Table 1. Summary of aGVHD severity and treatment response (N=49)

	Budesonide Single Agent (N=20)	Systemic Corticosteroids (N=25)	No Therapy or Topical Steroids (N=4)	Total (N=49)
N (%) Organs Involved				
Skin Alone	-	5 (20%)	3 (75%)	8 (16%)
GI Alone	9 (45%)	2 (8%)	-	11 (23%)
Liver Alone	-	1 (4%)	1 (25%)	2 (4%)
Skin/GI	9 (45%)	10 (40%)	-	19 (39%)
GI/Liver	1 (5%)	3 (12%)	-	4 (8%)
Skin/GI/Liver	1 (5%)	5 (20%)	-	5 (10%)
N (%) Grade aGVHD				
II	20 (100%)	5 (20%)	3 (75%)	28 (57%)
III	-	15 (60%)	1 (25%)	16 (33%)
IV	-	5 (20%)	-	5 (10%)
N (%) Day 28 Treatment Response				
CR/PR	7(35%)/9(45%)	8(32%)/12(48%)	3(75%)/1(25%)	40 (82%)
⟨PR	4 (20%)	5 (20%)	-	9 (18%)
N (%) Day 56 Treatment Response				
CR/PR	10(50%)/7(35%)	7(28%)/13(52%)	4 (100%)/ 0	41 (84%)
⟨PR	3 (15%)	5 (20%)	-	8 (16%)

inhibitor and mycophenolate mofetil. Forty-nine patients developed grade II-IV aGVHD by day 100 for a cumulative incidence of 50% (95%CI:40-60) grade II-IV and 26% (95%CI:16-35) grade III-IV, respectively. The median time of aGVHD onset was 39 days (range 14-99). Organs most commonly affected were skin/ GI (39%), GI alone (23%), and skin alone (16%). Single agent budesonide was used for the treatment of 20 patients with initial grade II GI aGVHD (Table 1). Complete or partial responses (CR/PR) were observed by day 28 in the majority (n = 16, 80%), which were maintained at day 56. Notably, only 3 of 20 budesonide patients required salvage with systemic corticosteroids (2 responded, 1 progressed). Twenty-five patients with predominantly grade III-IV aGVHD received systemic corticosteroids from the outset of therapy (Table 1). CR or PR was obtained in 80% by day 56. With a median follow-up of 24 months (range 4.5-60.5), the 1-year cumulative incidence of ongoing late acute or chronic GVHD was 35% (95%CI:26-45), and the 1-year progression-free survival is 65% (95%CI:56-75). Seven patients have died of GVHD, 2 patients initially treated with budesonide, and 5 with systemic corticosteroids. We conclude that double unit CBT is associated with a significant incidence of grade II-IV aGVHD and new strategies for prophylaxis are warranted. However, a significant number of patients with grade II GI aGVHD can be treated successfully with budesonide alone, and this approach warrants prospective investigation. Finally, new therapies are needed for CBT recipients with more severe aGVHD.

530

WEEKLY BORTEZOMIB FOR THE TREATMENT OF STEROID REFRACTORY CHRONIC GRAFT-VERSUS-HOST DISEASE (CGVHD)

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cGVHD is the most serious and common long-term complication of this allogeneic transplantation, occurring in 30-70% of patients surviving more than 100 days. cGVHD is associated with a high degree of morbidity and mortality and remains a major cause of late death. Initial therapy involves systemic corticosteroids which can contribute to further complications. In cases where steroids are ineffective or poorly tolerated, effective therapeutic options are limited. Anecdotal reports of myeloma patients treated with bortezomib after transplantation have shown improvement in cGVHD.

We have begun a trial of bortezomib in patients with steroid-refractory cGVHD. Patients receive 1.6 mg/m^2 q wk x 4 followed by one week of rest, for up to six cycles. To date 9 patients have been entered on trial and 5 have completed between 2 and 4 cycles. The treatment has been well tolerated with no grade 3 or higher adverse events (AE). AE have been grade 1-2 nausea (3), grade 1-2 diarrhea (6) grade 1-2 fatigue (4), one grade 2 transient neuropathy has been reported. There have been 3 treatment delays (1 patient) and dose reduction due to decreased hemoglobin and one due to transient neuropathy.

