from day +1 until neutrophil engraftment. GVAX was initiated between day +30 to +45 if there was adequate hematologic recovery and no grade II-IV acute GVHD. GVAX was administered ID/SC qwk × 3 doses, then q2wks × 3 doses. Taper of tacrolimus began after vaccine completion. Ten patients (6 URD, 4 MRD) have been transplanted to date: 8 AML, 2 MDS/RAEB-2. Seven had circulating myeloblasts at transplant. GVAX was successfully generated for all 10 patients. Median vaccine cell dose was 1.0×10^7cells (range, 0.4-1.0 × 10^7), and median 24-hr GM-CSF secretion by vaccine cells was 7.25 ng/ml/10^6cells (range <1.0-155.9). Only 4 of 10 patients were able to start vaccination post transplant. Reasons for failure to initiate vaccination included: death before day +30 (1); acute GVHD (2); insufficient count recovery (3). Among those who received GVAX, there was no GVHD or toxicity attributable to vaccination. Focal infiltrates of lymphocytes were observed in skin biopsies of the vaccination sites. Two of four vaccinated patients are alive: 1 in CR, and 1 in relapse 5 and 6 months post transplant, respectively. Overall, 7 of 10 patients have relapsed, 6 before day +100. Although results are preliminary and the high incidence of early relapse has hindered our ability to initiate vaccination, GVAX appears to be safe for patients with MDS/AML after NST. Further cytoreduction prior to NST is necessary for disease control and improve feasibility of GVAX vaccination in this very high-risk population.

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TREATMENT OF PATIENTS (PTS) WITH CHRONIC MYELOID LEUKEMIA (CML) AND IMATINIB FAILURE AFTER DEVELOPING BCR-ABL KINASE MUTATIONS WITH ALLOGENEIC STEM CELL TRANSPLANTATION (ASCT)

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ASCT is curative for many pts with CML, and may be effective after imatinib failure. Resistance to imatinib is most often associated with point mutations in the Bcr-Abl kinase domain. The outcome of pts with Bcr-Abl kinase mutations after ASCT is not known. We assessed the outcome of ASCT in 9 pts with CML (chronic phase [CP] = 3, accelerated phase [AP] = 3, blast phase [BP] n = 3) harboring 8 different protein kinase mutations. P-loop mutations were detected in 4 (44%) pts; T315I mutation was detected in 2 pts (one AP and one CP). Seven male and 2 female pts, median age of 44 years (range, 26-63 years), received their ASCT between June 2003 and July 2005. At the time of ASCT, one pt was in major molecular remission (MMR) (BP, Q252H), one was in major cytogenetic response (CP, T315I), and 2 were in complete hematologic response (2 BP, Y253H and E281A). Preparative regimen was busulfan + cyclophosphamide in 7 and fludarabine + cyclophosphamide in 2 pts. Donor was fully matched related in 4 (44%) and unrelated in 5 (56%) pts. Source of stem cells was peripheral blood and bone marrow in 7 and 2 pts, respectively. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and mini methotrexate. All patients engrafted; there was no treatment-related mortality. Chimerism studies at day 30 and 100 post ASCT were available in 7 pts and were 100% of donor type. Eight pts achieved a complete molecular remission (CMR); one pt with a T315I mutation achieved a MMR. Two (22%) pts (Q252H [BP] and T315I [AP]) relapsed after a median of 7 months; one of them (T315I) died of disease progression. All the remaining 7 pts were in CMR for a median of 13 months (range, 3-20+ months). We conclude that ASCT remains an important salvage option for pts who develop resistance to imatinib through Bcr-Abl mutations. Early introduction of such strategy may result in better outcome.

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IN VIVO BIOLUMINESCENCE IMAGING OF ACUTE PROMYELOCYTIC LEUKEMIA CELL TRAFFICKING AND MOBILIZATION BY AMD3100

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Novel approaches have been developed to mobilize hematopoietic stem cells (HSC) for patients undergoing autologous and allo transplantation. These strategies may provide insights into improved HSC collection and enhanced egress of leukemic cells and thus sensitivity to anti-leukemia therapy. CXCR4/SDF-1 axis regulates the trafficking of normal HSC to and from the bone marrow (BM). AMD3100 (AMD) specifically and reversibly blocks SDF-1 binding to CXCR4, and is a promising mobilizing agent currently in clinical development. We utilized a mouse model of acute promyelocytic leukemia in which the PML-RAR$_\alpha$ transgene was knocked into a single allele of the murine cathepsin G locus. We transduced banked leukemia cells with a dual function reporter gene that encodes a click beetle red (CBR) luciferase, a bioluminescence imaging (BLI) optical reporter gene, and EGFP for ex vivo cell sorting (CBR/EGFP). We isolated EGFP$^+$ cells using a MoFlo cell sorter, and passaging them in secondary syngeneic recipients that developed rapidly fatal acute leukemia. Upon intravenous (iv) injection of 10^6 APL cells into syngeneic recipients, APL rapidly migrated to the BM, with increased BLI signal in the femurs, spine, ribs, and skull, at 4 days after injection, followed by spleen infiltration and by death due to leukostasis by 14-16 days. To our knowledge, this represents the only mouse leukemia model in which leukemia cells home preferentially to the BM in a manner that is similar to what is seen in human AML. AMD (5 mg/kg) at the time of APL infusion or bid on days 0-7, had no impact on the engraftment of either normal HSC or the PML. We observed rapid mobilization of the APL cells when AMD was administered 11 days after APL injection. 40% of mice that received AMD on day +11 died 2 to 4 hours after AMD injection as a result of the rapid and massive mobilization of blasts. Interestingly, CXCR4 expression in mobilized tumor cells decreased from 33 ± 3% before AMD administration to 19 ± 6%, and 7.8 ± 0.6% after 2 and 12 hours (FACS; $P < .001$). AMD + AraC (200 mg/kg) on day +11 prolonged the overall survival of mice, compared with mice treated only with AraC. In summary, we developed a mouse model to study the APL cell trafficking, and we have shown leukemia cell mobilize from the BM into PB after AMD administration. In these preliminary results we observed that AMD may sensitize APL cells to AraC. We propose that CXCR4/SDF-1 is a key regulator for leukemia migration and homing to the BM.

