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HIGH DOSE CHEMOTHERAPY FOLLOWED BY STEM CELL RESCUE IN ADOLESCENTS WITH EWING'S SARCOMA

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Ewing Sarcoma (ES) is the second most common bone tumor in children and young adults. About two thirds of patients with localized disease will have long term survival. However, patients with metastatic disease at diagnosis and patients with progressive or recurrent disease have dismal chance of survival. High dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR) has not been shown to be unequivocally helpful in a randomized clinical trial. However, several smaller studies have shown clear benefit for HDC in a subset of patients. In this case series we report three consecutive patients with recurrent ES. Each subject or guardian signed an IRB-approved consent to participate in this study. Two patients had localized recurrence of their disease while one patient had bone marrow involvement at recurrence. Patients received carboplatin, etoposide (VP), cyclophosphamide (CPM) and topotecan for salvage chemotherapy. Once a complete remission (CR) was achieved, each patient went directly to transplant using a conditioning regimen of either CPM/VP/Thiotepa (TT) (UPN1) or Busulfan/Melphalan/TT (UPN2 and UPN3). The patient with positive BM involvement was ES negative by PCR prior to transplant. These regimens were well tolerated and none of the patients experienced serious adverse events in the peri or post transplant periods. Median graft size was 5.46 and range 3.0–10.0 $\times$ 10^6 CD34+/Kg All patients had myeloid engraftment on a timely basis (range 11–13 days) and had a range in length of stay of 37–44 days. Median survival was 19 months, with range of 10–24 months. All patients are alive and disease free to date. Following transplant, Lansky/Karnofsky scores were 80–90 at 2 months and all scores were $\geq$ 90 at 6 months. Conclusions that can be drawn from this small series include: 1) HDC followed by ASCR can be well tolerated; 2) durable remission can be achieved following this therapy; and 3) transplanted patients can be expected to have good quality of life post transplant.

Patient data

Patient ID	Age at ASCR	Primary site of disease	Site of recurrence	Time to relapse (mo)	Time from dx to ASCR (mo)	Initial therapy	Length of CR post ASCR (mo)
UPN1	15	spine	spine	47	54	Adria/VP/Ifos	24
UPN2	14	nasal fossa	spine	32	37	Vin/Adria/CPM	19
UPN3	19	chest	chest, BM	41	47	Vin/Adria/CPM	10

Adria: Adriamycin; Vin: Vincristine; Ifos: Ifosfamide.

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OUTCOME OF ALLOGENEIC STEM CELL TRANSPLANTATION FOR 26 CHILDREN WITH MYELOID LEUKEMIA IN SINGLE CENTER

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Background & Objective: Children with acute myeloid leukemia (AML) have poor prognosis. Treated with chemotherapy alone, they can hardly survive if the disease is refractory or relapse. Although the onset of chronic myeloid leukemia (CML) is relatively slow and treatment with Gleevec will further prolong the survival time, it still can not be cured by the targeting treatment. Allogeneic hematopoietic stem cell transplantation will be the only way to cure these diseases. The purpose of this paper was to clarify the role of hematopoietic stem cell transplantation treating patients with myeloid leukemia. **Methods:** A total of 26 consecutive patients with AML and CML in a single institution between May 2001 and September 2006 were included. Among them, 8 were chronic myeloid leukemia (CP = 5, AP = 2, BP = 1) and 18 were AML (CR1 = 9, CR2 = 7, Non CR = 2).5 out of 9 AML got CR1 after at least 2 courses of chemotherapy. The average age was 9.4 years old(range 2 years$\sim$17 years)and the average body weight 32.8 kg (range 11.5 kg$\sim$79 kg), Patients underwent allogeneic peripheral blood stem cell transplantation (allo-PBSCT) from HLA-identical siblings (n = 2), mismatched family donors (n = 4), and matched unrelated donors(n = 20). All patients received myeloablative regimens with 16$\sim$20 mg/kg busulfan and 200 mg/kg cyclophosphomide. For aGVHD prophylaxis patients with HLA-identical sibling donors received cyclosporine (CSA) and methetraxate, while patients with matched unrelated donors received CSA, methotrexate and 15 mg/kg rabbit ATG(Fresenius). After Jan.2004 mycophenolate mofetil were used to enhance GVHD prophylaxis for CML patients. **Results:** After a average follow-up of 20.5 months(9$\sim$55 months), 2 (7.6%)patients graft rejected, 7 (27%) patients developed grade 3$\sim$4 aGVHD (all with CML), 5 patients having extensive cGVHD. At present, 9 patients have died of relapse (4/26) and TRM (GVHD 4/26 and infection 1/26) while 17 (65%) patients are still alive with disease-free survival. **Conclusion:** Our evidences is convincing that allogeneic stem cell transplantation is conducive to improve the survival rate for children with acute myeloid leukemia and the GVHD associated with unrelated donor transplants can be controlled after take active prevention measures. As to whether the GVHD happened was more severe in children with CML than that of children with AML, It still remain to have more patients and more institutions collaboration to confirm such a conclusion.

