Volume-3, Issue-8, August-2014 • ISSN No 2277 - 8160

Research Paper Medical Science

Graft Versus Host Disease in Cord Blood Transplants

Aleem jan Department of Bone marrow transplant and cellular therapy, M.D.Anderson cancer centre university of Texas,U.S.A.

S. Parmar Department of Bone marrow transplant and cellular therapy, M.D.Anderson cancer centre university of Texas,U.S.A.

ABSTRACT

Umbilical cord blood is now used with a fair degree of confidence as an alternative source for haematopoetic stem cells for over past three decades; thus risk versus benefit ratio tends to lean towards CBT as a 10% grade III-1V GVHD probability is reported in CBT as compared to <30% in matched sibling donor transplant and 60%-90% in matched unrelated donor transplants.

KEYWORDS : GVHD , nTREGS,MMF

Background and Rationale: Ever since Thomas and colleagues (36) performed the first hematopoietic stem cell transplantation (HSCT) on an animal model 4 decades ago, much progress has been made.The credit of first successful cord blood transplantation goes to Gluckman and associates (4), who transplanted umbilical cord in a patient with fanconi anemia in 1988.Recipient engrafted well and continued to be disease free. Initially CBT was restricted to paediatric patients. In 1996 , three studies reported its extension to 4 adults who were successfully treated with unrelated donor CBT (5).

Apart from obtaining written consent from the delivering mother and confirming to the guidelines of the American Academy of paediatrics umbilical cord blood can be procured without many difficulties. Cord blood banking has made CBT even more accessible and assures more quality (1, 2, 3). Cord Blood Units can be safely cryopreserved for longer periods without adversely affecting HPC recovery. Since the first Cord blood bank was established in Indiana University school of Medicine in 1980 approximately 135 voluntary banks have been established.

An estimated that 14.6 million individuals have consented to donate haematopoietic progenitor cells (HPCs) . Despite this potentially available pool, the probability of finding a 10/10 HLA match is 35-40% for a Caucasian. CBU undergoes rigorous testing including ABO blood typing, HLA typing ,rhesus typing and infectious disease screening. Other parameters such as volume, weight, total nucleated count, CD34-positive cell count or colony forming units are also recorded. Guidelines for HLA testing have been laid and minimum requirement being HLA –A,HLA-B and HLA-DR. DNA based typing is preferred to serologic typing.(1,2,3,6)

Despite this testing graft versus host disease (GVHD) is a common complication of CBT;GVHD .it is a syndrome resulting from reaction of immunocompetent donor cells against the tissue of an immunocompromised recipient. The immunologic reaction is traditionally divided into an afferent phase and an efferent phase , which is characterized by the release of proinflammatory cytokines during immune activation and by tissue damage associated with conditioning therapy. Cytokines are critical to GVHD and their genetic variants ,influence its development. Indeed , the inactivation of chemokines of the adhesion molecules that attract donor T cells to Peyer's patches eliminates most GVHD deaths in mice. By suppressing release of inflammatory cytokines and the activation of T cells, interleukin 10[IL-10] promotes tolerance. Homozygosity for a common variant of IL 10 promoter appears to increase production of IL 10 and reduce the incidence of GVHD. Small variations in donor and recipient genes that encode a protein NOD2/CARD15 ,critical to response of macrophages to a bacterial toxin, and associated with severe GVHD,thus highlighting the importance of genotyping to estimate risk and severity.(7,19) GVHD is further sub classified as acute[a GVHD] and chronic [c GVHD] on the basis of duration , however this demarcation is arbitrary as overlap does occur.The International Bone Marrow Transplant Registry (IBMTR) Index tends to assign a higher overall grade for GVHD severity than the Glucksberg categorization. Patients with Glucksberg grade I GVHD were categorized as having an IBMTR Index of A or B, depending on whether the maximum extent of rash involved less than 25% or 25% to 50% of body surface area. Patients with Glucksberg grade II GVHD were categorized as having an IBMTR Index of B or C, depending on whether the maximum extent of rash involved 25% to 50% or greater than 50% of body surface area. Patients with Glucksberg grade III GVHD were categorized as having an IBMTR Index of C or D, depending on the absence or presence of stage 4 involvement in at least one organ. The IBMTR Index was designed to avoid the need for subjective assessment of performance status which has been included as an element in the Glucksberg scale. In practice, performance status is used in the Glucksberg grading system only to distinguish between grades III and IV GVHD. Use of the term "extreme" to describe the reduction in performance status associated with grade IV GVHD has been interpreted as a fatal outcome related to GVHD. The IBMTR Index was also designed to provide greater homogeneity in the risks of TRM and treatment failure among patients with GVHD of any given degree of severity.

