LYMPHOMA/MULTIPLE MYELOMA

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NONMYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION (NST) FOR LYMPHOID MALIGNANCIES USING PENTOSTATIN/LOW-DOSE TOTAL BODY IRRADIATION

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Between 9/01 and 8/03 13 patients with relapsed/refractory lymphoid malignancies have undergone NST. The median age at transplantation was 52 years (range 21-63). The median number of prior therapies was 5 (range 1-7). Diseases transplanted represented a broad variety of lymphoid malignancies including Hodgkin's disease (n = 3) and non-Hodgkin's lymphoma (n = 10). The conditioning regimen consisted of Pentostatin 4 mg/m2/day IV on days -21, -20, and -19, followed by low dose total body irradiation on day –1. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine/mycophenolate mofetil. Stem cell transplantation was from matched related (n = 5) or matched unrelated (n = 8) donors. All toxicities were minimal. At day +28 the median values for donor chimerism were 90% (range 55%-100%) for CD3+ cells and 95% (range 50%-100%) for WBC. At day +70 the respective median values were 95% (range 50%-100%) and 100% (range 80%-100%) respectively. Sustained engraftment has been observed in all cases to date and no patients have required donor leukocytes. Acute GVHD has been seen in 6/13 patients, and chronic GVHD in 6/8 evaluable patients. Treatment related mortality is 15% (one death from intracranial hemorrhage, one death from chronic GVHD). With a median follow-up for surviving patients of 11.2 months, the event-free survival and overall survival are presently projected at 73%. Of six patients who underwent autologous stem cell transplantation as their immediate prior therapy (excluding salvage therapy prior to NST), five have had remission durations which have exceeded their prior remission duration with autologous transplantation (P = 0.07 by logrank). An additional patient with Waldenstrom's macroglobulinemia had evidence of minimal residual disease (persistent marrow disease and an elevated IgM) for six months post transplant, and with no further therapy at one year post transplant has a normal marrow and IgM levels. The use of Pentostatin/TBI as a preparative regimen for NST in patients with refractory/relapsed lymphoid malignancies is associated with minimal toxicity, sustained engraftment, and an acceptable treatment related mortality given the patient population. The observation that a number of patients have had remission inversions (compared with immediately prior high-dose chemotherapy/autologous stem cell transplantation) and the occurrence of a late remission in the absence of other therapy offers indirect evidence of a graft-versus-lymphoma effect.

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LONG TERM DISEASE FREE SURVIVAL IN PATIENTS WITH MANTLE CELL LYMPHOMA FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Mantle cell lymphoma (MCL) is a B-cell lymphoma with tumor cells that are typically CD5+ and CD23- and overexpress cyclin D1. The response rate and overall survival in patients with MCL are significantly lower than other types of lymphoma. No chemotherapeutic regimen has been proven to be consistently curative for MCL. The role of hematopoietic stem cell transplantation (HSCT) in the treatment of MCL is unclear. Also it is not known which type of transplantation is more effective. Hence we studied the clinical course of the disease in patients who received autologous or allogeneic HSCT for MCL to determine if the type of transplant had an effect on the clinical outcome. Ninety seven patients who received HSCT for MCL were studied, including 80 patients who received an autologous HSCT and 17 patients who received an allogeneic HSCT from a matched sibling donor. None of the allogeneic transplants employed a reduced intensity preparative regimen. Primary end points were response at day 100, mortality at day 100, relapse rate (RR), event free survival (EFS) and overall survival (OS). Patients who received an autologous HSCT were older (median age: 56 yrs vs. 47 yrs) ($p < 0.01$) and were less likely to receive conditioning with total body irradiation (9% vs. 94%) ($p < 0.0001$). There was no significant difference in the complete response rate at day 100 between patients receiving autologous and allogeneic HSCT (73% vs. 62%). Mortality at day 100 was higher among recipients of allogeneic HSCT (19%) as compared to autologous HSCT (0%) ($p < 0.01$). The estimated 5-yr RR was 21% among patients receiving an allogeneic HSCT compared to 56% for those receiving an autologous HSCT ($p = 0.11$). The estimated 5-yr EFS was 44% for allogeneic HSCT and 39% for autologous HSCT ($p = 0.85$). The estimated 5-yr OS was 49% for allogeneic HSCT and 47% for autologous HSCT ($p = 0.51$). Ten patients (8 autologous HSCT, 2 allogeneic HSCT) received HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) prior to transplant and there have not been any relapses or deaths amongst these patients at a median follow-up of 16 months. In conclusion, allogeneic HSCT patients tended to have a lower relapse rate, although this difference was not statistically significant. However the OS and EFS were similar in both groups. Both types of transplants can lead to long-term disease-free survival in approximately 40% patients with MCL especially after chemotherapy with HyperCVAD.