LYMPHOMA/MULTIPLE MYELOMA

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POSITIVE POSITRON EMISSION TOMOGRAPHY (PET) PRE-AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) IN NON-HODGKIN LYMPHOMA (NHL) DOES NOT PRECLUDE SUCCESSFUL OUTCOME

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PET has become an important imaging modality for lymphoma, and has been reported to be of prognostic significance prior to ASCT for NHL. **Methods:** To assess the prognostic value of PET prior to ASCT in NHL, PET pre and post ASCT was prospectively obtained in all NHL patients. From May 2003 to December 2004, 100 patients underwent ASCT for NHL. PET was considered positive if it had abnormal FDG uptake; CT was positive if it had areas of lymphadenopathy as defined by the international response criteria. **Results:** Median age was 58 (range 17-74); 69% were male. Patients had received a median of 2 prior chemotherapy regimens (range 1-9). At relapse, prior to ASCT, the median IPI was 2 (range 1-5); 31% of patients were stage I or II; 69% were stage III or IV. Histology included DLBCL 50, transformed NHL 15, mantle cell NHL 11, low-grade NHL 8, T-cell NHL 6, primary CNS NHL 5, and high grade NHL 5. At ASCT, 43 patients were in CR, 49 in PR, 3 in untreated relapse, and 5 had resistant disease. The conditioning regimen was BEAM in 89; Zevalin/BEAM in 10. Pre-ASCT PET was not obtained in 8

patients. In the remaining 92, pre-ASCT PET was positive in 44 and negative in 48. Median follow-up was 8.7 months (range 1-25) for the entire group and 11.8 months (range 2-25) for surviving patients. Median remission duration for all patients was 7.1 months (range 1-25). Patients with a positive and negative pre-ASCT PET had an estimated 1 year OS of 61% and 77%, respectively (P = .08). Estimated 1 year EFS was 34% and 66% in patients with positive and negative pre-ASCT PET, respectively (P = .007). For the 50 DLBCL patients, median follow up was 6.5 months (range 1-25) for the entire group and 10.3 months (range 2-25) for survivors. Median EFS for the entire group 6.5 months (range 1-24). Pre-ASCT PET was obtained in 47 patients; 21 (44.6%) were positive, 26 (55.3%) were negative. 1 year OS was 52% for patients with a positive pre-ASCT PET and 68% for patients with a negative pre-ASCT PET (P = .06). 1 year EFS was 40% and 52% for patients with a positive and negative pre-ASCT PET, respectively (P = .11). **Conclusion:** Although a negative pre-ASCT PET in NHL patients does predict a significantly better EFS and a trend toward improved OS, a substantial number of patients with a positive PET pre-ASCT can achieve a good outcome and do not require more aggressive therapy. In DLBCL patients in particular, positive pre-ASCT PET did not predict a significantly worse OS and EFS (Table 1).

Table 1. *Overall and Event Free Survival Based on Pre-ASCT PET Results*

	Positive PET, %	1-y Overall Survival, Positive PET, %	1-y Overall Survival, Negative PET, %	P	1-y Event Free Survival, Positive PET, %	1-y Event Free Survival, Negative PET, %	P
Entire group (n = 100)	49	61	77	.08	34	66	.007
BLBCL (n = 50)	45	52	68	.06	40	52	.11

DLBCL diffuse large B-cell lymphoma.

