Preliminary results from an IRB-approved prospective, open label, phase II trial to test the efficacy of montelukast, a leukotriene inhibitor, for the treatment of BOS after HSCT. BOS diagnostic criteria included: FEV1 < 75%, FEV1/VC < 0.7 or air trapping on CT and RV > 120% or RV/TLC > 120% in the absence of infection and presence of another cGVHD manifestation. Eleven patients have enrolled to date. One withdrew prior to medication initiation and 9/10 are currently on study medication (10 mg montelukast po nightly). Patient characteristics include age range 15-60 years, 7/11 female, baseline FEV1 range from 33 to 71% predicted, and 3/11 patients requiring oxygen supplementation. Sixty-four % (7/11) have reached the primary endpoint (6 months of study drug). FEV1 increased by 6-10% predicted in 3 patients, remained stable in 3, and declined by less than 15% in 1. Slope of the FEV1 value generated as linear regression of FEV1 volume vs. days post-transplant revealed: 5/7 increase in slope, 2/7 decrease in slope from pre-study FEV1 values. Three patients had immunosuppression reduced during this time period with complete cessation of tacrolimus in 1, cessation of steroids in 1, and decreased tacrolimus in 1(including 2 with stable FEV1) and patient in 1 with increase in FEV1); 1 patient had an increase in steroid dose less than 1 mg/kg/day. Two patients had worsening of other cGVHD manifestations on study, including a skin flare that resolved without increasing systemic therapy (1) and gastrointestinal cGVHD flare that improved with increased steroids including local therapy (1). Montelukast was well-tolerated with one grade II attributable adverse event (insomnia) during the six-month collection period. Improvements were also noted in oral mucosa cGVHD manifestations in 3/7 and liver in 2/7. These preliminary findings suggest that montelukast may have a role in the therapy of BOS after allogeneic HSCT.

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A PROSPECTIVE STUDY OF DONOR IMMUKNOW® AS A BIOMARKER FOR ACUTE GvHD IN HEMATOPOIETIC CELL TRANSPLANTATION RECIPIENTS
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Introduction: Graft versus host disease (GvHD) occurs in ~40% of allogeneic hematopoietic cell transplantation (HCT) recipients and is associated with substantial morbidity and mortality. Immunological parameters of donor cells that predispose a recipient to GvHD will be of great value. The Cylex™ ImmuKnow® assay determines the strength of immune function by quantifying the amount of ATP released from phytohemagglutinin-stimulated peripheral blood CD4+ cells. In our current study, we utilized the ImmuKnow® to assess whether a donor’s immune response correlates with early outcomes in recipients post-HCT.

Patients and Methods: Twenty-six (26) donor-recipient pairs were included in our study (15 HLA identical sibling HCT and 11 haploidentical HCT). Recipients received an average cell-dose of 10.7 ± 4.9 × 10^6 CD34+ cells/kg. Blood samples obtained prior to G-CSF mobilization and prior to cell collection (approximately 2 weeks apart) were assayed for ImmuKnow values and cell counts (WBC, ANC, ALC & CD34+ count).

Results: G-CSF mobilization led to a significant increase in ImmuKnow® ATP values from 342 to 728 ng/mL (p < 0.001) along with an increase in all measured cell counts. Grade ≥ II acute GvHD occurred in 27% of haploidentical HCT recipients (3/11 patients) and 20% of HLA identical HCT recipients (3/15 patients). In haploidentical HCT, mobilized donor blood ImmuKnow® ATP values did not correlate with GvHD. However, donor ImmuKnow® values correlated with increased risk of acute GvHD in HLA identical sibling HCT. In HLA identical sibling HCT, ATP values in excess of 747 ng/mL predicted grade II or higher GvHD with a likelihood ratio of 4.00 (2.9-5.9, 95% confidence), sensitivity of 100%, and specificity of 75% (AUC = 0.889; p = 0.003).

Conclusions: If confirmed in larger studies, these data suggest that ImmuKnow can serve as an independent predictor/biomarker for the development of GvHD in HLA identical HCT.

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MYCOPHENOLATE MOFETIL AS THERAPY FOR STEROID DEPENDENT OR REFRACTORY GRAFT VERSUS HOST DISEASE: TEN YEARS EXPERIENCE FROM A SINGLE CENTER IN BRAZIL