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SUCCESSFUL COMBINED UNRELATED UMBILICAL CORD BLOOD HAPLOIDENTICAL TRANSPLANT IN NON MALIGNANT DISEASE

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Over the past decade, UCB transplantation has become a viable alternative donor stem cell source for HSCT in patients with catastrophic diseases treatable with transplantation therapy. UCB cell dose is the best predictor of outcomes after UCB transplantation. In patients receiving lower cell doses, there are significant delays and sometimes failures in myeloid and platelet engraftment. Combined unit transplantation is currently under study to overcome some of these barriers. We took an alternative approach to facilitate early myeloid engraftment after myeloablative preparative conditioning for a teenager with HLH and previous Aspergillus pneumonia. Our hypothesis was that as the immunocompetent UCB cells engrafted, the subject would reject the immunologically incompetent haplo-identical HSCT graft and the patient would convert to full UCB donor. We predicted faster myeloid engraftment in this setting. A 15 year old boy with common variable immune deficiency and HLH refractory to medical therapy underwent myeloablative conditioning with standard TBI/CY/ATGAM and received a composite graft consisting of a 1) 5/6 UCB which delivered 2.5 $\times$ 10^7 TNC/KG and 2) 2 $\times$ 10^6/KG CD34 selected PSSC collected from the father. The subject engrafted on day 9. Initial chimerism was predominantly (>80%) the haplo donor. This was followed by an increase in UCB chimerism (>90% on D + 17). The subject was fully reconstituted with UCB by D + 32. The subject later developed Grade IV GVHD of liver and intestine at the time of full UCB engraftment that was treated with MSCs and liver transplantation. This combined UCB/Haplo approach has the advantage of faster myeloid engraftment than double UCB transplant in subjects at high risk of infectious complications and or graft failure.

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UNRELATED CORD BLOOD TRANSPLANTATION (UCBT) IN PEDIATRIC PATIENTS: A SINGLE CENTER EXPERIENCE IN CHILE

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Umbilical cord blood (CB) from unrelated donors is being used increasingly in pediatric stem cell transplantation and it represents

an easily available source of stemcells for patients everywhere. The increasing worldwide repository of CB units is improving the chances of finding a matched unit for more patients. We present our experience with UCBT as a single source of stem cells for unrelated transplantation in these patients.

CB Search Methods: Matched unrelated CB searches were done for 67 pediatric pts (0–16 yrs) with malignant (MD, n = 44) and nonmalignant (NMD, n = 23) disease from 1995 to 2007 in the NY Blood Center and Netcord. The probability of finding a 5/6 CB unit with $> 3.0 \times 10$ 7/kg (optimal match) was calculated comparing the period 1995–2001 vs 2002–07. **Transplant Patients and Methods:** 32 pts. (MD = 19, NMD = 13) received UCBT between 1996 and 2007. 12 pts with MD were standard risk (SR) for transplantation (ALL CR1–2, ANLL CR1, CML CP, MDS RAEB/RAEBt).1 pt received a 3/6, 18 a 4/6, 13 pts a 5/6 graft. Median cell dose was 4.3×10^7/kg (2.6–16.3). 3 pts received a double graft. Conditioning regimens were adapted to diagnosis. NMD received BuCyATG. 17 MD pts and 1 NMD pt received TBI. GvHD prophylaxis was CsA plus prednisone (n = 26), mtx (n = 2) or MMF (n = 4). Engraftment and EFS analysis was done for the entire group of transplanted pts and the MDSR plus NMD subset (n = 25). HLA match (5/6 vs others), cell dose (<4.0 vs >4.0 10^7/kg) and year of UCBT (96–01 vs 01–07) were compared for engraftment and survival in this subset. **Results:** An optimal matched CB unit was found for 6/41 pts (14%) in the 1995–2001 period vs 17/26 (65%, $p > 0.001$) in the 2001–2007 period. 19 transplanted pts (61%) engrafted. TRM was 25%, MD relapse 22%. EFS was 31% with median f/u of 21 months. Subset analysis of MDSR plus NMD pts showed engraftment of 70% and 3 yr EFS of 36%. In this group the only prognostic factor for survival was HLA match (5/6 vs 3/6 and 4/6: Hazard Ratio 14, $p < 0.001$). **Conclusion:** CB is a good alternative for unrelated stem cell transplantation in children. HLA matching appears to be the most important prognostic factor given a cell dose $> 3.0 \times 10$ 7/kg. Increasing availability of optimal matched CB units worldwide will make this approach feasible for more patients.

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AUTOLOGOUS STEM CELL TRANSPLANTATION IN CHILDREN WITH REFRACTORY OR RELAPSED HODGKIN DISEASE IN COLOMBIA

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Here we report a retrospective analysis performed to evaluate the results of autologous hematopoietic stem cell transplantation in pediatric patients with Hodgkin Disease (HD) in a single center in Bogota, Colombia.

