recommendation. This includes patients who received only one of a recommended tandem autologous HSCT, or who received an autologous rather than a recommended allogeneic procedure. But given the limitations of this analysis, we conclude that restrictions imposed by health insurance coverage lead to significant delays in implementing the treatment plan for patients who receive HSCT.

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MEASURING THE SYMPTOM BURDEN OF CHRONIC GRAFT VERSUS HOST DISEASE

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Significance: Chronic graft-versus-host disease (cGVHD) is an autoimmune-like reaction that causes debilitating symptoms following allogeneic hematopoietic stem cell transplantation (alloHSCT). The major barrier to good management of these symptoms is inadequate assessment. **Theoretical Framework:** Symptom burden is the combined impact of all symptoms on a person's ability to function as one did prior to onset of disease and therapy. **Problem and Purpose:** There is scant literature addressing the symptom burden of cGVHD. Symptoms are subjective phenomena and can only be accurately measured by patient report. The purposes of this research are to develop a short, easily understood, valid, and reliable patient questionnaire for measuring cGVHD symptom burden and to describe the symptom burden of cGHVD. This abstract reports preliminary results. **Methods:** The 13 core symptom items and 6 interference items of the M. D. Anderson Symptom Inventory (MDASI), rated on a scale of 0 to 10, are the base for the MDASI-GVH. In addition, 14 cGVHD-specific symptom items were generated from interviews with patients and the ratings of an expert panel. 128 patients with cGVHD and 64 patients post alloHSCT without cGVHD will complete the MDASI-GVH. Information on performance status, quality of life, and a repeat MDASI will be collected on patients with cGVHD. Psychometric analyses will reduce the number of items to the optimal set describing symptom burden, determine predictive and discriminant validity, and establish internal consistency and test-retest reliability. The symptom burden of cGVHD will be described through descriptive, correlational, cluster, and factor analyses. **Results:** To date, 31 patients with cGVHD and 7 without have completed the MDASI-GVH. Average age is 49.3 years and 50% are male. Symptom severity and interference is displayed in Table 1. Patients with cGVHD reported a unique cluster of severe symptoms that included skin problems, eye problems, muscle weakness, and joint stiffness. By February of 2008, we will report data on 45 patients with cGVHD and 20 patients without cGVHD. **Implications:** Patients with cGVHD tend to report more symptom severity and interference than patients post alloHSCT without cGVHD. The most severe symptoms patients with cGVHD report are cGVHD-specific. Further testing is ongoing, but the MDASI-GVH is an easily completed method of quantifying symptoms of cGVHD for clinician monitoring and use in trials testing methods to treat cGVHD.

Table 1. *Symptom Severity and Interference in Patients With and Without cGVHD*

	cGVHD		No cGVHD	
Item	**Mean**	**SD**	**Mean**	**SD**
Severity of 13 Core Symptoms	1.91	1.41	1.45	1.40
Severity of 14 cGVHD-Specific Symptoms	2.24	1.41	1.53	0.87
Severity of All Symptom	2.05	1.33	1.49	1.05
Symptom Interference	2.80	2.19	2.60	1.75

SD = standard deviation.

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LONG-TERM NEUROCOGNITIVE FUNCTION OF PEDIATRIC PATIENTS WITH SEVERE COMBINED IMMUNE DEFICIENCY (SCID): PRE AND POST HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT)

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Background: Hematopoietic stem cell transplantation (HSCT) is the only cure for patients with severe combined immunodeficiency (SCID). The purpose of this study is to evaluate long-term neurocognitive function of patients with SCID following myeloablative chemotherapy and HSCT. **Materials and Methods:** Sixteen pediatric patients diagnosed with SCID were tested using the Bayley Scales of Infant Development and the validated Vineland Adaptive Behavior Scales (VABS) pre- and 1-year post-HSCT. Three years post HSCT there were 11 patients available for testing and four patients were available 5 years post-HSCT. Patients greater than 3 years of age were administered the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). Both raw scores and scaled scores were analyzed. Data were analyzed using multiple regression analysis. **Results:** There was a significant decrease 1-year post-HSCT in the Bayley Mental Developmental Index (MDI) [92.5 (pre) vs. 70.8 (1 yr post); p=<0.0001] and the VABS [99.73 (pre) vs. 79.87 (1 year post), p= <0.0001]. There was no change in the Bayley Psychomotor Development Scale (PDI) [82.4 (pre) vs. 84.8 (1 year post), p = 0.68]. There was a significant decrease over time in the MDI [95.00 (pre) vs. 70.4 (1-year post) vs. 69.20 (3 yr post); p < 0.0001), but no significant change between 1- and 3-years post- HSCT]. The PDI scores decreased over time [86.29 (pre) vs. 86 (1-year post) vs. 74.14 (3-years post), p = 0.045]. Although there was a decrease in scaled scores, there was not a loss of skills. Analysis of raw scores showed that there was an increase in the raw test scores, which indicated that these children acquired developmental skills, but at a slower rate than normal infants and toddlers. **Conclusions:** These findings may reflect the effects of the isolation and prolonged hospitalization that characterizes the immediate post transplant period. Patients miss out on social interactions and learning opportunities that normally occur at their respective stages of development. These restrictions keep patients from acquiring developmentally appropriate cognitive skills as well as gross and fine motor developmental milestones. Longitudinal follow-up will be important to quantify acquisition of skills.

