absolute neutrophil count of ≥500 cells/mm^3 with >75% donor chimerism (RFLP confirmed). The dominating CBU was defined by chimerism >75%. ALDH^{br} dosing was defined as high if the thawed CBU delivered >47,000 ALDH^{br} cells/kg which was identified as predictive of engraftment in single CBT in prior studies.
Results: The median patient age was 28.8 years (range, 3.7-64.8 years) and weight of 68.70 kg (range, 15.2-111.8 kg), 17 male, 13 CMV+. The median TNC per CBU was 2.2×10^7/kg (range, 1.2-10.3×10^7/kg) with the median combined TNC of 3.9×10^7/kg (range, 2.7-18.0×10^7/kg). 5 patients received two high ALDH^{br} units, 10 patients received one high and one low ALDH^{br} unit, and 12 received two low ALDH^{br} units. 23 patients were evaluable for engraftment. 10 of 12 patients receiving ≥1 high ALDH^{br} CBUs engrafted. The other 2 patients died of infection without engraftment (days 29 and 34 post-CBT). Conversely, 4 of 9 patients receiving low ALDH^{br} CBUs failed to engraft. In the high/low group, only the high ALDH^{br} CBUs engrafted. The sensitivity and specificity for ALDH^{br} dose is 0.71 and 0.67, respectively. The positive and negative predictive values are 0.86 and 0.44, respectively. Other graft parameters did not predict the dominating CBU.
Conclusion: Post-thaw ALDH^{br} dosing has a high positive predictive value for predicting engraftment in dCBT. Further studies are planned.

Table 1. ALDHbr Content of Units and Engraftment Status

	ALDHbr Content of Units		
	Low/Low	High/Low	High/High
Total Patients	12	10	5
Evaluable Patients	9	9	5
Engrafted	5	7 [all with high unit]	5
Non-Engrafted	4	2	

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COMPARATIVE EFFECTIVENESS ANALYSIS OF CD34 + SELECTED, T-CELL DEPLETED (TCD) HLA-MATCHED SIBLING GRAFTS ON ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) IN COMPLETE REMISSION

Pasquini, M.C.[1], Devine, S.[2], Mendizabal, A.[3], Baden, L.R.[4], Wingard, J.R.[5], Lazarus, H.M.[6], Appelbaum, F.R.[7], Keever-Taylor, C.[1], O'Reilly, R.J.[8,9], Soiffer, R.J.[4] [1] Medical College of Wisconsin, Milwaukee, WI; [2] Ohio State University Medical Center, Columbus, OH; [3] The EMMES Corporation, Rockville, MD; [4] Dana-Farber Cancer Institute, Boston, MA; [5] University of Florida, Shands Cancer Center, Gainesville, FL; [6] Case Western Reserve University, School of Medicine, Cleveland, OH; [7] Fred Hutchinson Cancer Research Center, Seattle, WA; [8] Memorial Sloan-Kettering Cancer Center, New York, NY; [9] On behalf of the Blood and Marrow Transplant Clinical Trials Network

Numerous single institution studies have demonstrated that TCD significantly reduces the incidence of graft-versus-host-disease (GVHD). However, concerns about leukemia relapse, graft rejection, and variability in technique have limited the widespread application of this approach. Promising results of TCD in patients with AML prompted the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) to study a single uniform technique of CD 34+ selection using the Miltenyi CliniMacs device in a Phase II clinical trial (BMT CTN 0303) of adult AML patients in first or second complete remission (CR1/CR2) receiving peripheral blood stem cell (PBSC), HLA-matched sibling donor transplants. We compared outcomes of the 44 patients transplanted on the BMT CTN 0303 trial to a contemporary cohort of 102 patients with AML enrolled on the BMT CTN 0101 – Phase III clinical trial of anti-fungal prophylaxis after myeloablative HCT with pharmacologic immune suppression post-transplant (IST). This analysis compared TCD (BMT CTN #0303) versus IST (BMT CTN 0101) with respect to the endpoints of: neutrophil engraftment (ENG), rates of acute and chronic GVHD, transplant-related mortality (TRM), relapse, disease-free survival (DFS), and overall survival (OS). Groups were similar for patient-, disease- and transplant specific characteristics except for the proportion of patients in CR2 (TCD 7% vs. IST 27%), unfavorable risk cytogenetics (TCD 32% vs. IST 18%), the use of mobilized PBSC (TCD 100% vs. IST 81%) and graft composition (TCD ≤1 x10^5 CD3+ cells/kg). The results revealed lower rates of grades II-IV acute (p = 0.046) and chronic GVHD (p = 0.01) in the TCD group with no difference in ENG, leukemia relapse and TRM. DFS and OS were similar between the two groups in the univariate setting and also after adjustment for potential prognostic factors using a Cox proportional hazards model. Reduction of GVHD rates without an increase in relapse rates and no requirement for post-transplant immunosuppression are distinct advantages of this method of TCD. These results support the extension of this approach to the unrelated donor setting and additional larger, prospective studies to definitively address the role of rigorous TCD in HCT.