The cumulative incidences of cGVDH using the seattle criteria was 0.27[27%]; according to NIH criteria,the incidences was 0.08 [8%].By NIH criteria,the classic form of c GVDH was was uncommon [5%] after CBT.Instead the Agvcd (71%) and overlap (24%)GVHD variant predominates. Grade II IV a GVDH was a significant risk factor for c GVDH by both seattle and NIH criteria. The study conducted that GVDH after D+100 after CBT typically carries features of a GVDH.(9,17).Moreever and in marked contrast to adult unrealated donor HSCT, the GVHD observed in this series didnot adversely affect survival.

The incidence of GVHD is influenced by a number of factors including degree of histoincompatibility, the patient's age, the intensity of the conditioning regimen, prophylaxis type and stem cell source. The probability of grade II-IV aGVHD is less than 30% in HLA matched siblings and is 60%-90% in mismatched unrelated donor transplants. The incidence rate of grade III-1V aGVHD is about 35% for 9 of 10 mismatched adult transplants but has only been observed in about 10% of mismatched CBT.(6,7)

Multiple regression analysis identified 3 risk factors for grade II-1V aGVDH

1. Using 2 CBU
2. Using nonmyeloablative conditioning,and
3. Not using antithymocyte globulin in conditioning regimen.(9,10)

GVHD prophylaxis:

The original aGVHD prophylaxis regimens developed during the 1970's used decade used folate antagonist methotrexate (MTX) owing due to its ability to delete proliferating donor lymphocytes. The initial MTX dosing regimen on days 1,3,6 and11 and then once weekly yielded an approximate 25% incidence rate of grades III-IV a GVDH. Cyclosporine [CSA] entered clinical trials of GVHD prophylaxis in the late

1970s and showed equivalency to MTX in prospective studies.True progress in GVHD prevention occurred when these regimns were**:**

Mycophenolate mofetil(MMF), via its metabolite mycophenolic acid, inhibits proliferation of lymphocytes and is synergistic with CNIs in preventing GVHD.MMF also facilitates donor engraftment and is now widely used in reduced intensity conditioning RIC transplantation from related or unrelated donors. However,using MMF rather than MTX does not seem to improve GVHD prevention.CNI based regimens, significantly decreased the incidence and severity of oropharyngeal mucositis with use of MMF."Strategies for prevention of GVHD," a state of art and science handout ,states that CNI combined with the short course of MMF is the most common GVDH prophylaxis regimen used in myeloablative and reduced intensity conditioning transplants ,whereas CNI combined with MMF is the most frequent regimen in nonmyeloablative – conditioned or CBT(15).

Although combining CNIs with MTX or with MMF has resulted in satisfactory rates of aGVHD and survival outcomes, these regimens are not uniformly effective and many patients die from GVHD and related complications.

Therefore, substantial efforts have been made to improve on these CNI based combinations.(12,13,14)

Anti T cell antibodies have been explored as part of preparative regimens. Despite the variability in interpretation of these data, the, best evidence for invivo antibody efficacy is for ATG in unrelated donor BMT transplantation after myeloablative conditioning. Prospective randomized trials are needed to define the role of optimal dose and timing of ATG administration(15).

