collected from inpatient and outpatient charts in a de-identified manner. This study was approved by the institutional review board of the University of Oklahoma Health Sciences Center. Patient comorbidity index scores were calculated within 30 days of transplant using the QxMD Hematopoietic Cell Transplantation-Specific Index (HCT-CI) calculator. Karnofsky Performance Status was determined by a physician during pre-transplant assessment. Additional pre-transplant data collected included: gender, age at transplant, date of transplant, donor type, donor source, preparative method, specific preparative regimen, disease status at the time of transplant, disease type, and insurance status. Post-transplant data collected included: survival at 100 days, 1 year, and 2 years post-transplant, cause of death, presence of graft-versus-host disease (GVHD), type of GVHD, organ affected by GVHD, and documented infections. Our results indicated that higher CMI scores were significantly associated with increased non-relapse mortality in patients undergoing myeloablative transplant preparative regimens ($P < .001$). Lower KPS scores were also significantly associated with poor survival ($P < .001$). Insurance was not significantly associated with non-relapse mortality ($P > .05$). Finally, 39% of all patient deaths were attributed to disease, 20% of patient deaths were attributed to non-relapse mortality, while 41% of patients survived.

377

A Novel Intermediate Alemtuzumab Schedule Optimizes the Incidences of Mixed Chimerism and Acute GVHD in Patients with HLH and XLP Undergoing Allogeneic HCT

Rebecca A. Marsh [1], Mi-Ok Kim [2], Denise Bellman [1], Laura Hart [3], Michael B. Jordan [4], Jack Bleesing [1], Parinda A. Mehta [1], Sonata Jodele [1], Kasiani Myers [1], Ashish Kumar [1], Michael Grimley [1], Stella Davies [1], Alexandra Filipovich [1]. [1] Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2] Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center; [3] Cincinnati Children's Hospital Medical Center; [4] Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center

Introduction: Reduced intensity conditioning (RIC) with alemtuzumab, fludarabine, and melphalan improves the hematopoietic cell transplant (HCT) outcomes of patients with hemophagocytic lymphohistiocytosis (HLH). Proximal dosing of alemtuzumab is associated with a high incidence of mixed chimerism (MC) whereas distal dosing is associated with less MC but higher incidences of acute GVHD following initial graft infusion. We hypothesized that an intermediate alemtuzumab schedule would optimize the incidences of MC and acute GVHD.

Methods: Twenty-five consecutive transplants were performed in patients with HLH or XLP using a RIC regimen with a novel *intermediate* alemtuzumab schedule of 1mg/kg beginning on day -14. The cumulative incidences of MC and acute GVHD were compared to 2 retrospective cohorts of patients with HLH and XLP treated with *distal* (n=15) or *proximal* (n=33) alemtuzumab schedules. All patients received fludarabine 150mg/M2 (1mg/kg if <10kg) divided over days -8 to -4, and melphalan 140mg/M2 (4.7mg/kg if <10kg) on day -3. Melphalan was reduced by 50% in one infant due to concern for toxicity. GVHD prophylaxis consisted of methylprednisolone and cyclosporine or tacrolimus in all but 2 patients who received methylprednisolone and MMF. Three patients additionally received methotrexate.

Results: The cumulative incidence of MC was less in the intermediate alemtuzumab cohort at 34%, versus 72% in the proximal and 40% in the distal cohorts ($P = .008$). The cumulative incidence of acute GVHD related to initial graft infusion (before MC) was 4% in the intermediate cohort and 0% in the proximal cohort ($P = .26$), versus 13% in the distal cohort ($P = .04$, proximal versus distal). There was a trend toward less *overall* acute GVHD (following graft infusion or following intervention for MC) in the intermediate cohort at 12%, versus 16% and 27% in the proximal and distal cohorts ($P = .55$).

Conclusion: This novel 14 day RIC regimen optimizes the incidences of MC and acute GVHD.

378

The Use of 5-Azacitidine in Allogeneic Hematopoietic Cell Transplantation: A Single Center Experience

Ana A. Martin Lopez, Maria Diez Campelo, Silvia Rojas Porras, Alba Redondo Guijo, Lucia Lopez Corral, Fermin Sanchez Guijo, Consuelo del Canizo. Hematology, Hospital Clínico de Salamanca, Salamanca, Spain

Introduction: The allogeneic hematopoietic cell transplantation (alloHCT) remains the only treatment modality with known curative potential in MDS, AML and CMML. The 5-azacitidine is the first line treatment in high-risk MDS that are not suitable for intensive therapy. On the other hand, there is not enough evidence for deciding which is the best option, either 5-azacitidine or induction chemotherapy, before alloHCT. In a similar way, the 5-azacitidine exposure in post-alloHCT relapse may be an attractive alternative, even though there are not definite results yet.

