapy for acute myeloid leukemia in first remission. : Results of MRC AML 10 trial. Lancet 1998;351:700-708.*

20. *Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. N Eng J Med 1998;339:1649-1656.*

21. *Zittoun RA, Mandelli F, Willemze R et al. Autologous or allogeneic Bone Marrow Transplantation compared with intensive chemotherapy in acute myelogenous leukemia. New Eng J Med 1995;332:217-23.*

22. *Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia : A Southwest Oncology Group /Eastern Cooperative Oncology Group study. Blood 2000;96:4075-4083.*

23. *Ogawa H, Ikegame K, kawakami M, et al. Impact of cytogenetics on outcome of stem cell transplantation for acute myeloid leukemia in first remission : a large scale retrospective analysis of data from the Japan Society for haematopoietic cell transplantation. Int J Hematol 2004;79:495-500.*

24. *Woods WG, Neudorf S, Gold S, et al.Children's Cancer Group . A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission. Blood 2001;97:56-62.*

25. *Ravindranath Y, AbellaE, krischer JP. AML in Down's syndrome is highly responsive to chemotherapy:experience on Pediatric Oncology Group AML study 8498. Blood 1992;40:2210-14.*

26. *Arico M, Valsecchi MG, Calmitta B et al. Outcome of treatment in children with Philadelphia Positive Acute lymphoblastic leukemia. N Eng J Med 2000;342:998-1006.*

27. *Manero GG, Thomas DA. Salvage therapy for refractory or relapsed acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2001;15:163-205.*

28. *Mori T, Manabe A, Tsuchida M, et al. Allogeneic bone marrow transplantation in first remission rescues children with Philadelphia chromosome-positive acute lymphoblastic leukemia: Tokyo Children's Cancer Study Group (TCCSG) studies L89-12 and L92-13. Med Pediatr Oncol. 2001;37(5):426-31*

29. *Sanders JE. Long-term effects of bone marrow transplantation. Pediatrician 1991;18:76-81.*

30. *Antin JH. Long term care after hematopoietic cell transplantation in adults. NEJM 2002;347:36-42.*

31. *Molassiotis A, van den Akker OBA, Milligan DW, et al. Quality of life in long-term survivors of marrow transplantation: comparison with a matched group receiving maintenance chemotherapy. Bone Marrow Transplant 1996;17:249-58.*

32. *Duell T, Van Lint MT, Ljungman P, et al. Health and functional status of long-term survivors of bone marrow transplantation. EBMT Working Party on Late Effects and EULEP Study Group on Late Effects. European Group for Blood and Marrow Transplantation. Ann Intern Med 1997;126:184-92.*