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A PHASE I/II STUDY OF XCELLERATED T CELLS™ AFTER AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN PATIENTS WITH MULTIPLE MYELOMA

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Previous studies in multiple myeloma have demonstrated a significant association between survival and lymphocyte recovery following autologous transplantation (Porrata et al., *Blood* 2001). Furthermore, in a murine model of myeloma, adoptive transfer of activated T cells following bone marrow transplantation has demonstrated a marked anti-tumor effect *in vivo* (Hou Fowler, *BBMT* 2003). We have initiated a clinical trial in patients with multiple myeloma to evaluate the activity of T cells activated and expanded *ex vivo* with the Xcellerate™ Process, which uses anti-CD3 and anti-CD28 antibodies covalently linked to magnetic beads (Xcyte™ Dynabeads®). Following induction therapy, patients undergo a leukapheresis to collect peripheral blood mononuclear cells for the Xcellerate Process. Patients then undergo stem cell mobilization and collection, followed by high dose chemotherapy with melphalan (200 mg/m^2). Three days following peripheral blood stem cell infusion, patients receive an infusion of 5-10 $\times$ 10^{10} autologous Xcellerated T Cells. Thirty-one of the planned 35 patients have been treated to date. T cells have been successfully activated and expanded in all patients. In the first 18 patients, T cells expanded 166 ± 44 fold (mean ± SD), with the final product being >99.0 ± 0.1% CD3$^+$. A bioreactor process was subsequently instituted, and T Cells expanded 253 ± 86 fold, with final product 98.0 ± 3.2% CD3$^+$ (n = 10). Xcellerated T Cell infusions have been well-tolerated, with no Grade 3 or 4 acute infusional toxicities. Lymphocyte recovery has been rapid, with counts reaching > 500/mm^3 generally within 1-2 days following T cell infusion (Day 4-5 post transplant). Historically, lymphocyte recovery to >500/mm^3 usually does not occur for 3 or more weeks post-

transplant in myeloma patients treated with this regimen, but without Xcellerated T Cells. The T cell receptor repertoire of leukapheresis samples as measured by V_β spectratyping demonstrates marked skewing. Following the Xcellerate Process, the repertoire returns to a more normal pattern (n = 5; p = 0.01). In addition, the T cell repertoire measured 25 days following T cell infusion (Day 28 posttransplant) demonstrates a more normal pattern than prior to T cell infusion (n = 5). This is in marked contrast to the severe skewing of T cell receptor diversity normally seen in myeloma patients following autologous stem cell transplantation (Mariani et al, *BJH* 2001). Data on clinical outcomes will be presented.

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LONG TERM OUTCOME FOLLOWING AUTOLOGOUS AND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR FOLLICULAR LYMPHOMA

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Follicular lymphoma (FL) accounts for approximately 25-35% of all cases of non-Hodgkin's Lymphoma (NHL). Autologous (ASCT) and allogeneic (alloSCT) hematopoietic stem cell transplantation can induce prolonged remissions in patients with FL, and studies of alloSCT demonstrate very low relapse rates and evidence of a plateau on event-free survival (EFS) curves, suggesting the possibility that some patients may be cured with this modality. We present the long-term outcome in 204 patients with FL treated with ASCT (n = 186) or alloSCT (n = 18) between 04/83 and 05/98. For ASCT and alloSCT groups respectively the median age was 45 vs. 39 years and the median time from diagnosis to transplant 27 vs 24 months. The majority of patients in both groups had follicular grade 2 histology, and the conditioning regimen was cyclophosphamide/total body irradiation (Cy/TBI) in 54% of ASCT and 72% of alloSCT. The median follow-up of surviving patients is 7.8 years (range 1.7 to 19.2 years). Patients who received an alloSCT had a superior five-year EFS (76% vs. 41%; p = 0.034), but not overall survival (OS) (76% vs. 61%; p = 0.18). To control for the possible confounding effect of preparative regimen we performed a limited analysis of all patients undergoing transplantation with Cy/TBI, and found that patients undergoing alloSCT had superior EFS (p = 0.034) and a trend toward improved OS (p = 0.18) compared with ASCT. Multivariate analysis of patients undergoing ASCT demonstrated an inferior EFS in patients who received ≥3 prior chemotherapies (hazard ratio [HR] = 3.5; 95% confidence interval [CI] = 1.8-7.0, p < 0.001) and in patients >60 years of age (HR = 4.7; 95% CI = 1.6-13.8, p < 0.001). Variables predicting for an increased risk of death in ASCT included ≥3 prior chemotherapies (HR = 5.0; 95% CI = 2.4-10.6, p < 0.0001), age >60 years (HR 9.2; 95% CI = 2.8-30, p < 0.001), female gender (HR = 2.4; 95% CI = 1.2-4.9, p = 0.013), and the presence of resistant disease (HR = 4.9; 95% CI = 1.8-13.6, p < 0.01). In conclusion, this data offers some evidence that with adequate follow-up alloSCT leads to superior EFS compared with ASCT, but because of morbidity/mortality associated with alloSCT OS is similar in both groups. Notwithstanding issues of selection bias, the observation that these differences are not accounted for by the intensity of the preparative regimen suggests that a lack of tumor contamination, an allogeneic graft-versus-lymphoma effect, or both may be responsible for the improved outcome.