TCD vs IST Outcomes

Outcome	TCD % (95% Confidence Interval) N = 44	IST % (95% Confidence Interval) N = 102
DFS at 6 mo	81 (66-90)	75 (68-87)
Relapse at 12 mo	19 (6-32)	19 (11-26)
TRM at 12 mo	19 (6-31)	22 (14-30)
ENG at 28 d	100 (86-100)	90 (79-100)
Acute GVHD II-IV at 100 d	20 (9-32)	37 (28-47)
Acute GVHD III-IV at 100 d	5 (0-11)	10 (4-16)
Chronic GVHD at 12 mo	19 (7-32)	47 (35-58)
Overall Survival at 12 mo	74 (57-85)	69 (59-77)

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PRECLINICAL EVALUATION OF HUMAN NOR-EPINEPHRINE TRANSPORTER (HNET)/MIBG REPORTER SYSTEM FOR IMAGING ADOPTIVELY TRANSFERRED EBV-SPECIFIC CYTOTOXIC T-LYMPHOCITES

Doubrovin, M., Doubrovina, E., Moroz, M., Pankov, D., Wang, X., Olszewska, M., Riviere, I., O'Reilly, R., Larson, S., Blasberg, R. Memorial Sloan-Kettering Cancer Center, New York, NY

Background: We previously demonstrated hNET/MIBG to be a reporter gene system feasible for non-invasive quantitative monitoring of cytotoxic T-cells (CTLs) in vivo. In this preclinical study, we test whether the hNET reporter gene construct, under conditions simulating adoptive immune cell therapy in patients, is potentially applicable imaging paradigm.
Methods: The hNET reporter gene was cloned into a clinical grade SFG pseudotyped MoMLV retroviral backbone, packaged in PG-13 retroviral producer cell line and was used to transfect EBV-specific T cells. Following the future clinical protocol, EBV-specific T cells were pre-generated from a normal donor by stimulation with autologous EBV-transformed B-cells, as we previously described. Based on expression of LNGFR, a selection gene in the same retroviral cassette, reporter-gene expressing cells (CTL-NIN) were selected by FACS sorting, characterized for cytotoxicity and frozen for long-term storage. Initially, ^{123}I-MIBG uptake was evaluated in the CTL-NIN retrieved from liquid nitrogen storage according to GMP requirements. In the preclinical study, upon thawing, prior to adoptive transfer, CTLs were preincubated with 100 microCi/ml (3.73 MBq/ml) of ^{124}I-MIBG for 2 hours and injected into the EBV-BLCL xenograft tumor model bearing NOD-SCID mice. Assessment MIBG radioactivity in CTL-NIN prior to injection and MicroPET imaging of the injected radiolabeled cells in a phantom and in the animals, with post-mortem ex-vivo radioactivity measurements were performed.
Results: CTL-NINs were produced according to GMP procedures appeared to have >90% reporter gene expression post-sorting with improved specificity to EBV-BLCL targets (35% with 10:1 E:T ratio). Storage and thawing decreased their cytotoxicity (25%) and ^{123}I-MIBG uptake (217 ml/g, compared to 330 ml/g pre-freezing). ^{124}I-MIBG labeling of CTL-NIN T cells ex-vivo was sufficient for in vivo imaging. In vivo microPET imaging confirmed our ability to detect 10^5 ^{124}I-MIBG ex vivo prelabeled CTL-NIN distributed in a 1 cm^3 tumor volume.
Conclusions: 1) hNET transduced CTLs produced and prepared for adoptive immune cell transfer according to a clinical protocol

that preserves their anti-EBV specificity and functionality, can be labeled with ^{124}I-MIBG and imaged by PET; 2) conditions for cell preparation following pre-transfer thawing requires further optimization for improving PET imaging sensitivity.

