Poster Session II

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NON-MYELOABLATIVE AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS

Burt, R.K.[1], Oyama, Y.[1], Statkute, L.[1], Quigley, K.[1], Weppner, C.[1], Krosnjar, N.[1], Verda, L.[1] Division of Immunotherpay, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

We have previously reported that autologous hematopoietic stem cell transplantation (HSCT) using a cancer-specific myeloablative regimen (cyclophosphamide [CY] and total body irradiation) failed to improve the neurologic disability (EDSS) score or even forestall progressive neurologic decline in patients with secondary progressive (axonal degenerative) multiple sclerosis. We, therefore, redesigned our approach to employ a non-myeloablative lymphoablative conditioning regimen composed of agents specifically used to treat multiple sclerosis (CY and CAMPATH-1H). Patients with relapsing-remitting (inflammatory) multiple sclerosis with pre-transplant EDSS of 2.0 to 6.0 were candidates for our study. Nineteen patients were treated. Peripheral blood stem cells were mobilized with intravenous (IV) CY 2g/m^2 and subcutaneous G-CSF 10 mcg/kg/day. Conditioning regimen consisted of IV CY 200 mg/kg and CAMPATH-1H 20 mg. Mobilization and conditioning regimens were well tolerated. No patient had either an early or late infection, only half of the patients had a neutropenic fever. Of those who developed fever during the transplant, fever lasted less than 24 hours and was related to CAMPATH-1H or stem cell infusion. One-half of the patients never required RBC transfusion and one quarter never required a platelet transfusion. The mean day of white blood cell engraftment was day +8. The mean day of hospital discharge was day +10. CD4 recovery occurred by 6 months. The EDSS neurologic rating scale that varies from 0 (normal) to 10 (dead from neurologic disease) is evaluated after HSCT every 6 months twice then annually. In 15 patients who were followed for 6 or more months, the EDSS has improved by at least one point in the majority (8 patients), remained unchanged in 6 and deteriorated in only 1. A randomized trial, the Multiple Sclerosis International Stem Cell Transplant (MIST) trial comparing autologous non-myeloablative HSCT to continued standard therapy for patients with refractory relapsing-remitting MS is currently registering patients. Reference: Burt RK, Cohen BA, Russell E, Spero K, Joshi, A Oyama, Y, Karpus WJ, Luo K, Jovanovic, J, Traynor AE, Burns, WH. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of intense immune suppression to prevent disease progression in patients with high disability scores. Blood, 102(7):2373-8, 2003.

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AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR REFRACTORY CROHN'S DISEASE, THE SUMMARY OF PHASE I TRIAL

Oyama, Y.[1], Craig, R.M.[1], Quigley, K.[1], Statkute, L.[1], Burt, R.K.[1] Division of Immunotherapy, Department of Medicine, Northwestern University Feinberg School of Meidicine, Chicago, IL.

Background: Crohn's disease (CD) is an immunologically mediated inflammatory disease of the gastrointestinal tract. In theory, immune ablation followed by autologous hematopoietic stem cell transplantation (HSCT) can induce disease remission by destroying old and reconstituting a new immune system. **Methods:** We conducted a phase I autologous non-myeloablative immunoablative HSCT trial in 17 patients with severe refractory CD. Patients were less than 60 years old with a Crohn's Disease Activity Index (CDAI) of 250–400 or Craig Crohn's Severity Index (CCSI) of ≥17 despite conventional therapy including infliximab. Peripheral blood stem cells were mobilized with intravenous (IV) cyclophosphamide (CY) 2g/m^2 and subcutaneous G-CSF 10 mcg/kg/day. The immunoablative conditioning regimen consisted of 200 mg/kg IV CY, and 90 mg/kg IV equine antithymocyte globulin. The graft was CD34$^+$ enriched. **Results:** There was no treatment related mortality. The procedure was well tolerated. Anticipated neutropenic fever, nausea, vomiting, diarrhea, and anorexia were common and responded well to medical therapy. The median days for neutrophil and platelet engraftment were 9 (range 7–11) and 9 (range 8–18, three patients never below 20 K/ul), respectively. The median infused CD34+ and CD3+ cell counts were 4.83×10^6/kg (range $1.73–24.88 \times 10^6$/kg) and 0.56×10^4/kg (range $0.0–3.09 \times 10^4$/kg), respectively. Pre-transplant median CDAI and CCSI were 282 (range 101–358) and 24 (range 18–33). After the transplant, symptoms and CDAI/CCSI tended to improve quickly and dramatically, and radiographic and colonoscopy findings have been improving gradually over months to years following HSCT. For patients with >6 months follow up, 12 out of 15 patients entered sustained disease remission defined by a CDAI ≤150 or reduction of a CCSI ≥10 after median follow-up of 29 (range 11–48) months. **Conclusions:** Autologous HSCT has a marked durable salutary effect on CD activity and is a safe intervention for patients with refractory Crohn's disease. A randomized study (KISS trial: C[K]rohn's Immune Suppression vs Stem Cell Transplant) comparing autologous immunoablative HSCT to standard therapy is now enrolling patients.