Objective: Evaluate the capacity of 5-azacitidine in reducing or stabilizing the disease before alloHCT, regarding associated toxicity, and its role in post-alloHCT relapses.

Patients And Methods: We retrospectively reviewed 36 patients who underwent alloHCT for high-risk MDS, AML and CMML between October 2006 and September 2012 in our center and who received 5-azacitidine before and/or after alloHCT.

Results: 30 patients received 5-azacitidine pre-alloHCT, 22 were MDS (73%), 6 AML (22%) and 2 CMML (7%), with high-risk cytogenetic (according to IPSS-R) in one third of them. The median of cycles was 5 (1-12), using the conventional dose and schedule, and presenting usual toxicity in only 38% of cases. Two thirds of evaluable patients achieved complete remission (CR) or partial response (PR) and 26% progressed. 83% of patients underwent alloHCT in some type of response and 17% in progression. The alloHCT characteristics were: median of age of 56 (35-67), peripheral blood as source of stem cells in 93%, related donor in 62%, and reduced-intensity conditioning in most cases (83%). At day +100, 82% of patients achieved CR and 18% had progressed. The global post-alloHCT relapse rate was 33%. The 2-years overall survival (OS) and event-free survival (EFS) were 66% and 50%, respectively. At 1 year, the relapse-free survival (RFS) was 65%, without having reached the median follow-up. We did not observe any significant statistical differences in OS after taking into account the following factors: sex, diagnosis, previous lines of treatment, response to 5-azacitidine, response at alloHCT and type of donor. However, cytogenetic risk did significantly influence survival in terms of OS, EFS and RFS, the same as source of stem cells, type of conditioning regimen and response at day +100 in OS. 16 patients received 5-azacitidine after post-alloHCT relapse with a median of cycle of 3.5 (1-19), reduced dose in some cases and limited toxicity (42%). The median of days after alloHCT to the beginning of treatment was 152 (32-529). Two thirds

of patients achieved CR and the 1-year OS in this group was 43%.

Conclusion: The 5-azacitidine is a treatment modality that can improve or stabilize the disease, allowing time for patients to reach alloHCT, with little toxicity, and can induce response after post-alloHCT relapses.

379

Monitoring Changes in Serum Albumin (SA) Concentrations As an Early and Objective Indicator of Potential CMX001-Associated Gastrointestinal (GI) Adverse Drug Effects

Herve Mommeja-Marin [1], Thomas M. Brundage [2], Dorothy J. Margolskee [2]. [1] Medical / Clinical, Chimerix, Inc., Durham, NC; [2] Chimerix

Background: CMX001 is an orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate converted inside cells to the active antiviral, cidofovir diphosphate. In the preclinical toxicology program, GI AEs (diagnosed as gastropathy and enteropathy; dose-related changes included flattening or loss of epithelial cells lining the lumen of the small intestine on chronic dosing) were dose-limiting after daily administration; however, there were no GI AEs or gross/microscopic gut changes when animals were dosed twice-weekly (BIW) up to 9 months. Radiolabel studies in mice confirmed that CMX001 concentrates in the gut mucosa more than in other tissues. In a Phase 2 dose-escalation study (CMX001-201; ClinicalTrials.gov identifier: NCT00942305) evaluating CMX001 for CMV prophylaxis in allogeneic hematopoietic stem cell transplant (HSCT) recipients, an increased rate of profuse watery diarrhea was seen at 200 mg BIW and was considered dose-limiting in this population. A program-wide safety monitoring and management plan that included an option for dose interruption ($\leq$ 2 weeks) in subjects with $\geq$ Grade 3 diarrhea was introduced. Subsequently, few subjects ($\leq$ 10%) discontinued therapy because of GI AEs, indicating that dose interruption is an appropriate strategy to manage CMX001-associated GI AEs and to achieve effective CMV suppression in this population.

Methods: Serum chemistry data were evaluated for changes in SA, a well-established marker of protein loss, to assess the potential relationship to diarrhea. Abnormally low SA concentrations were tabulated and the lowest value identified through +1 week post treatment. A clinically meaningful SA decrease was defined as value $\leq$ 30 g/L (lower limit of normal 33 g/L) and $\geq$ 4 g/L lower than baseline.