Nineteen patients with relapsed or refractory HD underwent autologous stem cell transplantation between 1998 and 2006. 8 female/11 male, with mean age of 10.9 years (7–14). At diagnosis patients were staged: I and IIA 10, IIB 1, IIIA 1, IIIB 4 and stage IV 6. The response to first line therapy was: 8 patients had failure to induction, and 6 early relapse (before 12 months). At transplantation: 10 patients were in 2nd complete remission, 2 in 3th complete remission and 7 were in partial remission. The conditioning regimen was BEAM in 14 patients and other protocols with carmustine, etoposide and cyclophosphamide or melphalan in 5 patients.

With a mean 26 months of follow-up, (8–66), the 5 year OS was 73.3% and EFS of 51.9%. 8/19 patients (42%) relapsed between 3 and 48 months after transplantation, the main cause of death was progressive disease. One patient died before day +100 with a severe fungal infection.

This study group is too small to establish prognostic factors for relapse after transplantation, although is important for countries with limited resources to have data about local results. The OS and EFS in this group are similar to results in developed countries. Near 50% of patients with refractory or relapsed HD can be successfully treated with high dose chemotherapy and autologous stem cell rescue. It's important to have a longer follow up on these patients so we can perform analysis on prognostic factors for relapse and survival.

SOLID TUMORS

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TREATMENT OF EPSTEIN BARR VIRUS POSITIVE NASOPHARYNGEAL CARCINOMA WITH ADOPTIVELY TRANSFERRED CYTOTOXIC T LYMPHOCYTES

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Background: The strong association of nasopharyngeal carcinoma (NPC) with Epstein-Barr virus (EBV) makes adoptive immunotherapy with EBV-specific cytotoxic T cells (EBV-CTL) an attractive therapeutic option. We have evaluated the safety and efficacy of EBV-specific CTL (EBV-CTL) in two Phase I clinical trials. In the first trial, EBV-CTL were given alone and in the second trial, we aimed to enhance *in vivo* expansion of EBV-CTL by lymphodepleting patients prior to CTL infusion. For lymphodepletion we used CD45 monoclonal antibodies (MAbs) that unlike chemotherapy or radiation do not result in nonspecific destruction of the resident immune system. **Study Design:** The primary objective of these Phase I clinical trials was to determine the safety of escalating doses of EBV-CTL with or without lymphodepletion in EBV-positive NPC patients. The secondary objective was to determine the expansion, persistence and anti-tumor effects of infused EBV-CTL. **Results:** Thirty two patients with advanced-stage NPC received autologous EBV-CTL. Patients received a median of 2 (range 1–6) doses of CTL at 2×10^7–2×10^8 cells/m^2 per infusion. CTL administration was well tolerated except for transient swelling at known disease sites in 4 patients. Prior to CTL infusion, 8 patients were in remission, 22 had active disease, and 2 had abnormal imaging studies of unknown significance. Seven of 8 patients in remission prior to CTL infusion remain in remission 6–64 months post CTL. For the remaining 24 patients, the best overall response rate was 50% with 6 complete responses (CR/CRu), 2 partial responses, and 4 with stable disease during a median follow-up of 9 months (95% CI 2–16 months). Of the 6 with a CR: 4 have been sustained for 2–4 years, and 2 relapsed more than 2 years post CTL. Ten patients with active disease received CD45 MAbs prior to EBV-CTL and 8 were evaluable for immune reconstitution analysis. Infusion of CD45 MAbs resulted in transient lymphopenia (resolved within 7 days), increased serum IL-15 levels in 6 patients, and significant expansion of EBV-CTL within 8 weeks post-infusion in 3 patients. **Conclusion:** Treatment of EBV-positive NPC with EBV-CTL appears safe and can be associated with significant anti-tumor activity. Lymphodepletion with CD45 MAbs prior to CTL infusion is also safe and results in expansion of adoptively transferred CTL in a subset of patients. These encouraging results warrant further exploration of EBV-targeted immunotherapies for NPC.

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REGRESSION OF EXPERIMENTAL OSTEOSARCOMA AND EWING'S SARCOMA FOLLOWING TRANSFER OF HER2-REDIRECTED T CELLS

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Background: New therapies are needed for osteosarcoma (OS) and Ewing's sarcoma (EWS) since the prognosis for patients with metastatic and/or recurrent disease has not improved over the last two decades despite aggressive multimodal therapies. For immunotherapies, HER2 is an attractive target since it is expressed in ~40% of OS and up to 25% of EWS. While the use of HER2 monoclonal antibodies has been limited by low levels of HER2 expression on sarcoma cells, we show here that T cells expressing HER2-specific chimeric antigen receptors (CARs) have potent anti-sarcoma activity in animal models. **Methods:** Mitogen-activated T cells were transduced with a retroviral vector encoding a HER2-specific CAR with a CD28.ζ-signaling endodomain (HER2-T cells). We