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PROMISING OUTCOMES OF ALLOGENEIC CORD BLOOD TRANSPLANT (CBT) FOR HIGH RISK ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN

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Background: Optimal therapy for high risk and relapsed acute lymphoblastic leukemia (ALL) remains uncertain. Wider availability of cord blood from related and unrelated donors has prompted studies of its use for hematopoietic stem cell transplant (HSCT). Graft rejection and lack of graft versus leukemia (GVL) effect could be drawbacks to CBT. In contrast, possible reduction in morbidity and mortality from graft versus host disease (GVH) argue for CBT. **Procedure:** We evaluated 26 consecutive cord blood transplants (CBT) for ALL performed at our center from 1996–2002 on studies using consistent conditioning therapy and graft-versus-host disease (GVHD) prophylaxis. Indications for CBT were CR1 with high risk cytogenetics (Ph^+, MLL rearrangement; N=9), CR2 following marrow relapse on therapy or <1 year off (N=10), CR3 or relapse with limited marrow disease (N=5). Median patient age was 8.5 years (Range, 0.5–24 y). CB was from unrelated donors (N=25) and a matched sibling donor (N=1). Among the unrelated donors, HLA matching was 6/6 (N=6), 5/6 (N=11), and 4/6 (N=8). Median infused total nucleated cell dose per kilogram (TNC/kg) was 3.26e7 (Range, 0.8–12.9e7). GVH prophylaxis consisted of cyclosporine and methylprednisolone (N=25) and cyclosporine alone (N=1; matched sib CBT). **Results:** With median follow-up of 548 days, 16/26 patients (62%) are event-free survivors (EFS). Six events were due to toxicity and/or infectious complications. Four events were due to relapse. Median time to event was 115 days (Range, 14–728 d.). ANC >500/mm^3 occurred at a median of 23.5 days post-CBT (Range, 14–61 d.). Platelet count >20,000/mm^3 without transfusion occurred at 65 days (Range, 25–222 d.). Acute GVHD developed in 14/24 evaluable patients, reaching grade III-IV in 7 patients. Chronic GVHD occurred in 10/22 evaluable patients. Multivariate analysis showed higher infused TNC/kg to be the strongest predictor of EFS. CR number at HSCT, degree of HLA match, time to neutrophil engraftment, time to platelet engraftment, and acute or chronic GVHD were not significant predictors of EFS in univariate analysis. Age was a significant EFS predictor in univariate analysis, however lost its significance in multivariate analysis when TNC/kg was included. **Conclusions:** We conclude that CBT can effectively treat ALL in children with high risk features and following relapse. Survival benefits may derive from more manageable GVHD with retention of adequate graft-versus-leukemia effect.

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RESIDUAL AML AT THE TIME OF ALLOGRAFT: OUTCOME ANALYSIS BASED ON NUMBER OF BONE MARROW BLASTS

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Background: AML patients who receive allogeneic hematopoietic stem cell transplantation for residual or refractory disease have poor outcome. Only 10–15% of these patients are long-term survivors. Predictors of long-term survival in these patients remain undefined. **Method:** In a retrospective analysis (between 1982-September 2004) we evaluated percentage of marrow blasts at the time of transplantation and disease-free (DFS)/overall survival (OS) in AML patients. Residual bone marrow disease was stratified in to 3 groups (group I: ≥5–9.9% blasts, group II: >10–19.9% blast and group III: ≥20% blast). We also analyzed other variables known to affect outcome of AML and allogeneic transplantation including age, cytogenetics, secondary AML (including prior MDS), extramedullary disease, matched related/unrelated donor, graft-versus host disease and performance status. **Results:** 37/112 (33%) AML pts received allogeneic transplantation for persistent leukemia. Of these, 5/37 (13.5%) pts were in group I, 7/37 (18.9%) were in group II and 25/37 (67.6%) patients had more than 20% blasts (group III). All 25 patients with marrow blast of >20% died at median of 4 month from the date of transplant (Progressive disease = 18, Non relapse mortality = 7). Of the 7 patients with blast count of >10–19.9%, 4 are alive without disease at median of 23 months (range 12–41 months); 3 patients died at median of 10 months (Progressive disease =2, Non relapse mortality = 1). One out of 5 patients with marrow blast count of 5–9.9% is alive at median of 15 months; 4 patients died at median of 2 months (Progressive disease = 2, Non relapse mortality = 2). Five of 37 (13.5%) patients are long-term survivors. Their characteristics include (Age = 31, 43, 44, 58, 62, MRD transplant = 4, MUD = 1, non-myeloablative transplant = 1, DLI = 2, Grade III aGVHD = 3, Grade II aGVHD = 2, limited cGVHD = 5, myelodysplasia = 1, extramedullary disease = 1, poor risk cytogenetics = 0). **Conclusion:** Although a threshold number of blast as a predictor of successful transplant is not defined, patients with more than 20% blast at the time of transplant had uniformly poor outcome. All 5 survivors had acute graft versus host disease and 4 have limited mild cGVHD. None of the survivors had poor risk cytogenetics; no other patient or treatment characteristics predicted survivor.

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THE USE OF MOUSE MODELS OF NORMAL AND MALIGNANT HEMATOPOIESIS TO DESIGN STRATEGIES FOR SELECTIVE PURGING OF PRIMITIVE ACUTE MYELOID LEUKEMIA (AML) PROGENITORS

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Normal and malignant human hematopoiesis can be maintained for many months in NOD/SCID (N/S) mice. The N/S mouse lymphomyeloid bone marrow (BM) repopulating cells (N/S RC) and N/S leukemia-initiating cells (N/SL-IC) are rare progenitors isolated from normal and AML blood or BM, respectively. Although these normal and malignant progenitors share a similar cell surface phenotype they differ in their response to ex vivo manipulations. When placed in culture in the absence of growth factors most N/SL-IC, although initially quiescent, rapidly enter active cell cycle over 24–48 h while quiescent normal progenitors remain in G0. Exit from G0 is associated with loss of engraftment potential in mice. Subpopulations of AML blasts enriched for N/SL-IC express high affinity interleukin-3 (IL-3) receptors (R) and can be killed by a truncated diphtheria toxin (DT388) IL-3 fusion protein while normal N/S RC are spared. Although the selectivity of DT388IL3 for malignant rather than normal progenitors is striking, killing of N/SL-IC is often incomplete. We have designed a variant DT388IL3 molecule with enhanced affinity for the IL-3R; DT388IL3 [K116W]. In initial studies this molecule has been shown to be ≥5-fold more potent than the parent compound against AML colony forming cells (CFC) while no increased kill of normal BM CFC was observed. >90% kill of AML-CFC was obtained for 6 of 10 AML samples exposed to concentrations of DT388IL3 [K116W] as low as 1 ng/ml × 24 h. The % kill of AML-CFC achieved with each patient sample showed a direct correlation ($r=0.6$, $p<0.05$) with the level of expression of the IL-3R βc subunit (but not the IL-3R α subunit) detected in AML blasts by real-time RT-PCR. Preliminary data suggest that N/SL-IC kill will also be enhanced with the DT388IL3 [K116W] fusion protein. These data suggest that candidate AML stem cells may be effectively purged from autografts in a simple culture system designed to inhibit their engraftment potential which includes a drug treatment which selectively targets malignant progenitors. Furthermore, it may be possible to use clinically applicable laboratory techniques to select patients most likely to benefit from this approach.