Poster Session II

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

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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

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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 × 10^6/kg) and 0.56 × 10^4/kg (range 0.0–3.09 × 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

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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 × 10^6/kg) and 2.03 × 10^8/kg (range 0.41–6.83 × 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-