Subjective improvement has reported in 6 of the first 8 patients, Improvement in general well-being has been noted as early as the first treatment. Two patients have had improvement in severe long standing sclerotic changes, including the ability to extend fingers that had long been contracted. Average Rodnan scores on 5 patients with sclerosis completing 2 or more cycles of therapy decreased from (31±9.6 to 13.8±7.5) One patient with non-healing suppurating lesions of his lower extremities has shown marked healing, another has significant decrease in chronic diarrhea.

Weekly bortezomib for cGVHD appears to be well tolerated and results in early improvement in long standing refractory disease. Our plan is to enroll twenty-five patients to determine if these encouraging findings are sustainable.

531

A SURVEY OF CHRONIC GVHD AND OTHER OUTCOMES – A SNAPSHOT OF BRAZILIAN ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) CENTERS

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Background: The great variability in the diagnosis of chronic GVHD and the long period required to complete clinical trials

due to slow patient accrual are, in part, responsible for the slow progress in this area. Participation of international centers in multicenter clinical trials is needed. Towards this effort, a Brazil-Seattle chronic GVHD consortium was established to conduct collaborative studies, which included a survey of chronic GVHD after allogeneic hematopoietic cell transplantation (allo-HCT) performed in Brazil.

Method: Thirty-six transplant services registered with the Brazilian Society of Bone Marrow Transplantation were invited to participate in a web-based survey containing 36 questions about routines and major outcomes of allo-HCTs performed in 2008.

Results: Seventeen (47%) centers performed allo-HCTs in 2008 and completed the survey between May and September 2010. The 17 responding centers have been performing allogeneic transplants for a median of 16 (range, 7-31) years. Among the 17 centers, the median number of allogeneic transplants reported in 2008 was 21 (range, 5-116), of which 91% were from a related donor. The median number of adult allo-HCTs was 16 (range, 2-84) and the median numbers of pediatric allo-HCTs was 3 (range, 0-51). Of the reported 510 allo-HCTs in 2008, near 60% were performed at four centers. For classification of chronic GVHD, 50% reported using the NIH criteria, 37% the Seattle revised classification and 12% both criteria. Eighty-eight percent of the centers reported performing chronic GVHD screening evaluation between days 80 -100 after HCT. Three centers reported seeing > 12 new cases of chronic GVHD in one year, 5 reported seeing 6-12 patients, and 9 centers reported seeing < 6 new cases. The overall disease-free survival (DFS) rates at 100 days were > 75% (7 centers), 50-75% (9 centers) and 26-50% (1 center). The overall DFS at 1-year was 50-75% as reported by 13 centers and was 26-50% as reported by 4 centers. The table summarizes the types of primary and secondary treatments reported for chronic GVHD.

Conclusion: The variability in diagnosis and treatment of chronic GVHD in Brazilian Centers is similar to that previously reported by American and European centers. The Brazil-Seattle chronic GVHD consortium network exemplifies the feasibility of collaborative research across the international borders of Western hemisphere and offers new opportunities for future collaborative studies.

Table 1. Chronic GVHD therapy reported

Therapy	First Line (%*)	Second Line (%*)
Steroid 1mg/kg/day	100	19
Cyclosporine	75	44
Tacrolimus	25	31
Mycophenolate mofetil	-	94
PUVA	-	62
ECP (photopheresis)	-	44
Thalidomide	-	44
Azathioprine	-	25
Sirolimus	-	12
Anti-CD20 antibody	-	12

*Frequency of therapy prescribed.

532

GENITAL GRAFT VERSUS HOST DISEASE: ACUTE VERSUS EARLY ONSET CHRONIC DISEASE

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Background: While genital chronic graft versus host disease (cGVHD) has become better characterized, genital acute GVHD (aGVHD), a rarer entity, remains poorly understood.

