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We previously reported that the maximum tolerated dose (MTD) of NLT for cGvHD was 200 mg daily for 16 subjects treated according to a standard 3+3 dose escalation schema (Chen et al, Blood 2011 118: Abstract 1986). We present new efficacy data and update prior safety and pharmacokinetic data in 28 subjects.

Methods: All subjects had extensive steroid dependent/refractory cGvHD previously treated with ≥ 2 agents. Glucocorticoid (GC) refractory was defined as progressive cGVHD despite prednisone ≥ 0.5 mg/kg/d for ≥ 1 month; steroid dependence was cGvHD requiring prednisone ≥0.25 mg/kg/d for ≥ 3 months. GCs and two other immunosuppressants were allowed. Prior imatinib use was allowed. GCs were tapered as tolerated and other immunosuppressant dosing remained constant. Safety was determined by observation of CTCAE v. 4.0 graded adverse events (AEs). Trough plasma NLT concentrations were determined by LC/MS before the daytime day 8 dose. Clinical activity of NLT was indicated by change in NIH composite skin (Δ ≥1) and Lee symptom skin scores (improvement Δ ≥13, worsening Δ ≥-20).

Results: Median (range) follow-up was 153 (19-581) days. Median age (range) was 50.3 (24.5-76.4) years. Mean time (range) to study enrollment from transplant was 3.8 (1.5-13.3) years and from cGvHD diagnosis 3.4 (0.3-12.6) years. The Table shows grade 2-3 AEs possibly or probably attributed to NLT. So far no grade 4-5 AEs attributed to NLT have occurred. Median trough concentration of NLT 1 week after drug initiation at the MTD (n=23) was 761 nM (range 120-2290 nM). 26 subjects were evaluable for response. 6 remain on drug. 20 were removed from the study for progressive disease (7), toxicity (7), withdrawal of consent (5), and progression of underlying malignancy (1). Skin disease responses could be evaluated in 19 subjects. NIH composite skin score was improved in 4, unchanged in 14, and worsened in 1. Lee symptom skin score was improved in 6 and unchanged in 13. Among the 7 subjects with progressive cGvHD, NIH composite or Lee symptom skin score was unchanged or worsened in 5, improved in 1, and unevaluable in 1.

Conclusions: Skin improvement in some patients suggests that NLT 200 mg daily may have clinical activity. Median trough concentrations that exceeded the IC50s for PDGFRA, DDR1, DDR2, ABL, and KIT but not NQO2 support this. 200 mg daily, however, is associated with significant toxicity. Lower daily doses or alternate day dosing may continue to generate disease responses while improving tolerability and should be explored.

Adverse Event	Grade 2 (n=28)	Grade 3 (n=28)
Arterial injury	1	
Decreased joint flexion	1	1
Dehydration	1	
LFT elevation	2	1
Hyponatremia		1
Hypophosphatemia (1 Φ)	6	3
Increased lipase (3 Φ)	2	2
Influenza B		1
Muscle cramping	1	1
Neutropenia (afebrile)	1	1
Pneumocystis carinii pneumonia (1 Φ)		1
Prolonged QTc	1	
Shingles	1	1
Suspected fungal pneumonia	1	
URI		1
Worsening Fatigue Φ DLT	2	

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Improved Survival of Patients (Pts) with Acute Graft-Versus-Host Disease (aGVHD) During Recent Years: Impact of Donor and Recipient Characteristics

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Background: Based on our clinical impression, pts with grade 3-4 aGVHD have had improved survival in recent years. In order to explore this observed trend, we evaluated factors associated with outcome in these pts.

Methods: Pts who had an allogeneic stem cell transplant (SCT) and who were evaluable for aGVHD by Glucksberg criteria were included, with SCT segregated into the following time periods (pds): 1990-1994, 1995-1999, 2000-2004, and 2005-2011. Pts undergoing cord or haplo-identical SCT were excluded. We evaluated the impact of variables of interest and time pd of SCT on overall survival (OS), defined as time from SCT to death, using univariate and multivariate analyses.

Results: 959 pts were included (See Table), and 62.5% had peripheral blood (PB) grafts. Of the 388 unrelated SCT's, 56% received anti-thymocyte globulin (ATG). Thirty-seven percent of all pts had reduced-intensity conditioning, and 91% were complete HLA matches. Median recipient age was 47 years (range: 18 − 75), but age increased with time pd of SCT (See Table; $P < .0001$). Use of a male donor also increased with time ($P < .0001$). Grade 3-4 aGVHD incidence was 16.6% and significantly differed by time pd (See Table;$P = .028$). It occurred in 17.6% of pts receiving ATG, compared to 28.7% of those who did not receive ATG ($P = .005$). After including time pd and other donor- and graft-related covariates, only ATG administration was a significant predictor for decreased grade 3-4 aGVHD ($P = .026$). Use of PB graft approached significance ($P = .053$). 568 pts have died, and median follow-up is 49 months (range: 3 to 253) in living pts. Median OS for pts with grade 3-4 aGVHD is 5.0 months, compared to 36.2 and 34.8 months for pts with grade 2 and grade 0-1 aGVHD, respectively ($P < .0001$). Among pts with grade 3-4 aGVHD, median OS is improved with more recent SCT (See Table;$P = .018$). Having a male donor ($P = .0018$) and a PB graft (0.017) are also associated with improved OS in univariate analyses,

Table

	1990-1994	1995-1999	2000-2004	2005-2011	All periods
# of Patients	122	173	207	457	959
Median Age	35	43	46	52	47
Percent male donors	57	52	57	72	63
Incidence Grade 3-4 GVHD (%)	18	23.1	17.4	13.3	16.6
Median OS, mo	19.6	25.5	11.0	37.9	22.3
Median OS, mo (pts with Gr 3-4 GVHD)	3.7	5.7	3.5	8.8	5.0

while related vs. unrelated donor, complete HLA match, ATG use, and recipient age are not. Multivariable analysis was challenging given the correlation among covariates. However, male donor is significantly associated with improved OS for pts with grade 3-4 aGVHD in all models, while time pd is not significant when adjusting for other factors.