Results: Increased grade and/or duration of diarrhea correlated with the decrease in SA concentrations over time as shown in the Kaplan-Meier plots with data grouped by "low" ($\leq$ 100 mg/week) and "high" ($\geq$ 200 mg/week) CMX001 dose vs. placebo. To rule out GI-GVHD (a common cause of diarrhea in HSCT recipients), the SA data from solid organ transplant (SOT) patients treated with CMX001 in an expanded access study (CMX001-350; ClinicalTrials.gov ID: NCT01143181) were also evaluated. A similar timing of decrease in SA concentrations was seen in these subjects who are unlikely to have GVHD; urinalysis data also excluded proteinuria as a cause.

Conclusions: Our clinical experience in the HSCT population is consistent with preclinical findings. On chronic dosing, CMX001 likely accumulates in the gut mucosa in some patients and causes diarrhea that may be more pronounced in individuals with other causes of diarrhea (eg, GI-GVHD). Dose interruption gives the gut mucosa time to recover, allowing subjects the opportunity to resume therapy. Monitoring SA changes in patients may provide an early and objective indicator of potential drug-related GI AEs.

380

Renal Safety of Broad Spectrum Antiviral CMX001 in the Prevention of CMV Infection Post- Allogeneic Hematopoietic Cell Transplantation (HCT)

Herve Mommeja-Marin [1], Thomas M. Brundage [2], Dorothy J. Margolskee [2]. [1] Medical / Clinical, Chimerix, Inc., Durham, NC; [2] Chimerix

Background: CMX001 is an orally bioavailable, broad spectrum, lipid acyclic nucleoside phosphonate converted intracellularly into the active antiviral, cidofovir diphosphate. Unlike cidofovir, CMX001 is not a substrate for the anion organic transporter and therefore is not concentrated in the kidney.

Methods: Study CMX001-201 was a 9-11 week randomized, placebo-controlled, double-blind, dose-escalation study (evaluating 40 mg weekly [QW], 100 mg QW, 200 mg QW, 200 mg twice-weekly [BIW] and 100 mg BIW) of CMX001 for the prevention of CMV infection post-HCT (ClinicalTrials.gov ID: NCT00942305). Treatment was initiated at the time of engraftment and continued until Week 13 post-HCT. Results presented elsewhere have shown that CMX001, at various doses, was active and well tolerated in the prevention of CMV infection or disease. Renal safety was assessed throughout the duration of therapy using serum creatinine, urinalysis and estimated glomerular filtration rate (GFR, MDRD4 formula).

Results: 230 subjects were enrolled in the study; 59 received placebo and 171 received CMX001 at various doses. 24 subjects (41%) on placebo and 77 subjects on CMX001 (45%) had BK viruria prior to dosing. One subject discontinued CMX001 40 mg QW due to acute renal failure; no other subject discontinued from the study due to renal adverse events. Results of calculated GFR by Study Cohort and over time are presented in Table 1 below. Overall, renal function tended to decline in placebo recipients while renal function appeared to improve in subjects who received CMX001 at 200 mg per week (either QW or divided into 2 BIW doses). The renal function decline in placebo recipients appeared to be associated by the presence of BK virus (BKV) in the urine at the time of treatment commencement, while the proportion of subjects with renal dysfunction was similar between BKV positive and negative subjects among CMX001 recipients. There was also a decreased incidence of microscopic hematuria in BKV infected subjects treated with CMX001 as compared to placebo recipients (6% vs. 25%).

Conclusions: CMX001 when administered at doses of 200 mg per week is not associated with signs of nephrotoxicity

Table 1
Study 201: Mean (N) Change from Baseline in GFR (mL/min/1.73m^2) by Visit and Dose

Visit	Placebo	CMX001 40 mg QW	CMX001 100 mg QW	CMX001 200 mg QW	CMX001 100 mg BIW
Week 2	-6.5 (56)	-7.7 (23)	-11.6 (26)	-9.5 (37)	-4.5 (49)
Week 4	-8.7 (46)	-9.4 (19)	-8.6 (25)	-12.4 (31)	-3.3 (44)
Week 6	-10.1 (35)	-7.0 (13)	-12.0 (22)	-1.9 (24)	1.3 (33)
Week 8	-18.5 (36)	-2.2 (12)	-11.3 (19)	5.8 (18)	12.2 (31)*
Week 10	-15.4 (21)	-7.3 (5)	-15.6 (13)	5.7 (14)	6.1 (21)*
Post-Week 1	-13.3 (57)	-5.8 (19)	-2.8 (25)	8.8 (35)	7.7 (49)*

* $P < 0.05$ t-test versus placebo