cord blood (UCB) transplantation (UCBT) have been conducted and therefore how to choose between these alternative stem cell sources is not known. Encouraging results of 60% long term disease-free survival (DFS) or better have been achieved using unrelated volunteer donors in highly selected patient groups such as young patients with chronic myelogenous leukemia (CML) who are transplanted early in their disease course using a 6/6 HLA-matched donor. However, HLA-mismatch, poor disease risk, older adult age and non-CML diagnosis are associated with a significantly worse outcome after unrelated BMT. Further, recently the importance of matching for HLA class I as well as class II alleles has been recognized. However, while matching at 8/8 HLA-A, B, C and DRB1 (or 10/10 if DQ is included) is associated with improved outcome, this strategy also reduces the "suitable" donor pool and can potentially prolong the donor search. The 2002 GAO report to Congress noted that despite considerable efforts on the part of the National Marrow Donor Program (NMDP) the number of transplants facilitated by the NMDP "represent about one tenth of those we estimate to be in need of unrelated donor transplants". As an alternative, UCB offers the potential to extend the donor pool. However, UCB is limited by cell dose and HLA match. For example, in a collaborative study led by the New York Blood Center (NYBC), pediatric recipients of 6/6 UCB units had a comparable and possibly improved outcome compared to matched BM, and a comparable outcome if they received 5/6 UCB units of at least 2.5×10^7 nucleated cells/kilogram (NC/kg). Inferior outcome was associated with 5/6 units $<2.5 \times 10^7$ NC/kg or 4/6 units. Notably, in the 4/6 setting, high cell dose could at least partially compensate for mismatch. Further NYBC analysis of the outcome of US patients transplanted with myeloablative conditioning and single units has demonstrated that a cell dose $>2.5 \times 10^7$ NC/kg is required in recipients of 5/6 units (bidirectional mismatch) to achieve at least 50% survival at one year whereas in 4/6 recipients the cell dose needs to be at least 5×10^7 NC/kg to achieve similar outcome. Therefore, not surprisingly, studies of adult single unit UCBT which have involved 4-5/6 matched units with a median cell dose of less than 2.5 have demonstrated poor survival. However, the fact that adult UCBT has had a comparable outcome to mismatched BM introduces UCB as a valid alternative to mismatched BMT and calls for new strategies to improve adult UCBT outcome. One possible strategy is double unit grafts which have been associated with a 2-year DFS of 60% in 31 patients at the University of Minnesota. This improved outcome is even despite the low cell dose of the engrafting unit suggesting intriguing biology of this approach. Overall the minimum acceptable criteria for both volunteer donor and UCB grafts have not been defined. Currently it is reasonable that all patients undergo a volunteer and UCB search at referral. Donor choice will depend on the patient diagnosis, the urgency of the transplant, the relative availability of an adequately matched volunteer versus a UCB unit of adequate dose and match, physician preference and research priorities. A volunteer donor may be preferred for a patient with CML in chronic phase or early accelerated phase and possibly for other diagnoses such as myelofibrosis or severe aplastic anemia. If the transplant is urgent (required in less than 6 weeks) UCB has a clear advantage although a volunteer donor could possibly be obtained using the NMDP ultra fast search strategy. Acceptable donors include readily available volunteers that are 7-8/8 matched (or 9-10/10) and 5-6/6 UCBs $>2.5 \times 10^7$ NC/kg or 4/6 $>5 \times 10^7$ NC/kg. Notably, given the interaction of HLA match and cell dose, a better UCB unit may be smaller but better matched. If selected volunteers become unavailable during the search then it is appropriate to default to UCB to prevent an excessively long search. In UCB selection issues other than HLA match and dose are also important. It is ideal to perform confirmatory typing from an attached segment and given CD34+ measurements are not standardized they should not be used unless two units of similar match and NC dose are available. Markers for infectious diseases need to be complete and negative with bacterial and fungal culture negative at freeze. In the future, greater information concerning the factors determining outcome after volunteer donor and UCB transplantation may guide more detailed algorithms for donor selection.