Sirolimus an mammalian target of rapamycin mTOR inhibitor has been developed as an addition to TAC and MTX for preventing GVHD. In addition to inhibiting effector T cells, sirolimus can also preserve regulatory T cells(Tregs) after transplantation, thereby further controlling GVHD control. Data transplantation and 46% for unrelated donor transplantation, with grade lll and 1V occurring in 12% and 8% of patients respectively. Perhaps the most impressive clinical result of CY regimen was the low cumulative incidence of cGVHD, which was 10%.However a recent phase II study from The University of Texas M.D.Anderson cancer using this strategy with RIC demonstrated higher rates of aGVHD compared with a matched cohort of recipients who received standard GVHD prophylaxis, suggesting that post transplantation CY might need to be combined with additional drugs when used with a less intensive conditioning regimen (8).

Nucleoside analogue pentostatin has been used for GVHD prophylaxis with CNI/MTX in matched unrelated donor mismatched allogenic transplant recipients. The majority of these patients also received low dose rabbit ATG. The results of this study showed that pentostatin at a dose of 1.5mg/m2/week for 4 weeks resulted in the highest fraction of living and GVDH free patients at day 100 post transplantation with no previous instances of grade III-IV a GVDH compared with the control arm . The rate of grade III-IV GVDH for this arm was 10.7 %with no cases seen in HLA – mismatched transplant recipients.

In order to refine GVHD management, the proteosome inhibitor bortezomib was added to TAC/MTX prophylaxis on days 1,4 and 7 post transplantation in 45 recipients of 1 or2 antigen mismatched, T cell - replete, peripheral blood transplantation after RIC. This phase I/II study found a 22% D-180 incidence rate of grade II-IV GVHD on day 180 and a 29% 1- year incidence rate of GVHD ,comparable to rates in a contemporaneous cohort of matched unrelated donor graft recipients who received sirolimus based GVHD prophylaxis at that centre. Mortality rate, the progression –free survival rate, and the overall survival rate were 34.4%,31.2%and 53.1% respectively(28).

One Literature review reflects the Minnesota group's experience of RIC regimens , in which they used CSA and MMF for GVHD prophylaxis; rates of grade II-IV aGVHD and cGVHD were 59% and 23% respectively. Eurocord presented results of 155 patients, median age of 47 years, who received RIC and results were comparable (2).

In one study, patients received CBT with conditioning regimens consisting of fludarabine, CY and TBI coupled with GVHD prophylaxis consisting of CSA and MMF.A total of 38% of patients received 2CBU. Cumulative incidence of neutrophil engraftment by D60 was 80% at a median of 20 days post transplant. Cumulative incidence rates of aGVHD acute and cGVHD were 37% and 39% respectively.(5,17,18)

Although GVHD in CBT has been addressed through many studies. Cord blood as an alternative to bone marrow for HSCT may lower GVHD. K.Ohnuma et al assessed the records of 113 recipient of cord blood from HLA-identical siblings between 1990 and 1997 and compared them with records of 2052 recipients of bone marrow from HLA – identical sibling during the same period.The study population comprised children 15 years of age or younger ,and the rates of GVHD,hematopoietic recovery,and survival using Cox propotional hazard models were assassed.Recepients of CBT from HLA identical siblings were found to have lower incidence rate of both a GVHD and c GVHD than did the recipient of bone marrow from HLA identical siblings.The study hypothesized that the difference between the cord blood and bone marrow may be the immunological properties of umbilical cord T cells that reduces their capacity to induce GVDH(22).

One study that assessed the relative risk of GVHD after unrelated donor CBT in 265 consecutive patients. concluded that a GVHD occurs less frequently after CBT. Two partially matched HLA CBU or double cord blood graft were used to meet minimum cell dose requirement. The incidence rates of grade III-IV GVHD was similar between cohorts. However the incidence rates of grade II-IV were higher among double CBT recipients. Transplantation related mortality rates at 1 year however were significantly lower after double CBT.(3,5,6,16)

CNI was associated with a decreased incidence of grade VII-IV GVHD compared with CNI alone or CNI plus prednisolone(14).CBT in children with acute lymphoblastic leukemia is feasible, and GVHD prophylaxis with MTX plus CNI is associated with significant favourable outcomes in preventing a GVHD and c GVHD and in survival advantages.

