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SOLID TUMORS

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PROMISING OUTCOMES WITH TANDEM AUTOLOGOUS STEM CELL RESCUE IN 'LATE' WILMS TUMOR RELAPSE

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Introduction: Optimal management of relapsed Wilms' tumor (WT) patients remains unclear. Modern second-line treatment consists of either salvage chemotherapy±radiation therapy or chemotherapy followed by high-dose chemotherapy and autologous hematopoietic stem cell rescue (HD-ASCR).
Methods: Fifteen consecutive patients with relapsed/ persistent WT from 2001-09, enrolled on IRB protocol with planned two tandem cycles of HD-ASCR. Myeloablative chemotherapy regimen for first cycle consisted of Etoposide 2400 mg/m2, Carboplatin 2000 mg/m2, Cyclophosphamide 3600 mg/m2; and Melphalan 180 mg/m2 and cyclophosphamide 4500 mg/m2 for the second.
Results: There were 6 males and 9 females with a median age at diagnosis of 4.6 y(range 3-16 y), and median time from diagnosis to relapse 1 y (range 0.1- 7.5 y). Median time from relapse to HD-ASCR was 5 m (range 3-31 m). Histology was favorable in 12 and anaplastic in three. Five of 15 patients received HD-ASCR for early relapse/ refractory disease within 6 months from diagnosis. Ten patients received planned two cycles of HD-ASCR while the remaining 5 received only 1 course of HD-ASCR due to disease progression or toxicity. Disease state at the time of HD-ASCR was CR in 7, VGPR in 5 and PR in 3. Post- ASCR, median time to neutrophil engraftment and unsupported platelet count >20 K was 12 and 21 days, respectively. Regimen related toxicity included infections (1 aspergillus, 1 klebsiella), hemorrhagic cystitis (1) and one fatal case of acute renal failure. At a median follow-up of 60 months, nine patients are alive and disease free. Six patients died from disease relapse in five and renal failure prior to engraftment in one. Five patients with refractory disease/early relapse (≤6 months from initial diagnosis) before undergoing HD-ASCR had significantly worse outcomes from relapse. ($p = 0.001$). The 5 year estimated event-free survival (EFS) and the overall survival (OS) in the remaining 'late' relapsed patients are 55% and 75% respectively. There was no correlation of outcome with disease stage at diagnosis, site of relapse, disease state at ASCR-HD.
Conclusions: Tandem HD-ASCR remains an effective, non-toxic treatment for patients with relapsed Wilms' tumor especially if greater than 6 months from diagnosis. Patients with persistent disease or early relapse within 6 months from diagnosis likely have different biological characteristics and should receive a novel modality of therapy.

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AUTOLOGOUS STEM CELL TRANSPLANT FOR ADVANCED STAGE PEDIATRIC SOLID TUMORS

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Autologous stem cell transplant (ASCT) potentially promotes the survival in high-risk pediatric solid tumors. Individual preparative regimen for each primary solid tumor is not yet determined owing to various conditions of disease status and previous treatment. We have transplanted 17 patients with advanced stage solid tumors using two different preparative regimens. Primary diagnosis included 10 patients (58.9%) with neuroblastoma stage 3 and 4, 2 patients (11.7%) with Wilms tumor stage 4, 2 patients (11.7%) with germ cell tumor stage 3 and 4, one each patient with stage 4 rhabdomyosarcoma (5.9%), Ewing's sarcoma (5.9%), and retinoblastoma (5.9%). Indication for ASCT was tumor recurrence in 7 patients (50%) and residual disease in 7 patients (50%). Eleven patients (65%) with previously treated high-dose cyclophosphamide received regimen 1 consisting of carboplatin, etoposide, and melphalan during conditioning. Regimen 2 (carboplatin, etoposide, cyclophosphamide) was chosen for 6 patients (35%) without previous treatment of high-dose cyclophosphamide. Most patients achieved engraftment within a median time of 11 days (range 7-18 days). There were 5 patients who alive and disease-free at the end of study. Median follow-up among survivors was 4.1 years (range 1.2-6.3 years). Disease progression-free survival (PFS) at 1- and 3-year post-ASCT was 47% and 32%. Overall survival (OS) at 1-, 3-, and 5-year post-ASCT was 71%, 36%, and 18%. There was no significant difference in PFS and OS between two different transplant regimens in univariate analysis ($p = 0.36$ and $p = 0.62$). Likewise, there was no significant difference in PFS and OS between two indications of ASCT (residual disease and tumor recurrence; $p = 0.37$ and 0.50), time from diagnosis to ASCT (< 1 year and ≥ 1 year; $p = 0.72$ and 0.24), and primary diagnosis (neuroblastoma and non-neuroblastoma; $p = 0.75$ and 0.87). No severe transplant-related toxicity and mortality was observed herein. Due to limited number of patients in both regimens, continuing investigation of ASCT role as salvage therapy for advanced solid tumors should be carried on.

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HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION ENHANCES ANTI-TUMOR ACTIVITY AGAINST RENAL CELL CANCER

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Allogeneic HSCT has been suggested as a treatment option for cytokine unresponsive, advanced renal cell cancer (RCC). However, tumor progression remains as the main problem post-transplant. We hypothesize that haploidentical (HI) HSCT might enhance graft versus tumor (GVT) activity against RCC and improve the outcome after transplant by tumor growth suppression. We first established a HI-transplant model using two different hybrid mouse strains as donor and recipient in the experiments. Lethally irradiated (CB6F1-(H2Kb/d) recipients were transplanted with T cell-depleted (TCD) bone marrow (BM) from B6CBAF1 (H2Kb/k). We found that B6CBAF1 TCD-BM cells engrafted well in recipients of HI-HSCT without graft failure when analyzed at varying time points after the transplant.

We then explored GVT activity in this HI-HSCT model. Lethally irradiated CB6F1 host were transplanted TCD-BM from the following donors; B6D2F1 (H2Kb/d), B6 (H2Kb), and B6CBAF1 (H2Kb/k). Animals received RENCA cells on the same day of the transplant. Low dose T cell ($1x10^5$) infusion was enough to elicit GVT effect but not GVHD and to provide murine RCC growth control and survival advantage in HI- HSCT. Recipients of HI-HSCT BM and T cells showed better anti-tumor activity than recipients of B6D2F1 or B6 BM + T Cells, respectively. Recipients of HI-HSCT BM and T cells did not reveal any tumor development in the first 50 days, and had a significantly better survival compared to other groups. Low dose haploidentical CD8+ T cells provided a better anti-tumor activity than CD4+ T cells but unseparated T cells resulted in significantly better survival than either subset alone. We concluded from this experiment that GVT activity against to RENCA cells is mainly driven by CD8+ T cells but they need CD4+ T cells help for optimal anti-tumor activity.

Our data suggested that HI-HSCT could provide substantial graft-versus-tumor effect against renal cell carcinoma that might suppress tumor growth and elicit survival advantage.

STEM CELL BIOLOGY

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HUMAN UMBILICAL CORD BLOOD (HUCB) DERIVED STEM CELLS ENHANCES WOUND HEALING

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Background: Recessive dystrophic epidermolysis bullosa (RDEB) is a severe inherited skin blistering disease caused by mutations in Col7a1gene, which encodes a major component in anchoring fibrils (Christiano et.al. *Nat Gen* 1993). An initial report has shown promises of Allogeneic (Allo) -SCT for the treatment of RDEB (Wagner et.al. *N Engl J Med* 2010). However no distinct anchoring fibrils were observed in the recipient skin and the functional cell populations are