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DOSE-REDUCED CONDITIONING WITH FLUDARABINE/MELPHALAN FOLLOWED BY ALLOGENEIC STEM CELL TRANSPLANTATION FOR PATIENTS WITH ADVANCED STAGE II/III MULTIPLE MYELOMA

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Sixty-four patients (pts) with advanced stage II/III multiple myeloma received a dose-reduced conditioning consisting of melphalan (100-140 mg/qm) and fludarabine (90-180 mg/qm) followed by related (n=36) or unrelated (n=28) allogeneic stem cell transplantation. Fifty-two pts additionally received a median of 30 mg/kg anti-thymocyte globulin (ATG Fresenius, Germany). Further GvHD-prophylaxis consisted of CSA and short course MTX (n=62) or CSA plus MMF (n=2). All pts received at least one prior high-dose chemotherapy followed by autologous (n= 63) or allogeneic (n=1) transplantation, in 27 pts as part of an autologous-allogeneic tandem protocol. The median age of the pts was 51 years (range 32-64). The median serum level of beta-2-microglobulin was 3 mg/dl (range 1, 3 - 8). Stem cell source was PBSC in 57 and BM in 7 cases. The median transplanted cell dose was 5.1 x106 CD34+ cells/kg. Sixty-three pts (97%) engrafted with ANC > 1 x109/L after a median of 16 days (r, 10-24). Acute GvHD grade II-IV was seen in 39%, severe grade III/IV in 16% of the patients. Limited and extensive chronic GvHD were noted in 25% and 22%, respectively. The treatment related mortality at one year was 23%, mainly due to GvHD (n=4) and infectious complications (n=4). After allografting 45% of the pts achieved a complete remission with negative immunofixation, while 45% achieved a partial remission, resulting in an overall response rate of 90%. After a median follow-up of 12 months, the 2 years estimated overall and progression-free survival is 55% (95% CI: 35-75%) and 38% (95% CI: 20- 56%), respectively. There was no difference in OS survival between related and unrelated donors (56 vs 55%), but a trend for better OS in patients transplanted without relapse (tandem auto-allo) after HD-chemotherapy (61 vs 41%, n.s.) and in patients without Del 13 in FISH analysis (78 vs 30%, n.s.). Melphalan/fludarabine based dose-reduced conditioning followed by allogeneic stem cell transplantation from related and unrelated donors induces high remission rate with acceptable toxicity.

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NORMAL HEMATOPOIETIC STEM CELL FUNCTION IN MICE FOLLOWING TREATMENT WITH BORTEZOMIB

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Bortezomib (VELCADE ™), formerly PS-341, is a novel proteasome inhibitor being evaluated in a randomized trial in patients with multiple myeloma, a disease frequently treated with autologous stem cell transplantation. Conventional cytotoxic agents have been shown to negatively affect hematopoietic stem cell function in patients undergoing autologous transplantation. In order to determine whether bortezomib produces similar effects on hematopoietic stem cells, we assessed whether treatment with bortezomib affected progenitor derived colony growth and engraftment in a murine bone marrow transplantation model. C57BL/6 mice were treated with four 21 day cycles of saline or bortezomib consisting of administration of drug or saline on days 1, 4, 8 and 11 followed by a 10 day rest period. Following treatment, bone marrow cells were harvested from femurs and tibias. The cells were used for hematopoietic progenitor cell assays (CFU-GM, CFU-E, and HPP-CFC assays) and for transplantation into lethally irradiated B6.SJL recipient mice. There was no difference observed in the number of hematopoietic bone marrow progenitor cells from saline or bortezomib treated animals in the in vitro assays performed. FACS analysis revealed no difference in the engraftment of donor derived bone marrow cells transplanted from saline or bortezomib treated animals. The peripheral blood cell counts of animals transplanted with marrow from either saline treated or bortezomib treated animals were compared. No difference was observed in the recovery of platelets, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils red blood cells, hemoglobin, hematocrit or reticulocytes. We conclude that bortezomib did not adversely affect murine hematopoietic stem cells in this study. Successful peripheral blood stem cell mobilization has been reported in multiple myeloma patients treated with bortezomib and data is being collected in ongoing clinical trials.

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IDIOTYPE VACCINATION FOLLOWING HIGH DOSE CHEMOTHERAPY + AUTOLOGOUS STEM CELL TRANSPLANT IN INDOLENT AND MANTLE CELL LYMPHOMA

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Cell-surface idiotype (Id) of indolent lymphoma patients is a specific tumor marker. Strategies to enhance immune recognition of Id have been attempted. Promising responses have been obtained in patients with lower tumor bulk at time of vaccination. This study evaluates Id complexed to keyhole limpet hemocyanin (KLH) administered with GM-CSF following autologous transplantation (ASCT). Patient specific Id is produced as intact recombinant antibody. Cellular and humoral responses (IR) of 4 patients completing treatment (5 vaccinations over 6 months), commencing at least 3 months post-ASCT are reported. Toxicities probably or possibly related to therapy and/or GM-CSF include: Grade 1 chills/rigors, itchy/watery eyes, nausea, axillary soreness, sternal discomfort, generalized body aches, and joint stiffness; Grade 2 injection site reaction, headache, fatigue, blurred vision; and Grade 3 leukopenia (present pre-vaccination). Anti-KLH antibody and anti-Id titers were evaluated (ELISA). After 2 vaccine treatments, patients 1 & 2 developed significant levels of anti-KLH (IgM and IgG1). Neither mantle cell patients developed anti-KLH. After 4 treatments patient #3 developed anti-KLH. Patients 1&3 made significant levels of specific anti-Id antibody co-incident with high titer anti-KLH. Patient #2 made non-specific antibody responses. For Id specific cell mediated immunity PBMCs from patients #1-3 were cultured with either KLH, patient derived recombinant Id or control Id. After 5 days cells were stained for surface expression of CD4 and CD25 and for cytoplasmic expression of TNF-alpha and interferon gamma. All three patients made sustained CD4+ anti-KLH T cell responses detectable at 1 month post vaccine #1. Patients 1&3 also made specific anti-Id T cell responses. Patient #2 made a specific anti-Id T cell response after vaccine #5. Patient #4 has not been assessed for T cell responses . These results suggest that humoral and cellular immune responses can be rapidly induced in indolent and mantle cell lymphoma patients following ASCT supporting the evaluation of Id vaccines in this setting.

Patient	Sex/Age	Histology	#prior chemo regimens	HDCT	Response pre V1	Response pre V4	Response 1 month post V5
1	M/54	Indolent	2	BEAM	PR	CRU	CR
2	F/54	Indolent	2	BEAM	SD	SD	SD
3	M/62	Mantle Cell	3	CEB	CR	CR	CR
4	M/62	Mantle Cell	4	BEAM	PR	CR	CR