Brunstein et al expanded Tregs obtained from 3 CBU's and infused them in 23 patients undergoing dCBT. No severe Treg related acute toxicities were observed and accrual to study continues, with refinements in Treg generating procedures.

To investigate whether expanded nTregs retained their inhibitory function in vivo, a xenograft model of lethal GVHD was used in mice. Weight loss of control mice receiving peripheral blood mononuclear cells (PBMC) and CD25 cells was significantly greater than that of mice that received PBMCs and expanded nTregs.By day 60 had delayed GVHD occurence or no sighns of GVHD. The T test group also had normal sized spleen as compared with the controls. Finally mice coinfused with expanded nTregs revealed no histological lesions compatible with GVHD and had improved overall survival then did the controls.(23,25-27).

REFERENCES

1.GluckmanE,Broxymer HA,AuerbachAD etal.Haematopiotic reconstitution in a patient with Fanconi anaemia by means of umbilical cord blood from HLA identical sibling.N Engl j Med.1989;321:1174-1178. | 2.Vanderson Rocha,john E. Wagner, Kathleen A,et al:Graft versus Host disease in children who have received cord blood or bone marrow transplant from HLA identical sibling.N Engl j Med.2000,342:1846-1856. | 3.wagner je,Kernan NA,Steinbuch M,etal,Allogenic sibling umbilical cord blood transplantation in children with malignant and non malignant disease.Lancet 1995;346:214-9. | 4.GluckmanE, Rocha V ,Boyer-chammard et al,outcome of cord blood transplantation from related and unrelated donors.N Engl j Med 1997;337: 373-81. | 5.Gluckman E, Rocha V etal,cord blood haematopiotic cells:biology and transplantation:Haematology 1998;1-14. | 6.Roncarlolo MG,Bigler M et al:immune reconstitution by cord blood cells.Blood cells 1994;20:573-85. | 7.Glucks H,Storb R,Fefer A et al.clinical manifestations of graft versus host disease in human recipients of marrow from HLA matched sibling donors.Transplantation1974;18:295-304. | 8.Rikhia chakraborty,Aruna Mahendravade,Serena K,et al. Robust and cost effective expansion of human regulatory Tcell highly functional in a xenograft model of graft versus host disease.Haematol 2012: 3324;1-10. | 9.Edward A copelan: Haematopiotic stem cell transplantation:N Engl j Med,2006:1813-23. | 10.Blythe G, Thompson,Kent A Robertson, Darla Gowan et al,Analysis of engraftment, graft versus host disease,and immune recovery following unrelated donor cord blood transplantation.Blood,2000;96:2703-11. | 11.John E wagner, Juliet N,BarkerTodd e, etal.Transplantation of unrelated umbilical cord blood in 102 patients with malignant and non malignant diseases:influence of CD34 cell dose and HLA disparity on treatment related mortality and survival.Blood,2002;100: 1611-18. | 12.Margaret M macmillan,Daniel j Weisdorf,et al;Acute graft versus host disease after unrelated donor umbilical cord blood transplantation: analysis of risk factors. Blood;2009;113:2410-15. | 13.C.cutler,KStevenson,HT Kim etal.Double umbilical cord blood transplantation with reduced intensity conditioning and Sirolimus based GVHD prophylaxis.Bone marrow transplantation,2011;46:659-67. | 14.A Al Sultan,R.H Giller,D.Gao et al;GVHD after unrelated cord blood transplant in children:characteristics,severity, risk factors and influence of outcome:Bone marrow transplantation;2011:46;668-75. | 15.Susan Staba Kelly,SIMRIT PARMAR,ELIZABETH SHPALL et al:overcoming barriers to umbilical cord transplantation:Cytotherapy 2010:12;121-130. | 16.Kaji