LEUKEMIA

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ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (Allo-HCT) FOR PHILADELPHIA CHROMOSOME POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIAS: IMPACT OF IMATINIB ON RISK OF RELAPSE AND SURVIVAL

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The utility of Imatinib use in either the pre-or-post-transplant period for Philadelphia positive (Ph+) Acute Lymphoblastic Leukemia (ALL) is unknown. Additionally, there have been concerns regarding Imatinib and cardiac toxicity (congestive heart failure) in some series. Therefore, we investigated the outcome of transplantation in patients with Ph+ ALL and treated with Imatinib. Thirty-two patients with Ph+ ALL received allo-HCT at the University of Minnesota between 1999 and 2006. The median age at HCT was 21.9 (range; 2.8–55.2) years. Eighteen (56.3%) patients were male. Twenty patients were in first remission (CR1) prior to HCT and 12-patients were in second remission (CR2). Donor source was HLA matched and mismatched unrelated umbilical cord blood (n = 17), HLA matched sibling bone marrow (n = 12) and HLA matched unrelated bone marrow (n = 3). All patients were conditioned with cyclophosphamide and total body irradiation. GVHD prophylaxis was with CSA/MTX (n = 15), CSA/MMF (n = 13) or CSA methylprednisone/ATG (n = 4). Of the 32 patients with Ph+ ALL, fifteen received Imatinib therapy pre/

post-HCT (10-pre-HCT and 5-post-HCT) comprising the Imatinib group and the remaining 17-patients, who either never received Imatinib (n = 13) or received it at time of relapse (n = 4), were the non-Imatinib group. Overall survival and relapse-free survival at 2 years was 73% and 65% for the Imatinib group compared to 34% and 35% for the non-Imatinib group (p = 0.14 and 0.1, respectively). However, the incidence of relapse for these two groups was 8% (95% CI: 0.00, 0.24) and 41% (95% CI: 0.17, 0.66), respectively (p = 0.02). Transplant related mortality at 2-years was similar between groups (27% and 24%; p = 0.81). Of note, cardiac toxicity [defined as a reduction in left ventricular ejection fraction of >20% below baseline, cardiac hypertrophy or EKG abnormalities (ST changes, T-wave abnormalities, ischemia and/or infarction)] was less in the Imatinib group, 23% (95% CI: 0.00, 0.49) versus 47% (95% CI: 0.22, 0.72) (p = 0.09). In conclusion, the use of Imatinib therapy in patients with Ph+ ALL in either the pre-or-post-HCT setting decreases the rate of relapse with a trend toward improved RFS and OS. Furthermore, Imatinib treated patients have no obvious increased risk of cardiac toxicity.

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GENERATION OF AUTOLOGOUS LEUKEMIA-REACTIVE CYTOLYTIC T CELLS (CTL) USING A NOVEL EXPANSION CULTURE SYSTEM: EFFECT OF ANTI-CTLA-4 VERSUS IL-2

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Background: Evidence supports a role for immunotherapy in acute myelogenous leukemia (AML). We previously reported a novel method to generate autologous AML-reactive CTL from the blood mononuclear cells (MNC) of pts with AML. The strategy employs differentiation of AML blasts into dendritic cells (DC) followed by expansion of autologous CTL. We further reported that inclusion of anti-CTLA-4 in the culture system between days 1–8 augmented the cytotoxicity and interferon-γ (IFN-γ) release of the expanded T cells (Cytotherapy 2006;8(1):3012). The purpose of the current studies was to investigate whether similar augmentation of T cell function could be achieved by low dose IL-2 during days 1–8 of culture. **Methods:** Primary AML peripheral blood or marrow MNC were cultured in 96 well plates for 7 days in AIM-V/RPMI-1640 with 10% AB serum, GM-CSF (50 ng/ml), IL-4 (1000 u/ml), and either anti-CTLA-4 (5 mcg/ml) or IL-2 (20 IU/ml) from days 1–8 of culture, followed by T cell expansion using OKT3 starting on day 14 and IL-2 (1000 U/ml) when T cells represented > 99% of all cells present, for up to 42 d. CTL activity was assessed by lysis of 51-Cr labeled autologous AML-blasts and by overnight generation of IFN-γ. **Results:** Using this system we previously showed (n = 18) that CD33+AML blasts decreased from 80 ± 28% preculture to <1% on d 35 while CD3+ T cells increased from 3% to > 99%. CTL produced 42 ± 23% lysis of autologous AML blasts at an Effector:Target (E:T) ratio = 20:1 and was blocked by anti-MHC class-I, but not MHC class II. CTL caused < 5% lysis of autologous PHA blasts and non-hematopoietic cells. Incubation of CTL with autologous AML blasts decreased colony growth >95% at E:T = 2:1 (n = 3). We now show, in cultures from 7 different AML patients that the mean IFN-γ generation using IL-2 during days 1–8 of culture was similar to that using anti-CTLA-4 (243 ± 244 pg/ml vs 254 ± 335; p = 0.9) and in 2 studies (12–24 replicates) that AML cell lysis using CTL generated with IL-2 was similar to that with anti-CTLA-4 (30 ± 13% vs 26 ± 12; p = 0.2). **Conclusion:** A novel AML culture method employing DC differentiation of AML cells followed by T cell expansion generated CTL that were highly reactive to autologous AML blasts. Inclusion of low dose IL-2 early during culture was equally as effective as anti-CTLA-4 in activating the CTL. This finding will facilitate the design and conduct of immunotherapy trials of autologous expanded CTL in patients with AML.

