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MYELOABLATIVE CONDITIONING WITH TBI/VP-16 WITH ALLOGENEIC STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA: HIGH RESPONSE RATE AND PROLONGED PROGRESSION FREE SURVIVAL

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Although High Dose Therapy with autologous peripheral blood stem cell transplantation has improved the complete response rates and overall survival for patients with Multiple Myeloma (MM), making it the standard of care for many patients (pts) with chemosensitive disease; autotransplantation has not demonstrated curative potential despite extensive evaluation with long-term follow-up. Despite the demonstration of an immunologic graft vs myeloma effect, the overall success of myeloablative conditioning with allogeneic transplantation for patients with MM has been limited by treatment related mortality (TRM) as well as relapse. Whereas novel strategies such as non-myeloablative conditioning may lower the early TRM, they have thus far have had only marginal success in long term disease control. Novel myeloablative conditioning regimens with acceptable toxicity carry the potential advantage of tumor cytoreduction and establishment of donor chimerism to improve long term disease control. We report the long term follow-up of 14 consecutive patients with MM who have undergone myeloablative conditioning with either BuCy2 (n=7) or TBI/VP-16 (n=7) followed by allogeneic bone marrow stem cell transplantation from HLA-identical sibling donors. Median age for all patients is 46 years. The probability of Overall Survival (OS) at 2.5 years for all patients, BuCy2 pts, and TBI/VP-16 pts is 36% (SE 13%), 14% (SE 13%), and 57% (SE 19%), respectively. The probability of Event-Free Survival (EFS) at 2.5 yrs is identical to the OS. Of note, the probability of Progression-Free Survival (PFS) at 2.5 years, in which treatment related deaths are censored, is 78% (SE 14%) for all pts, 50% (SE 25%) for BuCy2 pts, and 100% for TBI/VP-16 pts. Surviving patients after myeloablative conditioning have been followed without relapse for a minimum of 4 years. 100 day TRM for all pts was 28%. Although this analysis is limited by sample size, these results demonstrate prolonged disease free survival for pts with MM after myeloablative conditioning with high dose TBI/VP-16 followed by allogeneic stem cell transplantation. This regimen is well tolerated and warrants further investigation as a potentially curative strategy in young MM patients with HLA-identical donors.

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NON-MYELOABLATIVE STEM CELL TRANSPLANTATION (SCT) IS SAFE AND EFFECTIVE FOR PATIENTS WITH MULTIPLE MYELOMA

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Allogeneic SCT can be curative in multiple myeloma (MM), however the high transplant related morbidity and mortality (TRM) limit this therapy to young, low-risk patients. Purpose: The purpose of this study was to determine safety and efficacy of non-myeloablative stem cell transplant (NST) for high-risk patients with MM. Patients and Methods: From September 1999 to June 2001, eight MM patients with a median age of 49 years (range, 44 to 62), received allografts from HLA-matched siblings (n=6) or unrelated donors (n=2). Prior to NST none were in complete remission (CR) and 4 had progressive disease (PD). Six patients had a prior autologous transplant. Median time from diagnosis to NST was 33 months (range, 5 to 64). The conditioning regimen included fludarabine, anti-thymocyte globulin and busulfan. Peripheral blood stem cell grafts were administered to all patients. Results: All patients had prompt myeloid and platelet engraftment. Acute graft versus host disease (GVHD) (three grade I, two grade III) occurred in 5 of 8 patients (62%), at a median time of 26 days (range, 11 to 106 days). Four patients (50%) developed chronic GVHD (2 limited, 2 extensive). Two patients with no GVHD and PD received donor leukocyte infusion (DLI) ($1x10^8$ CD3/kg). One patient receiving DLI subsequently developed grade I acute GVHD. The conditioning regimen was well tolerated with no patients developing VOD or severe mucositis. During neutropenia, only one patient developed a line-associated gram positive bacteremia. While on immunosuppressants, seven patients developed opportunistic infections, including CMV and HSV colitis, cutaneous zoster, polyoma BK cystitis, mucocutaneous candidiasis, pulmonary aspergillosis and Strongyloides infection. Only one patient died of opportunistic infection. With a median follow-up of 13 months, three (38%) achieved CR, two (25%) PR, one MR, one SD, and one PD. All disease responses were observed after development of GVHD. Two patients (25%) died before 100 days: one of CNS failure secondary to possible FK506 toxicity and another due to opportunistic lung infection. One year EFS and OS are 50% and 75%, respectively. Conclusions: NST with fludarabine, anti-thymocyte globulin and busulfan conditioning is well tolerated in high-risk patients with MM. In addition, a graft versus myeloma effect is observed.

