complete remission (CR) rates and long-term survival, however, it remains associated with significant treatment related mortality (TRM) and it remains unclear whether a CT- or TBI-based MA regimen is most efficacious. RIC has also been shown to achieve durable long-term survival with a lower TRM (15-25%) and has been generally used for older patients. To attempt to compare these procedures an analysis of CLL patients undergoing first treatment for Leukemia Antigen (HLA)-matched sibling donor (MRD) HCT between 1995 and 2007 was performed, focusing on differences between: 1) MA vs. RIC transplants; and 2) CT- vs. TBI-based MA conditioning.

Among 297 patients, 163 MA vs. 134 RIC, significant differences in baseline characteristics included: Median age: source of stem cells; median donor age; use of antithymocyte globulin (ATG); graft versus host disease (GVHD) prophylaxis; and the year of transplantation. Multivariate analysis demonstrated that MA conditioning was associated with a higher incidence of acute GVHD (p = 0.002) and a higher TRM (p = 0.003), but a lower relapse rate (p = 0.005). Although there was no difference in survival before year 2000, after year 2000, MA conditioning was associated with reduced survival by almost 2-fold (p = 0.019). Among 163 patients who had MA conditioning, 110 were TBI-based and 53 were CT-based. Significant differences in baseline characteristics were: Rituximab at diagnosis, stem cells source, and the use of ATG (0 vs. 11%, p<0.001). As compared to the CT-based transplants those with TBI tended to be performed earlier with the majority being before year 2000 (p = 0.052). Although there were no significant differences between the groups regarding GVHD, neutrophil engraftment, relapse or survival, the CT-based conditioning group had higher TRM (p = 0.006) and treatment failure risk.

We conclude from this large retrospective comparison that RIC HCT from a MRD is effective in an older CLL population with superior survival and less TRM than that observed with MA conditioning. However, due to the higher relapse rate in the RIC group, future strategies to enhance the anti-leukemic effect are warranted. In the MA setting, TBI-based conditioning may be superior to a CT-based approach; however, recognizing the emerging efficacy of RIC HCT, a prospective comparison is unlikely to be performed.

234 PRECLINICAL MODEL TO PREDICT ANTI-LEUKEMIC ACTIVITY OF BUSULFAN AND IRRADIATION

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We tested the in vitro effect of physiologic doses of busulfan (Bu) and ionizing radiation (IR) to address whether additive antileukemic activity can be demonstrated in two leukemic cell lines, one sensitive (HL60) and one resistant (K562) to radiation. Cells were treated for 24 hours with Bu doses ranging from 0 to 200 μg/ml, or IR at 1.5, 3 or 6 Gy, or with Bu at 12.5 or 25 μg/ml for 24 hours, followed by IR at 1.5 or 3 Gy. Cells were then tested for proliferation, expression of annexin-V and caspase-3, and colony formation. Exposure to Bu or IR induced a variable but dose dependent inhibition of proliferation and colony formation in HLA-60 cells. On the contrary, we could observe a significant cytotoxic effect in K562 cells by using IR at 6, but not 1.5 or 3 Gy (p = 0.000). In addition, treatment with either Bu or IR caused apoptosis with increased caspase-3 expression in HL60 cells, but not in K562 cells. To test a possible synergistic effect of the combination of Bu and IR, we treated the cells with Bu for 24 hours followed by radiation. HL60 cells were strongly inhibited by both agents when separate or combined. In contrast, treatment of K562 cells with low dose IR (3Gy) alone inhibited colony formation by 28% and with low dose Bu by 77%. The inhibitory effect of low dose Bu + IR 3Gy increased up to 86%, suggesting that Bu could induce radio-resistant leukemic cells to become more radio-sensitive. In order to identify genes associated with a response to Bu, we formed a linear regression model controlled for cancer type using GI10 and Stanford cDNA array data from the NCI-60. 7 genes were identified: most strongly correlated with Bu response (p<0.001 and FDR ~0.5%). The most significant genes were then tested in the Affymetric U133 plus 2.0 platform. Our analysis identified six genes (ERC2, HCLS1, CD74, KCNH2, HLA DQB2, CD53) which are significantly associated with response to Bu (p<0.05). Our in vitro study demonstrated an additive effect of Bu and low dose IR even on radioresistant leukemic cells. The identification of a genomic signature for response to Bu validated by in vitro functional assays represents a novel approach for a personalized chemo-radiotherapy in patients with AML undergoing an allogeneic stem cell transplant.

235 TARGETING LEUKEMIA BY CD123 SPECIFIC Chimeric ANTIGEN RECEPTOR

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Chimeric antigen receptors (CARs) are employed to genetically modify T cells to redirect their specificity to target antigens on tumor cells. Typically a second generation CAR is derived by fusing an extracellular domain derived from the scFv of monoclonal anti-body (CAR) specific to targeted antigen with CD3ζ and CD28 en-dodomains. CD123 (IL3RA) is expressed on 45% to 95% of acute myelogenous leukemia (AML) and B-cell lineage acute lymphoblas-tic leukemia (B-ALL). Expression of CD123 is high in the leukemic stem cell (LSC) population, but not in normal hematopoietic stem cells. Thus, CD123 appears to be potential target for immunother-apy in leukemias through chimeric antigen receptor (CAR). We hypothesized that the generation of CD123 specific CAR can redirect the specificity of T cells to CD123 and this was tested by cloning the scFv of CD123 mAb in our CAR construct. The sleeping beauty system was used to express the CAR and DNA plasmids were electro-ported into peripheral blood mononuclear cells and cells were numerically expanded on artificial antigen presenting cells genetically modified to express co stimulatory molecules CD86, 4-IBBL, membrane-bound IL-15, and CD123 antigen in presence of IL-21 and IL-2. CAR+ T cells normally expanded to clinically relevant num-bers and showed antigen specific cytotoxicity in leukemic celllines. CAR+ T cells expressed both effector and memory markers showing the potential for in vivo persistence after T cell infusion. The bone-marrow homing receptor CXCR4 was expressed by CAR T cells shows the potential to target LSC that reside in BM niches. The preliminary data suggests that mirroring an approach we are using to manufacture clinical grade CD19 specific CAR+ T cells.

236 INCREASED ABILITY TO TRANSPLANT AND IMPROVED SURVIVAL IN PATIENTS WITH HIGH RISK ACUTE MYELOID LEUKEMIA (AML) AFTER INDUCTION WITH HIGH DOSE CYTARABINE AND MITOXANTRONE (HIDAC/MITO)

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Background: Patients with high risk AML have a poor prognosis and inferior outcomes after 7+3 induction. Complete remission (CR) rates range from 6-51% and induction death rates between 9-48%. We present a single institution experience in high risk AML patients treated with HIDAC/MITO induction regimen (Blood 2010; 116: 3290).

Methods: We have retrospectively analyzed the outcome of 43 patients with AML who received HIDAC/MITO induction at our institution from January 2009- September 2011. High risk features included at least one of the following such as age>60, high risk cytogenetics, high age adjusted Charlson comorbidity index (CCI) and non donor AML. Therapy related, antecedent hematological disorder or relapsed AML). The endpoints analysed were CR (marrow blasts <5%) at day 30, induction mortality within 30 days of induction, ability to proceed to transplant, number of days to transplant, overall survival (OS) and progression free survival (PFS) of transplanted vs non transplanted patients, calculated from day 1 of induction.

Patient characteristics: The median age was 67 years (47 - 83), median age adjusted CCI was 6 (4 - 12), 26 (60%) were males and 17