Chronic graft-versus-Host-Disease (GvHD) is observed in up to 50% of long term survivors of hematopoietic stem cell transplants (HSCT) and is associated to important morbidity and mortality. Mycophenolate Mofetil (MMF) has been used as therapy for refractory chronic GvHD with good efficacy and tolerability. We describe our experience at Hospital de Clínicas of Federal University of Paraná-Brazil during the last ten years on the use of this drug as rescue for refractory chronic GVHD.
We retrospectively analysed 22 patients (10 females e 12 males) who received HSCT between 01/1999 and 01/2009 and developed as complication chronic GVHD steroid refractory or dependent and who received MMF as second line therapy. Diagnosis: Fanconi Anemia (8); Chronic Myeloid Leukemia(3); Others(9). Cell source was marrow in 16, peripheral blood (pb) in 3, and cord blood in 3 patients. Eight patients received HSCT from related and 14 from unrelated donors. Immunophylaxis was: CSA e methotrexate (MTX) (15); CSA e CTC(2); CSA, MTX and methylprednisolone (5). All patients had extensive chronic GVHD. As we reclassified them according to the NIH consensus criteria, 15 (68%) of them had severe disease and 7 (32%) had moderate disease. Thirteen (59%) had progressive, 8 (36%) had "de novo" and 1 (5%) quiescent GVHD. Liver, oral mucosa and skin were the sites most frequently involved. Nine patients had more than 3 organs involved, 6 were using steroids at the time of diagnosis and 5 had thrombocytopenia lower than 100.000/mm3. Overall response defined by improvement in at least one organ or stabilization of GVHD was observed in 15 (68%) patients. Eleven patients (50%) stopped steroids after a median of 16.5 months. Eight patients (36%) stopped all immunosuppression in a median time of 43 months. Four patients died for reasons related to their GVHD and 3 others received another drug for failure with MMF. We did not observe grade 2-4 toxicity leading to suspension of the drug.

In conclusion MMF was a safe drug as therapy for chronic steroid dependent or refractory GVHD with an overall response of 68% in this population. Prospective trials are necessary for a better evaluation of the efficacy of this drug as second line therapy for chronic graft-versus-host-disease.

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EXTRACORPOREAL PHOTOPHERESIS IN REFRACTORY ACUTE AND/OR CHRONIC GRAFT VERSUS HOST DISEASE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Introduction: Graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation (HSCT) is associated with high morbidity and mortality rates. Corticosteroids and calcineurin inhibitors are the first line treatment of GVHD. There are many second line therapies with few controlled studies. Extracorporeal Photopheresis (ECP) is an immunomodulatory treatment which has recently been proof as steroid sparing procedure (Flowers et al, Blood. 2008 Oct 1;112(7):2667-74)

Objective: We describe our experience at the Hospital de Clinicas from the Federal University of Parana- Brazil, with ECP in patients with steroid refractory or dependent acute or chronic GVHD.

Patients and Methods: We reviewed between February 2002 and June, 2009, the data of 19 patients who received allogeneic hematopoietic stem cell transplantation (HSCT) and developed as complication acute and/or chronic GVHD refractory to corticosteroids and cyclosporine therapy and were then treated with ECP (20 procedures: one patient had been submitted twice). Four patients were excluded because they had received less than six sessions; fifteen patients were evaluated (female:13 male:2). The mean age at HSCT was 11 years (range 3 to 49).
Partial response was defined by an improvement in at least one involved organ and complete response as resolution of all symptoms of GVHD. The clinical characteristics of these patients are in Table 1.

Results: Median overall survival after HSCT was 2 years (range 3 m-13y). Five patients were submitted to ECP due to acute GVHD and 13 due to chronic GVHD (2 patients had overlap syndrom GVHD).Three of 5 patients with acute GVHD (60%) had total response, 1 (20%) partial response and 1 (20%) had no response. Nine of 13 patients with chronic GVHD (70%) had partial response, 2 (15%) total response and 2 (15%) had no response. Ten patients (67%) reduced the dosage of corticosteroid to less than 0.5 mg/kg/d. There were no severe adverse effects related to ECP.

Conclusion: ECP is an effective alternative in the treatment of GVHD in this study, with no severe adverse effects observed. The procedure allowed reduction of corticosteroids in 67% of our patients. Prospective trials are necessary for a more precise evaluation of this procedure in GVHD therapy.

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SOLUBLE HUMAN LEUKOCYTE ANTIGEN G (SHLA-G) IN HEMATOPOIETIC CELL TRANSPLANTATION IS ASSOCIATED WITH SEVERAL CLINICAL COMPLICATIONS AFTER TRANSPLANT
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HLA-G is a non classical class I HLA molecule with low level of polymorphisms and with 7 isoforms, 4 are membrane bound and 3 are soluble. Another differential characteristic is it is tissue restricted and have been described in adult thymic medulla, cornea, pancreatic islet and endothelial cell precursors. Several immune modulatory functions have been attributed to this molecule such as the interaction between B, T, NK and antigen presenting cells. Due to their immunomodulatory properties we investigated the possible role of soluble HLA-G (sHLA-G) in the allogeneic hematopoietic cell transplantation (HCT) setting. A cohort of 37 patients, who underwent HCT, were studied, 13 patients had acute myeloid leukemia, 8 patients had myelodysplastic syndromes (preleukemia disease) while the rest of the patients had non myeloid malignancies. Twenty eight patients received reduce intensity conditioning regimen, while the rest of the patients received myeloablative conditioning treatment. Plasma samples from all patients were obtained before the conditioning regimen and after transplant at different timepoints. Soluble HLA-G concentration was measured in duplicates of plasmas by a specific enzyme-linked immunosorbent assay (ELISA) using the MEMG/9 as the capture antibody. Pre transplant variables were age, gender, disease, type of transplant (related, unrelated), infused marrow cell dose and donor gender. Post transplantation variables