15

AUGMENTATION OF HOMING OF CORD BLOOD STEM CELLS

Broxmeyer H.E., Christopherson II K.W., Hangoc G., Campbell T.B. Department of Microbiology and Immunology and the Walther Oncology Center, Indiana University School of Medicine, Indianapolis, IN; Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas Health Science Center, Houston, TX

The field of cord blood (CB) transplantation has come quite a way since its inception and the first clinical transplant in October 1988. CB hematopoietic stem (HSC) and progenitor (HPC) cells have been used to treat a wide variety of genetic disorders and malignancies. These transplants were possible because the cells could be cryopreserved for prolonged periods of time and stored in CB banks for future use. The vast majority of CB transplants have been performed in children and low weight recipients. Fewer CB transplants have been done in adults and higher weight individuals because of the limiting numbers of CB cells that are available for collection and storage at the birth of babies. A number of procedures have been and are being investigated to enhance the efficiency of CB transplantation for adults. This includes attempts at ex-vivo expansion of HSC, which has not yet provided a clinical breakthrough because we don't know enough of the biology regarding stem cell self-renewal and proliferation to truly expand the HSC. Transplantation of multiple CB units is ongoing with early clinical success, but this procedure has apparently not greatly reduced the time to engraftment and only one of the transplanted CB units seems to survive for longer term engraftment. Not all mouse HSC home with absolute efficiency, effects consistent with clinical experience in which limiting numbers of cells result in graft failure. The chemokine stromal cell derived factor-1 (SDF-1)/CXCL12 and its Gα protein–linked seven transmembrane spanning receptor CXCR4 are involved in chemotaxis, mobilization and homing of HSC and HSC. CD26 is a cell surface dipeptidylpeptidase IV, which can truncate SDF-1/CXCL12. We found that inhibition or deletion of CD26 on target populations containing or highly enriched for human CB and human and murine bone marrow HSC/HPC greatly enhanced the chemotactic responsiveness of these cells to SDF-1/CXCL12. Inhibition/deletion of CD26 in mice was associated with greatly decreased ability to mobilize HPC with G-CSF. Based on these finds we hypothesized that enhancement in homing of HSC to the bone marrow niche needed for support of the self-renewal and proliferative capacity of HSC would lead to increased engraftment with limiting numbers of HSC. We tested this hypothesis, first with mouse bone marrow cells transplanted into lethally irradiated congenic mice in the setting of non-competitive and also competitive repopulation, each followed by repopulation in a non-competitive repopulation assay in lethally irradiated secondary congenic mice. Mouse bone marrow donor cells pretreated with CD26 inhibitors Diprotin A (Ile-Pro-Ile) or Val-Pyr or from CD26 gene knock-out (−/−) mice had greatly enhanced capacity to home to the bone marrow of recipients, and this was associated with enhanced engraftment, especially with dose-limiting numbers of donor cells. Recent work from our laboratory has found that in vitro inhibition of CD26 on human $CD34^+$ CB cells enhances engraftment of these cells in sublethally irradiated NOD/SCID mice. These encouraging results with CB cells suggest that targeting CD26, or other means to enhance homing/engraftment may be of practical value in a clinical setting to use limiting numbers of CB HSC for successful transplantation.

16

STANDARDIZATION OF CORD BLOOD BANKING PROCEDURES NMDP NETWORK

Kurtzberg, J., Chell, J., Boo, M., Halet, M., Welte, K. The NMDP Cord Blood Committee

The National Marrow Donor Program established a cord blood banking program in 1999. Currently, 14 U.S. banks have joined the network. A steering committee comprised of bank directors, laboratory supervisors, ethicists, obstetricians, scientists, transplanters and experts in information technology and regulatory affairs and ad hoc representation from HRSA and the Navy was established and meets on a quarterly basis. The purpose of the committee is to advance cord blood transplantation, improve clinical practice and