despite persistently elevated plasma BAFF levels. High BAFF to B cell ratios are associated with increased proportions of activated peripheral B cells. B cell reconstitution occurs during constant exposure to allo- and neo-autoantigens after HSCT. We hypothesize that failure to delete these potentially pathologic cells in cGVHD is due to BAFF signaling. We recently found that B cells from patients with active cGVHD have decreased pro-apoptotic Bim (Wooten et al ASH 2010, Abstract 216). BAFF is known to enhance B cell survival by counteracting pro-apoptotic Bim, but upstream BAFF-driven survival signaling in cGVHD (and other diseases) remains undetermined. HSCT patients who were >12 months post-HSCT, not receiving high dose steroid, with or without active cGVHD were studied. We first examined apoptotic rates by flow cytometric analysis of 14 freshly isolated (to >95% CD19+ purity) B cell samples cultured over time. Patients with active cGVHD (n = 4) had significantly decreased apoptosis at 48 hours, compared to either patients who had never developed disease (n = 5) or to healthy controls (n = 5) ($p < 0.005$). While BAFF-driven B cell survival can be modulated by altered expression of apoptotic factors, it can also be affected by cellular metabolic fitness. To examine B cell metabolic fitness we measured cellular protein content in freshly purified B cells from 28 HSCT patients. Significantly increased B cell protein content was found in active cGVHD patients (n = 10) compared to patients who never developed disease (n = 7) ($p<0.005$). Increased protein content was also found in patients who had inactive disease (n = 11) although this did not reach statistical significance. Since BAFF is known to induce metabolic fitness via phosphorylation of AKT in murine B cells, we examined AKT activation by immunoblotting freshly isolated B cell lysates from 18 HSCT patients. B cells from patients with active cGVHD (n = 8) had significantly increased phosphorylated AKT (pS743 normalized to total AKT) compared to patients with inactive disease (n = 7) ($p<0.005$). By contrast, no difference in Erk phosphorylation was found between groups. Our study reveals that B cells in cGVHD have increased survival due to increased AKT pathway driven metabolic fitness. Thus, we provide rationale for study of small molecule inhibitors of the AKT pathway in cGVHD patients.

Table. B cells from patients with cGVHD have increased cellular protein content and AKT activation

cGVHD Group	Cellular Protein Content (μg protein / 1 x 10^6 cells) Mean +/- SE	One-way ANOVA, versus No	Normalized pAKT (pS743 / AKT) Mean +/- SE	One-way ANOVA, versus Inactive
No	35.4 +/- 5.4, n = 7	-	0.16 +/- 0.09, n = 3	NS
Inactive	56.9 +/- 5.2, n = 11	NS	0.05 +/- 0.02, n = 7	-
Active	75.8 +/- 9, n = 10	p < 0.005	0.63 +/- 0.15, n = 8	p < 0.005

NS; Not significant.

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PHASE II PILOT STUDY OF IMATINIB MESYLATE FOR THE TREATMENT OF SEVERE SCLEROTIC SKIN CHRONIC GRAFT VERSUS HOST DISEASE (ScGVHD)

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Background: ScGVHD is characterized by progressive fibrosis of the dermis and subcutis and develops in 4-13% of patients with cGVHD. The clinical risk factors and mechanisms responsible for ScGVHD remain unclear; however, the profibrogenic platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) signaling pathways have been implicated. Imatinib mesylate is a tyrosine kinase inhibitor that has activity against both PDGFR and TGF-β as well as a well-established safety profile for the treatment of chronic myelogenous leukemia.

Methods: Eligible patients had ScGVHD limiting range-of-motion (ROM) of at least 1 joint by >25%. Initially, patients were given 400mg (pediatric 260mg/m2) imatinib daily (cohort 1), with dose reduction allowed for toxicity. Due to a high incidence of adverse effects (AEs) and subsequent dose reduction, the study was amended to start 100mg with escalation to 200mg daily at 1 month. The 6 month primary endpoint was based on percent improvement of the deficit compared to baseline at 1-3 target joints: partial response (PR) = increase of >25%; progressive disease (PD) = decrease of >25%, or >1 steroid pulse per 3-month period; stable disease (SD) = all other. Secondary endpoints included toxicity; multi-modality skin assessments (MRI, skin score, and patient-reported measures); quality of life and functional measures; steady state serum drug concentrations (cohort 2); and response of other cGVHD-affected organs.

Results: Twenty patients were enrolled (8 cohort 1, 12 cohort 2). Two patients had PD; 5 PR; 7 SD; and 6 were non-evaluable (Table 1). Of 11/14 (78.6%) patients with any ROM improvement, the average gain in ROM was 31%. No significant improvement was seen in other cGVHD manifestations. Frequent AEs included hypophosphatemia, GI upset, fatigue, muscle cramping and pain. Other clinically significant AEs were tinnitus (n = 4) and pulmonary edema requiring hospitalization (n = 2). Steady state serum concentrations in cohort 2 (200mg daily) ranged from 592-2255ng/mL (mean 1157ng/mL), which is within the inhibitory range of imatinib on PDGFR.

Table 1. Patient Responses

Patient Number	Age	Gender	Time from cGVHD Dx (mos)	Baseline ROM % predicted	% change in deficit from baseline at 6 mos	Response	Final Dose
1	56	Male	48.5	37%	Off-withdrawal	N/A	N/A
2	60	Male	48.2	56%	94%	PR	300mg
3	10	Female	39.1	73%	Off- 3 mos PD	PD	N/A
4	52	Female	28.9	7%	Off- toxicity	N/A	N/A
5	30	Male	87.0	34%	Off - withdrawal	N/A	N/A
6	51	Male	88.1	47%	Off - withdrawal	N/A	N/A
7	55	Female	42.5	61%	35%	PR	200 mg
8	58	Male	39.1	35%	16%	SD	200 mg
9	60	Male	79.4	42%	Off - withdrawal	N/A	N/A
10	53	Male	20.3	-7%	21%	SD	200 mg
11	28	Female	15.8	56%	Off - cancer relapse	N/A	N/A
12	56	Male	80.3	37%	16%	SD	100 mg
13	34	Female	21.4	27%	61%	PR	200 mg
14	46	Male	40.6	32%	27%	PR	200 mg
15	55	Male	33.5	22%	22%	SD	200 mg
16	55	Male	4.8	71%	3%	SD	200 mg
17	7	Female	25.4	64%	-25%	SD	100 mg (peds)
18	21	Male	58.9	54%	-2%	SD	200 mg
19	48	Male	112.9	33%	31%	PR	200 mg
20	18	Male	35.0	-5%	15%	SD	200 mg

cGVHD = chronic graft versus host disease, Dx = diagnosis, mo = month, ROM = range of motion, PD = progressive disease, PR = partial response, SD = stable disease, N/A = not assessed.

Conclusions: Treatment with imatinib mesylate for 6 months led to improved ROM in most patients. This data suggests that low-dose imatinib therapy has efficacy for ScGVHD; however, despite serum drug concentrations in the expected range for the doses prescribed, tolerability was a significant limitation for the use of imatinib mesylate in patients with ScGVHD.

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TARGETED JANUS KINASE-2 INHIBITION OVERCOMES LIMITATIONS OF IL6-RECEPTOR-ALPHA BLOCKADE IN CONTROLLING HUMAN DC-STIMULATED ALLOREACTIVITY

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Graft-versus-host disease (GvHD) is a serious challenge to the success of hematopoietic stem cell transplantation. The cytokine