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THE CITY OF HOPE EXPERIENCE WITH NOVEL TRANSPLANT REGIMENS THAT INCORPORATE STANDARD AND ESCALATED DOSE ^{90}YTTRIUM IBRITUMOMAB TIUXETAN (^{90}Y-ZEVALIN®) RADIOIMMUNOTHERAPY (RIT) FOR AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA (NHL): TARGETED INTENSIFICATION WITHOUT INCREASED TOXICITY AND ELIMINATION OF TOTAL BODY IRRADIATION (TBI)

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Background: ^{90}Y-Zevalin was the 1st FDA-approved RIT for treatment of pts with relapsed or refractory CD20+ low-grade, follicular, or transformed B-cell NHL, including rituximab-refractory NHL. Two COH clinical trials are currently investigating whether standard (0.4 mCi/kg) or escalated doses of ^{90}Y-Zevalin can be combined safely with myeloablative regimens for ASCT. **Methods/Results:** 1) A dose escalation study of ^{90}Y-Zevalin with dosimetric guidance (maximum radiation dose to the liver of 1000 cGy) + high-dose VP-16 + cyclophosphamide (CY) has accrued 26 pts who are evaluable for efficacy and safety. Median age was 49 (25-58). Median dose of ^{90}Y-Zevalin delivered was 71 mCi (37-105 mCi). All pts with measurable disease achieved remission, except one pt had a positive PET scan. 4 pts received IF-XRT to sites of prior bulky disease. Median day to ANC >1,000 was 10 days (8-17). Median days to platelet count >50, 000 was 20 (12-123). With a median follow-up of 20 months (range 1-40), 21 pts (81%) are alive and in remission. 2) The standard-dose study of ^{90}Y-Zevalin (0.4 mCi/kg) + high-dose BEAM has accrued 12 pts, primarily over the age of 60. Dosimetry was not performed. Median age was 61 (56-78). All pts engrafted promptly after ASCT and there were no transplant-related deaths. The median total dose of ^{90}Y-Zevalin was 32 mCi (range: 20.7-40). Because stem cell support was used, a maximum 40 mCi dose of Zevalin was allowed. With a median follow-up of 9 months (range, 4-16), 2 pts have relapsed, and one of these died from progressive disease. The remaining 10 pts (83%) are well without evidence of NHL. **Conclusions:** Results from the dose escalation study suggest that high-dose ^{90}Y-Zevalin can be safely administered with high-dose VP-16/CY; that high-dose ^{90}Y-Zevalin can be used in place of TBI without the need for a lead-shielded isolation room; and that this new high-dose combination is effective in heavily pre-treated pts with poor-risk NHL. Results from the second study indicate that the combination of conventional-dose ^{90}Y-Zevalin + high-dose BEAM is a well-tolerated and easily administrated ASCT regimen for older pts with aggressive CD20+ NHL and does not require dosimetry. These preliminary results taken in aggregate suggest that incorporation of ^{90}Y-Zevalin into novel SCT regimens provides a targeted intensification of the transplant regimen and potentially increased anti-tumor activity without added toxicity.

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ZEVALIN DOSE-ESCALATION FOLLOWED BY HIGH-DOSE BEAM AND AUTOTRANSPLANT IN CD20+ RELAPSED OR REFRACTORY NON-HODGKIN LYMPHOMA (NHL)

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^{90}Y Zevalin was added to high-dose BEAM followed by autotransplant in 22 patients with relapsed or refractory CD20+ NHL with the goal of increasing progression-free and overall survival (PFS, OS). Cohorts of 3-6 patients were treated at doses calculated to result in increasing radiation exposure(100, 300, 500, 700 cGy) to the critical organ (liver, lung or kidney). On D -22, rituximab(R) 250 mg/m^2 was administered followed by the imaging dose of ^{111}In Zevalin (5 mCi). Imaging was performed immediately and at 4, 24, 72, and 144 hours post-injection; dosimetry was performed on D -15. On D -14, R at 250 mg/m^2 was administered followed by ^{90}Y Zevalin at a dose calculated to deliver the cohort-prescribed absorbed radiation dose to the critical organ. On D -6 through -1, patients received BEAM. On D 0, a minimum of 2.0×10^6 CD34+ cells/kg was infused and G-CSF 5 μg/kg SQ daily was begun. The median age was 53 (range: 25-72). 5 patients had mantle cell lymphoma, 9 had diffuse aggressive NHL, 4 had low grade NHL, and 4 had transformed NHL. The majority (55%)