kato, Ayami yoshima Etsurolto etal.cord blood transplantation from unrelated donors for children with acute lymphoblastic leukemia in japan: The impact of Methotrexate on clinical outcomes.ASBMT:2011,:17,1814-21. | 17. Yashaki Atsuta,Yasuo Morishima,Ritsuro Suzuki etal.Comparison of unrelated cord blood transplantation and HLA –Mismatched unrelated Bone marrow transplantation for adults with Leukemia.ASBMT:2012:18;780-787. | 18.. Qaiser Bashir,Simon Robinson et al;Umbilical cordblood transplantation: Clinical advances in Haematology and oncology:2010;8;11:786-801. | 19Amin M.Alousi,Stephenie i.Lee etal:Graft versus host disease:State of Science;Biol Blood marrow Transplant;2013;19:102-108. | 20..Colleen Delaney,Elizebath Shpall etal;Cord blood graft engineering:ASBMT:2013;19:74-78. | 21.Storb R, Antinjh,Cutler C.Should methotrexate plus calcineurin inhibitors be considered standard of care for prophylaxis of acute GVHD?Biol Blood marrow transplant.2010;16(1suppl);s18-24. | 22.Storb R,Deeg HJ,whitehead j etal.Methotrexate with cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for acute leukemia.N Engl Med.1986;31 4(12):729-735. | 23.chao nj,Schimdt GM,Niland JC,et al.cyclosporine, methotrexate,and prednisolone compared with cyclosporine and prednisolone for prophylaxis of acute graft versus host disease.N Engl. J Med.1993;329:1225-1230. | 24.Antin JH. Tcell depletion in GVHD:Less is more? Blood 2011;117(23)6061-6062. | 25.Luznik L, Bolanos-Meade j,Zuharak M etal. High dose cyclophosphamide as single agent, short course prophylaxis of graft versus host disease.Blood 2010;115(16):3224-3230. | 26.Wolf D,von Lilienfeld-Toal M, Wolf AM et al. Novel treatment concepts of graft versus host disease.Blood.2012;119(1):16-25. | 27.Martin pj,Inamoto Y, Carpenter PA,Lee SJ,Flowers ME.Treatment of chronic graft versus host disease.Past.present and Future.Korean j Haematol.2011;46(3):153-163. | 28.Koreth J,Mtsuoka K, Kim HT et al. Interleukin-2 and regulatory T cells in graft versus host disease.N Engl J Med.2011;365(22):2055-2066. | 29.Carpenter PA. How i conduct a comprehensive chronic graft versus host disease assessment.Blood 2011;118(10):2679-2687. | 30.Ohnuma K, Isoyama K, Ikuta K etal. Cord blood transplantation from HLA-mismatched donors as a treatment for children with haematological malignancies. Br J Haematol.2001;112:981-987. | 31.Rocha V, Gluckman E . Improving outcomes of cord blood transplantation.:HLA matching,cell dose and other graft and transplant related factors. Br J Haematol. 2009;147:262-274. | 32.Cutler C, Stevenson K, Kim HT,et al. Double cord blood transplantation with reduced intensity conditioning and sirolimus based GVHD prophylaxis. Bone marrow Transplant.2011;46:659-667. | 33.Brunstein CG, Miller js,Cao Q, et al. Infusion of ex vivo expanded Tregulatory cells in adults transplanted with umbilical cord blood: Safety profile and detection kinetics. Blood.2011;117:1061-1070. | 34.Godfrey WR, Spoden DJ, GE YG. Cord blood CD4+,CD25+ derived Tregulatory cells express Fox p3 protein and manifest potent suppressor function.Blood 2005;105:750-758. | 35.Xing D, Ramsay AG,Gribben JG et al.cord blood natural killer cells exhibit impaired lytic immunological function that is reversed with IL-2 ex vivo expansion. J Immunother. 2010;33:684-696. | 36. Thomas ED, Lochte HL, Lu WC et al. (1957). "Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy". New England Journal of Medicine 157 (11): 491–496. doi:10.1056/NEJM195709122571102.PMID 13464965. |