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AUTOLOGOUS NON-MYELOABLATIVE HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR DIFFUSE SCLERODERMA

Oyama, Y.[1], Statkute, L.[1], Barr, W.G.[1], Krosnjar, N.[1], Yaung, K.[1], Weppner, C.[1], Burt, R.K.[1] Div. of Immunotherapy, Dept. of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

Patients with diffuse cutaneous scleroderma with visceral involvement have an overall 10-year survival of 35–68%. There is no known therapy that is able to alter the natural course of the disease. Here we report outcomes of autologous HSCT phase I study utilizing non-myeloablative lymphoablative conditioning regimen. Nine patients with diffuse scleroderma and poor clinical features were enrolled. Candidates were less than 65 years old and had either Rodnan skin score of more than 14 or lung diffusion capacity of carbon monoxide (DLCO) less than 80%, interstitial lung disease, elevated ESR, renal involvement, or abnormal electrocardiogram. Patients with pulmonary hypertension (pulmonary artery systolic pressure >45 mmHg) were excluded. Peripheral blood stem cells were mobilized with intravenous (IV) cyclophosphamide (CY) 2g/m^2 and subcutaneous granulocyte colony-stimulating factor 10 mcg/kg daily. The graft was not manipulated. The conditioning regimen consisted of CY 200 mg/kg and rabbit antithymocyte globulin (rATG) 7.5 mg/kg. The procedure was well tolerated. Anticipated cytopenias, neutropenic fever, and mild fluid overload were easily controlled. White blood cells and platelets both engrafted on average day 8 (range days 7–9 and days 0–10, respectively). The median numbers of infused CD34+ and CD3+ cells were 8.31×10^6/kg (range $2.35–14.7 \times 10^6$/kg) and 2.03×10^8/kg (range $0.41–6.83 \times 10^8$/kg), respectively. We observed a marked improvement of skin score in all subjects, whereas cardiac function (ejection fraction, pulmonary artery systolic pressure), pulmonary function (DLCO) and renal function (creatinine) remained stable. One patient with advanced disease and poor performance status died 2 years after the transplant from progressive disease. Two patients developed recurrence of skin tightness without compromising organ function, however, with institution of mycophenolate mofetil both showed gradual improvement of skin scores. After median follow-up of 20 (range 5–32) months, the overall survival is 89% (8 out of 9 patients) and progression-free survival with continuing improvement is 67% (6 out of 9 patients). Autologous HSCT with CY/rATG conditioning regimen is safe and effective. A randomized study (ASSIST: American Sclero-

derma Stem Cell vs Immune Suppression Trial), comparing HSCT to IV pulse CY is now enrolling patients.

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LONG TERM REMISSION IN SEVERE AND REFRACTORY LUPUS (SLE) AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

Arnold, R.[1], Massenkeil, G.[1], Tamm, I.[1], Alexander, T.[2], Thiel, A.[3], Radbruch, A.[3], Hiepe, F.[2] 1. Department of Internal Medicine, Hematology/Oncology, Charité University Medicine Berlin, Berlin, Germany; 2. Department of Internal Medicine, Rheumatology, Charité University Medicine Berlin, Berlin, Germany; 3. German Rheumatism Research Centre, Berlin, Germany.

The concept of autologous stem cell transplantation (ASCT) is a resetting of the immune system. High dose chemotherapy and immune ablation destroys the immune system (autoreactivity) of the patient followed by a T cell depleted stem cell transplant with development of a tolerant immune system. Seven patients (age 19–48 years) with life threatening SLE characterized by severe organ involvement with persistent active disease despite treatment with standard immunosuppressive drugs were treated in the Berlin phase I/II trial since 1998 with a median follow up of 55 (8–90) months. Treatment includes mobilization of hematopoietic stem cells with cyclophosphamide (CY) 2 g/m^2 and G-CSF (10 ug/kg/day), leukapheresis and enrichment of CD34+ cells, conditioning with CY 200 mg/kg and rabbit antithymocyte globuline (ATG) 90 mg/kg followed by ASCT. Clinical and serological remission could be achieved in 7/7 patients. One of 7 patients died due to cerebral aspergillosis on d + 90, 1 patient had a flare at 17 months and died due to uncontrolled SLE 36 months post ASCT. At the time of flare change of autoantibody profile occurred and naive Th-cells and naive B-cells declined compared to the remission patients. Five patients are alive in clinical remission. These patients are autoantibody negative and no autoreactive Th-cells directed to nucleosome could be detected after ASCT. One of these patients gave birth to a healthy boy 35 months post ASCT. Open questions in ASCT for treatment of SLE are: Is TRM associated with stage of disease at ASCT/intensive pretreatment? Why do some patients relapse? Methods of prevention of relapse after ASCT? In Germany, a multicenter clinical trial protocol is initiated to answer these questions.

