January 2001 for CML at our institution were retrospectively reviewed. Imatinib-refractory CML was defined as either lack of any cytogenetic response (CGR) after at least 6 months of imatinib, loss of CGR or progression to a more advanced disease stage (accelerated or blast phase) during imatinib therapy. Using the EBMT risk score (Lancet 1998; 352: 1087), transplant outcomes for imatinib refractory CML were compared with all other CML transplants performed during the same time period. Survival analysis was performed using the Kaplan-Meier product-limit and comparison of survival data via the log-rank test.

Results: Of 31 allogeneic transplants (19M; 12F) performed for CML, 12 had been performed for imatinib refractory CML (no CGR to imatinib n=3; loss of CGR n=3; progression to AP n=3; progression to BC n=3), 5 in patients with imatinib responsive CML, and 14 in patients never exposed to imatinib. Median age at SCT was 40yrs (range 19-63yrs). Donor source included HLA-matched unrelated donors in 14 cases, HLA-identical siblings in 16 and other matched family donors in 1. Graft source consisted of PBSC (17), BM (8) and G-BM (6). Conditioning regimens included Cy/TBI (20 cases), Bu/Cy (8 cases), Flu/Mel (2 cases) and Flu/Cy (1 case). CsA + MTX was used as standard GVHD prophylaxis (29), CsA alone (1) and Tacrolimus/Mycophenolate (1). EBMT risk scores were 1(4 cases), 2(6 cases), 3(8 cases), 4(5 cases), 5 (3 cases) and 6 (5 cases). At median follow-up post-SCT of 37mths (range 6-64mths), median PFS and OS are not reached; at 2yrs PFS, EFS and OS are 81%, 58% and 61% respectively. For patients with EBMT risk scores of 1-2 versus 3-4 versus 5-6, OS at 2yrs post-SCT is 80%, 62% and 38% respectively (p=0.01) (4). Use of EBMT risk score, no significant differences in PFS, EFS or OS were observed when comparing SCT for imatinib-refractory versus imatinib-responsive / imatinib-naive CML.

Conclusion: Our experience suggests that survival post-SCT for imatinib-refractory CML is similar to SCT for imatinib-responsive / imatinib-naive CML. The EBMT risk score remains useful in predicting survival post-SCT in imatinib-refractory CML.

58 mTOR inhibitors (MTI) are synergistic with methotrexate: An effective combination to both prevent post-HSCT relapse of ALL and prevent GVHD

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Many adults and some children with ALL relapse and may require HSCT for cure. We have previously demonstrated that MTI, including sirolimus and its ester temsirolimus, are active against primary human ALL in preclinical models. Recent data in HSCT indicate efficacy of sirolimus-based GVHD prophylaxis. Thus, MTI have the potential to both control GVHD and eliminate minimal residual ALL after HSCT. MTI downregulate cyclin D1 which is involved in dihydrofolate reductase (DHFR) synthesis. Sensitivity to methotrexate has been shown to correlate with DHFR expression. Thus, MTI may increase sensitivity of ALL to methotrexate through decreasing DHFR by increasing turnover of cyclin D1. We hypothesized MTI and methotrexate would exhibit synergy against human ALL, suggesting that this combination could be used as an effective means to prevent both recurrence and GVHD. We used the relevant preclinical model of NOD/SCID mice xenografted with primary ALL patient samples. The MTI sirolimus and temsirolimus significantly decrease ALL in xenografted mice with large disease burdens. To test possible synergy, after establishment of disease, mice were randomized to treatment with control, temsirolimus (daily or weekly), methotrexate (5mg/kg/weekly) or both drugs combined. Disease was evaluated weekly by FACs of peripheral blood for CD9+ and CD45+ ALL cells. The combination of methotrexate and temsirolimus demonstrated an additive and potentially synergistic effect. Control mice died after 21 d. Mice treated with temsirolimus or methotrexate alone had initial improvement in ALL followed by progression after 4-5 weeks. Mice treated with both drugs had a complete and durable resolution of peripheral blasts by d 21. After d 42 treatment was stopped. Mice treated with both drugs remained in remission and were disease free when sacrificed 2 months later in contrast to either single agent treatment group which died of disease. Kaplan-Meier analysis of time to progression demonstrated a statistically significant difference, comparing all treatment arms to control (p<0.01), and comparing the combination of drugs to methotrexate only (p<0.03) and temsirolimus only (p<0.07) in both samples.

Conclusion: We found methotrexate and MTI are an effective and potentially synergistic combination in ALL. These agents could be used to both treat ALL and prevent GVHD, making it an ideal combination for use as GVHD prophylaxis for ALL patients undergoing HSCT.

59 GM-CSF secreting leukemia cell vaccinations after allogeneic reduced-intensity peripheral blood stem cell transplantation (SCT) for advanced myelodysplastic syndrome (MDS) or refractory acute myeloid leukemia (AML)

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Bone marrow disease relapse is a frequent cause of treatment failure in patients undergoing reduced intensity allogeneic SCT for advanced MDS and AML. Prior studies with GVAX, a cancer vaccine composed of irradiated autologous myeloblasts modified to secrete GM-CSF, suggested antitumor activity in MDS/AML after autologous SCT or in primary therapy. We investigated the feasibility and safety of administering GVAX after allogeneic SCT. Patients with MDS-RAEB or AML with >5% marrow blasts and with a donor matched at HLA-A,B, DRB1 were eligible. Prior to SCT, autologous myeloblasts were collected from the marrow or blood and transfected with an adenovirus vector bearing the GM-CSF gene to generate the GVAX vaccine. Conditioning consisted of fludarabine 30mg/m2/d IV and busulfan 0.8mg/kg IV q12H days -6 -3 prior to allogeneic PBSC infusion. GVHD prophylaxis included tacrolimus and mini-methotrexate. GM-CSF (Leukine) 250 mg/m2 SC QD was administered from day +1 until engraftment. GVAX was administered SC/ID weekly for the first three doses, then q2wks for the last three doses starting between day +30 to +45 if there was neutrophil recovery and no grade II-IV acute GVHD. Tacrolimus was tapered after vaccine completion. Twenty patients (11 URD, 9 MRD) have been transplanted to date: 14 AML, 4 MDS/RAEB, 2 CML myeloid blast crisis. Median age was 63 (range, 41-71 yrs). Median marrow blast content at SCT was 22% (range, 6-91%). GVAX was successfully generated for all 20 patients. Median vaccine cell dose was 1.0 × 10^7 cells (range, 0.1-1.0 × 10^7), and median 24-hour GM-CSF secretion by the vaccine was 8.2 ng/ml/10^6 cells (range 0.4 - 195). Eight patients did not initiate vaccination due to: poor neutrophil recovery/re- lapse(4); aGVHD (2); IPS (1); sepsis(1). Two patients were recently transplanted and have not started vaccination. Among 10 patients who received GVAX, vaccination was well tolerated. Donor chimerism was not adversely affected by vaccination. Six of 10 patients who started GVAX are alive at a median follow up of 7.5 months post transplant (range 1-16 mos), and all are in complete remission (4 AML, 2 MDS-RAEB) between 3 and 16 months after transplant. Histologic examination of vaccination and leukemia cell DTH sites revealed significant infiltration with inflammatory cells and eosinophils. These preliminary results suggest GVAX vaccination is safe and may have antitumor activity in patients with MDS/AML after allogeneic SCT.

60 A high lactate dehydrogenase (LDH) level predicts for shorter survival following HLA-matched sibling bone marrow transplant (BMT) for patients with acute myelogenous leukemia (AML)

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