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MECHANISM OF BUSULFAN RESISTANCE OF MYELOID LEUKEMIA CELLS

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Busulfan (Bu) resistance is a major obstacle to hematopoietic stem cell transplantation (HSCT) of patients with myelogenous leukemia (CML and AML/MDS). To study cellular resistance phenomena we established two Bu-resistant leukemia cell lines that were phenotypically characterized. The CML B5/Bu250[6] cells are 4.5-fold more resistant to Bu than their parental B5 cells. The AML KBM3/Bu250[6] cells are 4.0-fold more Bu-resistant than KBM3 parental cells. We then used gene expression analysis to identify differentially expressed genes associated with Bu resistance. The results suggest that Bu resistance is multifactorial and includes constitutively up-regulated expression of genes involved in anti-apoptotis (*BCL-X_L*, *BCL2*, *BCL2L10*, *BAG3* and *IAP2/BIRC3*), stress response (*HSP90* and *STAT3*), busulfan metabolism (*GSTM*), and DNA repair (*PARP1*, *ATM* and *Ku70/80*). Furthermore, the Bu-resistant sublines evade Bu-mediated G2-arrest and caspase-dependent apoptosis. *GSTM3* is up-regulated in KBM3/Bu250[6] cells; its ectopic expression in the KBM3 parental cell line imparts partial resistance to Bu. Inhibitors of HSP90 activity, STAT3 phosphorylation and PARP1 functions were found to sensitize busulfan-resistant cells. The role of DNA break repair on Bu resistance is currently being investigated. Analysis of cells derived from patients classified as either clinically resistant or sensitive to high-dose Bu-based chemotherapy indicated alterations in gene expression that were analogous to those observed in the *in-vitro* model cell lines, confirming the clinical relevance of this model for mechanistic studies of cellular Bu resistance.

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LONG TERM REMISSION IN PHILADELPHIA-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (Ph+ ALL) PATIENTS AFTER ALLOGENEIC MYELOABLATIVE HEMATOPOIETIC CELL TRANSPLANTATION (HCT) USING MATCHED RELATED DONORS: THE 20 YEAR EXPERIENCE AT STANFORD UNIVERSITY AND CITY OF HOPE NATIONAL MEDICAL CENTER

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Due to the inherently poor prognoses of patients with Philadelphia-positive ALL, allogeneic HCT is offered early in their treatment course if a suitable donor is available. We report the 20 year experience from 1985 to 2005 at Stanford University and City of Hope National Medical Center in which 79 patients with matched related donors received a myeloablative conditioning regimen. The median age of all patients (pts) was 36 years (range 2–57 years). At the time of HCT, forty-nine pts (62%) were in first complete remission (CR1) and 30 pts (38%) were beyond CR1 (>CR1). The majority of pts (85%) received the conditioning regimen of fractionated total body irradiation (FTBI, dose = 1320 cGy) and high dose VP16 (60 mg/kg), 11 (14%) patients received FTBI/VP16/cyclophosphamide and one patient received the FTBI/V16/busulfan regimen (1%). The most commonly used graft vs host disease (GVHD) prophylaxis regimens were cyclosporine (CSA) and methotrexate (47%) and CSA/methotrexate/methylprednisolone (29%). The 10-year outcomes are listed in the table below. At diagnosis, forty percent of pts had chromosomal abnormalities in addition to t(9;22) but this was not found to affect survival outcomes. Pre-HCT factors that significantly affected event free survival (EFS) and overall survival (OS) were WBC at diagnosis (<30,000 vs ≥30,000) and disease status (CR1 vs >CR1). The development of grade 2–4 acute GVHD was an adverse factor for DFS and OS by both univariate and multivariate analysis. Factors significantly associated with increased nonrelapse mortality (NRM) were a history of radiation therapy prior to HCT for extramedullary disease and disease status with the >CR1 pts experiencing a significantly higher NRM. The inferior EFS and OS for the >CR1 pts was attributed to the higher NRM. The median time to relapse for the CR1 patients was 12 months (range, 1–27 months) and for the >1CR patients was 9 months (range, 3–19 months) indicating