Objective: To describe genital aGVHD in a cohort with genital GVHD.

Methods: A cohort of 68 women were diagnosed with genital GVHD. Among these 68, some with gynecologic symptoms were assessed within 100 days post-transplant as part of transplantation protocols. We evaluated time from hematopoietic cell transplant (HCT), other GVHD manifestations, gynecologic history, vulvar/vaginal findings, clinical course and treatment to better characterize genital aGVHD.

Results: Of 68 patients, 6 were diagnosed with genital GVHD prior to 100 days post-HCT (median 79: range 14-92). Of these 6 patients, 4 were diagnosed with aGVHD involving the skin (2) or skin and gastrointestinal tract (2) prior to diagnosis of genital aGVHD (median 29.5: range 6-54 days). One other patient presented with genital aGVHD the day before skin aGVHD was diagnosed. Only 1 genital aGVHD patient had no other tissue site of involvement. Only 1 patient had an early donor lymphocyte infusion, which was administered at 42 days post-HCT; this patient was diagnosed with genital aGVHD at 92 days post-HCT. 5 of 6 patients (83.3%) had Grade II genital GVHD at presentation (as defined by Stratton et al 2009), while one patient presented with Grade I disease. These Grade II patients were treated with topical clobetasol or topical tacrolimus. Of these 5 treated patients, 4 returned for follow-up care. Over a one-year observation interval, one patient had a complete response, one patient had a partial response, and two patients progressed from Grade II to Grade III disease. One patient with vaginal synechiae was treated with an estradiol vaginal ring, with complete response observed.

Conclusions: Our findings indicate that genital GVHD can occur before 100 days after allogeneic HCT. Considering that 5 of 6 (83%) affected patients in this series had acute GVHD of other organ systems, gynecologic issues should be included in the GVHD evaluation of female transplant patients. Finally, because genital aGVHD was, in general, amenable to topical treatments, our findings offer hope that with appropriate diagnosis and intervention, genital aGVHD can be effectively treated to improve the quality of life of female transplant survivors.

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533

A PILOT STUDY OF PHARMACOKINETICS-BASED MYCOPHENOLATE MOFETIL DOSING FOR ACUTE GRAFT-VERSUS-HOST-DISEASE PROPHYLAXIS

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Mycophenolate mofetil (MMF) is an ester prodrug of mycophenolic acid (MPA) which has been used successfully in the prevention and treatment of acute graft-versus-host-disease (aGVHD). Previous pharmacokinetics (PK) studies have shown low MPA exposure in BMT recipients, especially in the period following conditioning therapy, which is associated with inferior transplant outcomes. Multiple strategies, including empiric fixed-dose-escalation or higher dose per kg body weight, have failed to achieve consistent target MPA exposure. Attempts at giving MMF as short-infusion doses have been unsuccessful in maintaining desired trough concentrations (Ctrough) of MPA, especially in pediatric BMT patients. We hypothesized that a PK-based dosing strategy using a novel continuous infusion of MMF will be able to achieve and maintain target MPA exposure. The primary aim of this pilot study is to evaluate the safety and feasibility of this approach.

Continuous infusion MMF was evaluated in 5 pediatric patients undergoing unrelated donor myeloablative transplant between July, 2009 and June, 2010. Mean age was 8.5 y (2-17 y) (4 F, 1 M). Patient diagnoses were MDS (2), ALL in CR2, Kostmann syndrome, and congenital erythropoietic porphyria. Three patients received MMF for GVHD prophylaxis and two for treatment of severe aGVHD. In all cases, total MPA Ctrough levels remained < 1 mcg/mL with intermittent IV dosing (15 mg/kg/dose q8 hourly). PK measurements on this schedule were used to estimate MPA clearance in order to predict the rate of a continuous infusion to maintain total MPA steady-state concentrations (Css) between 2.5-5 mcg/mL. Rates of infusion used ranged