and DCT were similar (50%) with no significant differences in frequency of viral, fungal or bacterial infections ($P = 0.74$). Most importantly, infection was the primary cause of death at 100 days for SCT (9/20) whereas for DCT, there were no infection-related deaths! TNC and $CD34^+$ cell dose did not differ between engrafting and non-engrafting units; however, we found that the engrafting units had a lower absolute lymphocyte count (ALC) in 8/10 evaluable cases.

Conclusion: DCT is an effective approach to overcome the TNC dose-limiting therapeutic benefit of CB transplantation. Although 100-day post-transplant infection frequency remains high, deaths from infection are markedly reduced and OS is significantly improved in DCT recipients; however, additional studies are needed to define the mechanism. For DCT, the engrafting unit does not have a higher TNC or CD34 cell dose but, paradoxically, a lower ALC dose may be predictive.

8

HLA MATCHING FOR TRANSPLANTATION: LESSONS FROM BONE MARROW

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HLA matching strongly affects the outcome of unrelated donor bone marrow transplantation. How these effects translate to other hematopoietic cell sources, such as cord blood and peripheral blood stem cells, is only partially clarified. Much of the available data concerning bone marrow transplantation comes from studies published by the Japan Marrow Donor Program, the Fred Hutchinson Cancer Research Center, and the National Marrow Donor Program (NMDP). In general, the studies show that matching for HLA A, B, C and DRB1 influences important endpoints such as survival, engraftment and graft versus host disease. Although antigen level matching is important, allele level mismatches are also detrimental. Matching for HLA DQ is important in some studies, but not in others. A clear role for HLA DP matching has not been identified.

For bone marrow transplantation, the NMDP recommends 8 of 8 allele matching at HLA A, B, C and DRB1. If this level of matching cannot be achieved, a single allele mismatch is preferable over an antigen mismatch. At the present time, each locus should be considered of equal weight, that is, no locus is clearly more important than the others. When multiple mismatches are unavoidable, it is unclear how to compare alleles and antigens, e.g., are two mismatched alleles preferable to a single antigen? More data are needed to answer this question [1-5].

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9

ANALYSIS OF 608 UMBILICAL CORD BLOOD (UCB) TRANSPLANTS: HLA-MATCH IS A CRITICAL DETERMINANT OF TRANSPLANT-RELATED MORTALITY (TRM) IN THE POST-ENGRAFTMENT PERIOD EVEN IN THE ABSENCE OF ACUTE GRAFT-VS-HOST DISEASE (AGVHD)

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With the recognition of the critical importance of UCB cell dose upon hematopoietic recovery, neutrophil recovery after UCB transplantation (UCBT) has improved. However, TRM in the early post-engraftment period (days 30-180) remains a barrier to transplant success. How graft characteristics impact upon the risk for TRM during this period is important but has not been well characterized. Therefore, we analyzed the impact of cell dose and HLA-match upon TRM between days 30-180 in recipients of single unit 3-6/6 HLA-A,B antigen and DRB1 allele matched UCBT who were transplanted for leukemia or myelodysplasia with units from the National Cord Blood Program and achieved sustained donor engraftment. Patients dying from days 0 to 29 or those with primary or secondary graft failure were excluded, and patients were censored at the time of relapse.

Six hundred eight patients fulfilled study criteria and had a median age of 9.0 years (range 0.4-58 years). The cumulative incidence of TRM was 36% (95% CI: 32-39). Using 2.5-4.9 $\times 10^7$ TNC/kg as the reference (n = 229), the impact of cell dose was analyzed. While patients (n = 141) receiving a lower dose of 0.7-2.4 had a relative risk (RR) of TRM of 1.5 ($P = 0.009$) during this period, TRM in patients receiving higher doses were similar to the reference [5.0-9.9 (n = 160) RR 0.9, $P = 0.4$; ≥10.0 (n = 78) RR 0.8, $P = 0.4$)]. However, HLA-match had an impact upon TRM at all levels of match [reference: 5/6 recipients (n = 194); 6/6 (n = 32) RR 0.3, $P = 0.063$; 4/6 (n = 342) RR 1.7, $P = 0.001$; 3/6 (n = 40) RR 2.2, $P = 0.003$]. To exclude the possibility that disease stage contributed to this finding, a multivariate Cox regression analysis was performed that included TNC dose, HLA-match and disease stage, and showed that low cell dose and HLA-mismatch were the significant predictors of TRM. Further, when patients were divided into those without significant aGVHD (only grade 0 or 1) (n = 292) vs patients with grade 2-4 aGVHD (n = 301), the effect of HLA-match on TRM was most pronounced in those *without* significant aGVHD [reference: 5/6 recipients (n = 102); 6/6 (n = 25) RR 0.0, P = NS; 4/6 (n = 151) RR 2.4, $P = 0.004$; 3/6 (n = 14) RR 2.8, $P = 0.050$]. Of the transplant-related deaths (n = 60) from days 30-180 in this "without significant aGVHD" group, infection was reported to be a major cause of death in 36 (60%).

In summary, above the threshold of 2.5 $\times 10^7$ TNC/kg, cell dose has no demonstrable effect on the risk for day 180 TRM in the *post*-engraftment period, whereas the adverse impact of HLA-mismatch is both striking and retained even in the absence of aGVHD. We postulate that the adverse effect of HLA-mismatch is mediated not only by induction of aGVHD, but also by an effect on immune reconstitution as manifested by death from infection. These data have significant implications for graft selection implying that both dose and HLA-match should be considered, and investigation of how to "trade-off" each of these factors should be a priority. Further, it argues that recipients of HLA-mismatched grafts will require aggressive supportive care and strategies to augment immune reconstitution. Finally, improved outcome in UCBT may be dependent upon the ability to obtain units that are both of sufficient size and match which will require an increase in the global UCB inventory.