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NONMYELOABLATIVE UNRELATED DONOR (URD) HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR THE TREATMENT OF PATIENTS (PTS) WITH POOR-RISK, RELAPSED OR REFRACTORY MULTIPLE MYELOMA

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We carried out HLA-matched URD peripheral blood stem cell (PBSC) transplantation in 24 pts with poor-risk multiple myeloma after nonmyeloablative conditioning with fludarabine (90 mg/m^2) and 2 Gy total body irradiation. Postgrafting immunosuppression consisted of cyclosporine and mycophenolate mofetil. The median age of the 19 men and 5 women was 53 (range, 23-66) years. Conventional metaphase cytogenetics obtained in 14 pts showed Δ13 in 6 pts and complex abnormalities in 9 pts. Stage III disease was present in 83% and 17% had stage II disease. The median time from diagnosis to URD HCT was 25 (range, 8-130) months, and 96% were beyond 1st complete remission (CR) or had never achieved CR1, despite multiple lines of chemotherapy (median 4.5, range 2-10). At study entry, 17 pts (71%) had chemotherapy-refractory disease and 14 pts (58%) had failed prior autologous HCT. Thirteen pts had planned autologous-URD tandem HCT, while 11 proceeded directly to URD HCT, with the treatment plan based on availability of autologous PBSC. The median follow-up was 2.5 years after allografting. One pt experienced non-fatal graft rejection. The incidences of acute grades II, III and chronic graft-versus-host disease were 54%, 13% and 75%, respectively. Non-relapse mortality was 22% at 2.5 years. CRs were observed in 11 pts (46%) and partial remissions (PR) in 3 (13%). Best disease responses were seen in pts given tandem autologous-URD HCT with CR in 8 pts and PR in 2 pts (77% CR + PR rate). The estimated overall survival (OS) at 2.5 years for all 24 pts was 65% and progression-free survival (PFS) 41%. Pts receiving tandem autologous-URD HCT had superior OS and PFS, 76% and 63%, compared to pts proceeding directly to URD HCT, 52% and 14%, respectively (PFS P value = .03). Risk factors for worse OS included pts with significant medical comorbidities (P = .03), chemotherapy-refractory disease prior to HCT (P = .03), and pts who had failed autologous HCT (P = .07). Pts who failed prior autologous HCT had 48% OS and 30% PFS at 2.5 years. For pts with poor-risk, relapsed or refractory multiple myeloma, cytoreductive autologous HCT followed with nonmyeloablative conditioning and URD HCT is very promising treatment with low non-relapse mortality, high complete remission rates and prolonged PFS. The results also suggest that URD HCT may provide improved graft-versus-myeloma effect compared with HLA-matched sibling HCT without an increase in the risk of non-relapse mortality.

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REDUCED-INTENSITY ALLOGENEIC HEMOPOIETIC STEM CELL TRANSPLANTATION INDUCES DURABLE RESPONSES IN PATIENTS WITH CHRONIC B-LYMPHOPROLIFERATIVE DISORDERS

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Thirty-six patients with chronic B-lymphoproliferative disorders underwent reduced-intensity allogeneic stem cell transplantation from 1999 to 2004. Diagnoses included relapsed or refractory follicular lymphoma (FL) (n = 17), mantle cell lymphoma (MCL) (n = 9), small lymphocytic lymphoma (SLL) (n = 2), and chronic lymphocytic leukaemia (CLL) (n = 8). The median age at transplant was 51 yrs (range, 30-66 years), time from diagnosis to transplant was 6 years (range, 0.7 to 9.5 years), and number of prior treatment regimens was 3 (range, 2 to 6). At the time of transplant 28% of patients were in CR, 36% were in PR, and 36% were chemorefractory. Thirty-five patients received peripheral blood stem cells from an HLA-identical sibling, and one from another HLA-identical relative. Median number of CD34$^+$ stem cells infused was 5.0×10^6 per kg (range, 0.9-18.9). Conditioning therapy consisted of fludarabine (125-150 mg/m^2) and either cyclophosphamide (60-120 mg/kg) (n = 27) or melphalan (120-140 mg/m^2) (n = 9). Prophylaxis of graft versus host disease (GVHD) included cyclosporin (CsA) and methotrexate (n = 22), CsA and mycophenolate mofetil (n = 12), or CsA alone (n = 2). Median time to achievement of an absolute neutrophil count of $> 0.5 \times 10^9$/L and a platelet count of $> 20 \times 10^9$/L was 14 days (range, 8-22 days) and 14 days (range, 8-30 days), respectively. One patient with CLL failed to engraft despite two donor lymphocyte infusions. Seven patients died of causes not related to relapse including severe acute GVHD (n = 3), infection, either alone (n = 1) or in association with chronic GVHD (n = 2), and intra-abdominal bleeding (n = 1). Treatment-related mortality was 8% at day 100, and 17% at both one and two years. The cumulative incidence of grades II-IV acute GVHD was 69% (95% CI, 54-85%). Among evaluable patients, limited chronic GVHD was seen in 25% and extensive chronic GVHD in 56%. Of the 33 patients assessable for response, 88% achieved a CR and 9% a PR while one patient had stable disease. No patients have relapsed or had progressive disease. The Kaplan-Meier estimate of the proportion of patients alive, and without disease progression, at a median follow-up of 37 months (range, 9-69 months) is 83% (95% CI, 76-89%). We confirm that reduced-intensity allogeneic transplantation in chronic B-lymphoproliferative disorders can result in high and durable complete response rates with limited toxicity but with a significant incidence of both acute and chronic GVHD.