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VIRAL INFECTIONS DURING CD34+ CELLS PURIFIED AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION FOR THE TREATMENT OF REFRACTORY AUTOIMMUNE DISEASES

Nagafuji, K.[1], Tsukamoto, H.[1], Numata, A.[1], Miyamoto, T.[2], Harada, M.[1] 1. First Department of Internal Medicine, Kyushu University Hospital, Fukuoka, Japan; Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka, Japan.

Aims: We retrospectively analyzed viral infections during CD34+ cells autologous peripheral blood stem cell transplantation (PBSCT) for the treatment of refractory autoimmune diseases (AD). **Materials and Methods:** 9 cases of systemic sclerosis (SSc) with interstitial pneumonia(IP),1 case of amyopathic dermatomyositis (ADM) with IP, 1 case of Wegener granulomatosis (WG) with exophthalmous. Except one SSc patient No. 9, all patients had been treated with steroid, and were administered with steroid during peri-transplant period. PBSC were mobilized with cyclophosphamide (CY) 4 g/m^2+G-CSF, and CD34+ cells were purified with CliniMACS. Pre-transplant conditioning consisted of CY 200 mg/kg. Acyclovir (ACV) 250 mg/day was administered from day1 to day 35. **Result:** Before PBSC mobilizations, patient No. 2 with ADM was positive for cytomegalovirus (CMV) antigenemia and treated with gancyclovir (GCV). After PBSC mobilizations, 3 patients became positive for CMV antigenemia (3/11 27%) treated with GCV, and 1 patient developed genital herpes simplex virus infection treated with ACV. After transplantations, 5 out of 11 patients (45%) became positive for CMV antigenemia treated with GCV. Median day becoming positive for CMV antigenemia was 22.5 days post-transplant ranging 10 to 38 days. Two patients, No.1 and No. 8 (18%), developed adenoviral hemorrhagic cystitis (adeno HC) on day 64 and day 33, respectively, treated with cidofovir (CDV). **Discussion:** Before transplantations, most of AD patients had received immunosuppressive therapy. CD34+ cells PBSCT is an immunosuppressive therapy. Thus, during peri-transplant period, AD patients developed various viral infections. Infection surveillance and diagnostic work-up, same as with those used in allogeneic recipients seem to be necessary (Table1).

Patient No.	Age/ Sex	Diseases	Pre-mobilization Steroid Tx	Pre-mobilization Viral Infections	Post-mobilization Viral Infections	Post-transplant Viral Infection
1	54/F	SSc/IP	yes			day 38 CMV, day 64 adeno HC
2	54/F	ADM/IP	yes	CMV	CMV	day 21 CMV
3	55/M	SSC/IP	yes		CMV	
4	58/M	SSc/Ip	yes			day 10 CMV
5	54/F	SSc/IP	yes			day 24 CMV
6	53/F	SSC/IP	yes			
7	21/M	WG	yes			
8	49/F	SSc/IP	yes		CMV	day 31 adeno HC, day 33 CMV
9	33/F	SSc/IP	no			
10	63/F	SSc/IP	yes		genital HSV	
11	61/F	SSc/IP	yes		CMV	day 21 CMV

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TARGETED TOTAL MARROW IRRADIATION USING 3D IMAGE GUIDED TOMOGRAPHIC INTENSITY MODULATED RADIATION THERAPY: AN ALTERNATIVE TO STANDARD TBI

Wong, J.Y.C.[1], Liu, A.[1], Schultheiss, T.[1], Popplewell, L.[1], Stein, A.[1], Rosenthal, J., Forman, S.[1], Somlo, G.[1] City of Hope Cancer Center, Duarte, CA.

Purpose: TBI is an important part of many hematopoietic stem cell transplant (HSCT) conditioning regimens. Dose escalation of TBI has been difficult due to associated organ toxicities. A method to deliver a more targeted dose of TBI to sites of greatest tumor burden is needed to reduce dose to normal organs, reduce toxicities, and permit dose escalation. The purpose of this study was to evaluate the delivery of targeted myeloablative doses of radiation to bone and marrow using a recently developed image guided tomographic intensity modulated radiation therapy delivery system (tomotherapy). **Methods:** CT data sets from 3 patients (2 AML and 1 multiple myeloma) were used for dosimetry planning studies to evaluate two strategies: total marrow irradiation (TMI), where the target region was defined as the skeletal bone, and total marrow and lymphoid irradiation (TMLI), where the target regions were defined as bone, major lymph node chains, liver, spleen, and sanctuary sites, such as brain. Organ doses and dose distributions were compared to conventional TBI. **Results:** A 1.7 to 7.5-fold reduction in median organ dose was observed with TMI and TMLI compared to conventional TBI. Dose-volume histogram analysis predicted for the potential to escalate dose to bone and marrow up to 20 Gy with TMI, while maintaining doses to normal organs at lower levels compared to conventional TBI to 12 Gy (Table). Results were similar for the adult and pediatric patients indicating that this method will be applicable to most patients regardless of frame size. TMI to 10 Gy was delivered as part of an autologous tandem transplant regimen to the patient with multiple myeloma. Clinical results confirmed treatment planning predictions. After TMI, the patient experienced the expected blood count nadir,