211

A STANDARD DEFINITION OF HLA MATCHING FOR HEMATOPOIETIC STEM CELL TRANSPLANT OUTCOMES STUDIES

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HLA matching is not currently described consistently in the hematopoietic stem cell transplant outcomes literature. Terms like "high-resolution" are often used with different underlying meanings. As the question of the clinical impact of various degrees of HLA matching is investigated in detail, it is useful to have a consistent definition so that studies can be compared. We propose a definition of HLA matching that is based on 2 assignments per locus (1 for each allele) and with 4 degrees of match per assignment based on the resolution of the available HLA typing: HM—high-resolution match, Hmm—high-resolution mismatch (low/intermediate resolution match), IM—intermediate/low resolution match, Imm—intermediate/low resolution mismatch. High-resolution matching between two high-resolution HLA types is defined as follows: (1) a unique 4-digit HLA allele; (2) a combination of possible HLA alleles that share the same antigen-binding domain; and (3) a combination of possible alleles where only one is defined as being non-rare (eg, DRB1*1501 or 1509 compared to DRB1*1501 or 1508 since DRB1*1508 and DRB1*1509 fit the definition of rare). Identity in the antigen-binding domains is based on identical protein sequences encoded by exon 2 for Class II and exons 2 and 3 for Class I. The definition of non-rare is an allele that occurs at a frequency of greater than or equal to 1/100,000 for HLA-DRB1 or 1/50,000 for HLA-A, -C, -B, and -DQB1 in the National Marrow Donor Program (NMDP) database. Intermediate/low resolution matching is defined using either serologic types or serologic equivalents determined from DNA-based types. The World Marrow Donor Association—Information Technology Working Group has defined an electronic reference (http://www.anthonynolan.org.uk/HIG/nomen/wmda.html) for DNA allele, serologic relationships, DNA-serology relationships, and HLA alleles with equivalent "antigen-binding domains". The NMDP has made an electronic reference available for alleles that are rare within the NMDP database (http://www.nmdpresearch.org/HLA/allele_tally.html). This set of definitions is intended to promote consistency in approach and ease of incorporating a matching analysis into non-HLA focused studies, eg, disease specific, treatment specific, or analyses of other immunogenetic loci (KIR, cytokines, mHAgs, etc. . .), and has been adopted for use by the Center for International Blood and Marrow Transplant Research (CIBMTR) and the NMDP.

212

REVEALING THE EFFECTS OF T CELL DEPLETION ON ENGRAFTMENT OF UMBILICAL CORD BLOOD USING THE B^2MICROGLOBULIN−/−/NOD/SCID XENOGRAFT MODEL

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Clinical experience and animal models have shown that donor T cell depletion adversely effects engraftment of hematopoietic stem cells. While it is likely that donor T cells are acting to overcome residual host immune barriers, they may also exert effects independent of host resistance via direct or indirect interactions with stem cells and/or the stem cell niche. In order to more precisely define the effect of T cells on engraftment, we have performed human umbilical cord blood (UCB) transplants into B^2microglobulin−/−/NOD/SCID mice under limiting dilution conditions, and evaluated the transplanted mice for both short and longer term hematopoietic engraftment. UCB mononuclear cells (MNC) or UCB depleted of T cells using CD2+ immunomagnetic separation were transplanted into sub-lethally irradiated (300 cGy) B^2microglobulin−/−/NOD/SCID mice. CD3+ T cells comprised 34% of CB MNC and 1.2% of T cell depleted (TCD) UCB. Cohorts of mice received UCB MNC or TCD UCB at 5 dose levels between 5×10^4 and 5×10^6 total cells, with CD34+ cells comprising 0.58% of TCD UCB and 0.39% of UCB MNC. Percent human CD45+ cells in bone marrow were analyzed by flow cytometry to assess for engraftment between days 22 to 27 or 39 to 45 post-transplantation. Overall, mean engraftment in the UCB MNC recipients (n = 27) was 6.25% (range 0–29.8%) versus 2.2% (range 0–12.8%) in the TCD UCB recipients (n = 22) (P = .033). For both MNC and TCD recipients, engraftment was <1% at the 5×10^4 cell dose and increased with increasing cell dose. At each dose level at or above 10^5 cells, engraftment was higher in recipients of UCB MNC. These results, in a model where there are minimal host immune barriers to overcome, suggest that T cells possess additional graft-facilitating properties. Further experiments in this model will be used to evaluate the role of T cell subsets and in vitro T cell activation on the short- and long-term engraftment of UCB.

213

CLINICAL RESULTS OF CORD BLOOD STEM CELL TRANSPLANTATION IN KOREA

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Since the first successful cord blood stem cell transplantation (CBSCT) for a pediatric patient with relapsed ALL in April 1998, the cases of CBSCT have been increasing in Korea. The medical insurance for CBSCT in children aged less than 15 years has been covered since January 2003, when the cases of pediatric CBSCT have been abruptly increased. We analyzed the data of 163 pediatric patients who received CBSCT at 13 transplant centers between Oct 1996 and April 2005. A minority of patients (n = 11) received double cord blood units. The median age and weight of recipients were 6.4 years (range, 0.6–16.9 years) and 21 kg (range, 7–67.8 kg), respectively. The diagnosis was as follows: acute leukemia (n = 114), SAA (n = 12), genetic or metabolic disorders (n = 11), Fanconi anemia (n = 7), JMML (n = 7), CML (n = 5), MDS (n = 4), and solid tumors (n = 3). The median infused nucleated cell dose was 4.5×10^7/kg (range, 0.27–13.6×10^7/kg). Neutrophil recovery was attained in 144 patients (88.3%) at a median of 19 days (range, 10–62 days). Notably, all 11 patients receiving double units engrafted successfully. It took 45 days (range, 14–394 days) for platelet recovery in 119 patients. Grade 2–4 and grade 3–4 acute GVHD were developed in 40% and 12.6% of patients, respectively. Nineteen out of the 90 evaluable patients (21.1%) developed chronic GVHD (10 limited, 9 extensive). The incidence of acute GVHD ≥grade 2 was higher in the 2-antigen mismatched group compared with that of the 0- or 1-antigen mismatched group (P = .03), but the incidence of chronic GVHD was not different between each groups (P = .1). The 7-year overall and event-free survival was 50.6% and 39.0%, respectively, and there was no survival difference between 0- or 1-antigen mismatched transplants and 2-antigen mismatched ones (P = .21). Transplant-related causes (n = 48) were responsible for the 72.7% of all mortalities. Our results suggest that special efforts should be made to reduce the transplant-related mortality for the better outcome of CBSCT.