Conclusions: While OS for pts with grade 3-4 aGVHD has improved, it continues to impact >13% of pts and has poor outcomes. The use of a male donor may predict improved OS for pts with grade 3-4 aGVHD independent of time pd. Additional study is warranted to validate these findings and improve therapies.

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Ethnic Variation in Chronic Graft-Versus-Host Disease (cGVHD) Manifestations

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Risk of acute GVHD varies among different ethnic population. Thus, we evaluated potential differences in cGVHD manifestations in two ethnic distinct cohorts. The study included a Brazilian cohort diagnosed with cGVHD by 2005 NIH criteria who were enrolled in a prospective multicenter longitudinal study at 5 centers in Brazil and compared with a North American cohort reported by the cGVHD consortium (Arai S. et al. *Blood* 2011). Pts. were assessed using standardized clinical data forms every 3 months (124 visits). Any elevation of liver function tests was scored as cGVHD. The Brazilian study cohort included 36 pts. with a median age of 44 (13-64) years and 21 (58%) were male. At study enrollment, 24 (67%) had classic cGVHD, and 12 (33%) pts. had overlap subtype (with feature of both acute and chronic). Distribution of organ involvement attributed to cGVHD for the Brazilian and the North American cohorts at study enrollment is shown in the Figure. Liver severity scores at study enrollment was mild in 10 (34%), moderate in 12 (40%) and severe in 8 (26%) pts. among Brazilian cohort, and it was mild in 113 (76%), moderated in 36 (24%) and none severe in the North American cohort. Overall, cGVHD global severity at study enrollment was calculated from reported data as mild in 2 (5.5%), moderate in 17 (47%) and severe in 17 (47%) of Brazilian cohort compared to 32 (10%), 175 (59%) and 91(31%) in the North American cohort, respectively. Similar to North American cohort, distribution of global severity was similar in the Brazilian cohort across 22 incident (enrollment < 3 months of cGVHD diagnosis) and 14 prevalent cases (enrollment 3 or 6 months after cGVHD diagnosis) and, between pts. with classic and overlap cGVHD. Prevalence of organs involvement at study enrollment was significant different between the two population. Compared to the North American cohort, the Brazilian cohort had higher rates of liver involvement (83% vs. 50%; $p < .001$) and lower rate of lung (8% vs. 50%; $p < .001$), respectively. The cause for the high incidence and severity scores in the liver among the Brazilian cohort is unknown, but we speculated potential contributors. For instance, 100% of Brazilian cohort was CMV positive and pre-emptive treatment for CMV reactivation is not used after day 100 posttransplant, thus reactivation of CMV may have contributed to the elevation of liver function tests. Moreover, it is not standard practice in Brazil to add ursodiol to treat elevation of liver tests attributed to GVHD, thus allowing for further potential increase in liver severity score. The lower rates of lung in the Brazilian cohort may reflect non-standardization of pulmonary function test in Brazil. In conclusion, prevalence of organ manifestations in cGVHD varied between the two ethnic distinct cohort studied. Attention should be taken into consideration when evaluating prognosis and outcomes in cGVHD in different ethnic population.

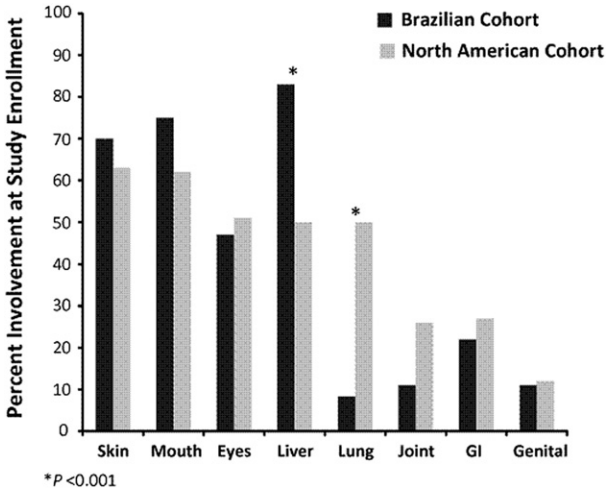

Figure 1.

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Clinical Features of Acute Cutaneous Graft-Versus-Host Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Acute graft-versus-host disease (aGVHD) is a frequent complication of allogeneic hematopoietic stem cell transplantation (HSCT). Although the presence of a skin eruption is a cornerstone in the diagnosis of aGVHD according to the Glucksberg criteria and the 2005 NIH Consensus Conference, specific cutaneous features such as morphology and anatomic distribution have not been studied in a systematic manner. Subsequently, the relative incidences of specific skin lesions remain unclear and contribute to the ongoing challenge of delineating aGVHD from other commonly seen skin eruptions early after HSCT.

Methods: A retrospective review of all patients receiving an allogeneic HSCT from 2010 to 2011 at Northwestern Memorial Hospital identified those individuals with cutaneous aGVHD. Each case of aGVHD was confirmed by both skin