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A PILOT STUDY OF MYELOABLATIVE (MA) AUTOLOGOUS STEM CELL TRANSPLANTATION (AUTO SCT) FOLLOWED BY REDUCED INTENSITY (RI) ALLOGENEIC TRANSPLANTATION (ALLO SCT) IN CHILDREN AND YOUNG ADULTS WITH RELAPSED LYMPHOMA

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Patients with relapsed HD and NHL treated with MA AutoSCT have a high risk of relapse (40-60%) and secondary MDS/AML (5-20%). MA AlloSCT may confer a graft versus lymphoma effect but with considerable regimen-related mortality (Jones et al, Blood 77:649, 1991). Recently, Carella et al (JCO 18:3918, 2000) demonstrated the feasibility of MA AutoSCT followed by RI AlloSCT in adults with refractory HD. We investigated MA AutoSCT followed by RI AlloSCT in relapsed pediatric HD/NHL. MA: Cyclo 1500 mg/m^2 x 4d, BCNU 100 mg/m^2 x 3d, VP-16 800 mg/m^2 x 3d, and AutoSCT. After recovery, patients with CD20$^+$ lymphoma (3/4) received Rituximab (375 mg/m^2/wk/x 4), and all patients received IFRT (2-3 Gy). RI: Flu 30 mg/m^2 x 5d, Bu 3.2 mg/kg x 2d, and Thymoglobulin® 2.0 mg/kg x 4d (UCB recipients only) and AlloSCT (1 related 6/6 PBSC, 3 4/6 UCB). GVHD prophylaxis: FK506 (0.03 mg/kg CIVI) on day-1 - +60 (wean started) and MMF (15 mg/kg) day +1 - +28. There were 3 HD (2 CR + 1 PR after Ifos/Carbo/Etop reinduction), age 17, 18, and 22 years, 1 stage IIA, 1 stage IIIB, 1 stage IVA, and 1 anaplastic large cell lymphoma (ALCL) (PR after Topo/Ifos/Carbo reinduction) age 11. Tandem MA AutoSCT + RI AlloSCT was well tolerated. Median time to RI AlloSCT after MA AutoSCT was 124 d. Median F/U is 380 d. One pt has grade 3 hematuria and grade 2 pulmonary toxicity. Following RI AlloSCT, myeloid recovery occurred on day +15 (MRD) day +15, +18, +23 (UCBT), platelet recovery on day +11 (MRD), day +25, +31, +170 (UCBT). The 3 HD patients have 100% donor chimerism and are NED at day +474, +286 and +473, respectively, and the pt with NHL is 95% donor and NED at day +140. No patient developed AGVHD. One patient developed limited chronic liver GVHD responding to alternating CSA + Pred. Estimated OS at 1 year is 100%. In conclusion, MA AutoSCT followed by IFRT, targeted monoclonal antibody therapy, and RI Allo SCT is feasible and well tolerated in pediatric patients with relapsed HD/NHL. A larger study with longer follow up is required to determine if this approach will reduce relapse and/or MDS and improve EFS.

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THE CHOICE OF CONDITIONING REGIMEN REGARDING THE HOST T-CELL LEVELS SEEMS TO BE AN EFFECTIVE WAY HOW TO ACHIEVE THE DONOR CELLS ENGRAFTMENT INCLUDING EFFECTIVE TUMOUR CONTROL AND REDUCE THE TOXICITY OF SOME NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATIONS IN LYMPHOMAS

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"Graft versus lymphoma" (GvL) reaction plays the key role in the tumour control of patients undergoing allogeneic stem cell