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SAFETY OF MICAFUNGIN IN NEUTROPENIC PATIENTS INCLUDING THOSE UNDERGOING HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Wingard, J.R.[1], Chandrasekar, P.[2], Seibel, N.[3], Sirohi, B.[4], Ruhnke, M.[5], Powles, R.[6] [1] University of Florida Shands Cancer Center, Gainesville, FL; [2] Wayne State University School of Medicine, Karmanos Cancer Center, Detroit, MI; [3] National Institutes of Health, Bethesda, MD; [4] Max Cancer Centre, Max Healthcare, New Delhi, India; [5] Campus Charité Mitte, Humboldt University, Berlin, Germany; [6] Parkside Oncology Clinic, Wimbledon, London, United Kingdom

Polyenes and azoles have potentially deleterious drug interactions that can lead to important renal and hepatic toxicities in HCT recipients. The echinocandins may offer safety advantages in such patients. In this analysis using data from 8 clinical development studies, we examined renal and hepatic parameters in 588 neutropenic patients who received micafungin for prophylaxis of fungal infections (n = 375), treatment for invasive candidiasis/candidemia (IC/C; n = 120), or treatment for invasive aspergillosis (IA, n = 93). The renal and hepatic function laboratory parameters for the 3 indications are shown in Table 1; changes in laboratory parameters were calculated for each indication and, for the prophylaxis patients, for type of HCT. The proportion of patients with an increase in creatinine from <2*ULN at baseline to ≥2*ULN at EOT and an increase in bilirubin and ALT <2.5*ULN at baseline to ≥2.5*ULN were provided by indication. Overall, the changes in hepatic and renal function laboratory parameters were consistent with the underlying conditions of the patients, and HCT patients did not appear to experience greater increases in levels of creatinine, bilirubin, and ALT compared to patients in the other groups.

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SUCCESS WITH A SHORTER COURSE PREEMPTIVE TREATMENT FOR CYTOMEGALOVIRUS (CMV) REACTIVATION AFTER MYELOABLATIVE HLA MATCHED SIBLING DONOR HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Naik, S.[2], Shaenman, J.[1], Kim, J.H.[1], Wong, R.[2], Arai, S.[2], Johnston, L.[2], Brown, J.[1,2] [1] Stanford University Medical Center, Stanford, CA; [2] Stanford University Medical Center, Stanford, CA

The optimal duration of preemptive treatment of CMV reactivation following HCT is unclear. We analyzed 355 evaluable patients (pts) who underwent myeloablative HCT from an HLA matched sibling donor at Stanford University Medical Center between 1996 and 2008. Either donor or recipient was seropositive for CMV at the time of transplant for 287 (79%) pts. Median follow up time was 3.8 years (0.3-10.4). Patients were screened weekly for reactivation in plasma using a qualitative (1996-2000) or quantitative PCR CMV test (2001-2008) (Amplicor, Roche Molecular Diagnostics) through day 100 post-HCT. CMV viremia was detected in 127 (44%) of the 287 pts. Any positive result prompted pre-emptive treatment with ganciclovir at 5 mg/kg IV twice daily for two weeks and a concurrent investigation for signs or symptoms suggestive of CMV disease. For patients without evidence of CMV disease in whom CMV viremia resolved during the first three weeks, ganciclovir was administered at 5 mg/kg daily for an additional week. In patients with CMV disease or in whom viremia persisted, daily ganciclovir was administered for an additional 4 weeks. There were no substantial differences between groups with respect to sex, age, race, or underlying disease. The relative paucity of CMV reactivation in the D+/R– group is predicted by previously published observations. Pts who successfully resolved CMV viremia with the administration of only 3 weeks of ganciclovir were less likely (1) to have received a preparative regimen containing TBI, (2) more likely to have a lower initial CMV load as compared with patients who met criteria for 6week treatment. However, no difference between the groups was noted regarding GVHD or treatment with steroids at the time of initial viremia. Our data supports the utility of a 3

Description of laboratory parameters in micafungin neutropenic patients

Parameter	All patients (n = 588)	All prophylaxis patients (n = 375)	Prophylaxis, non-HCT patients (n = 30)	Prophylaxis, autologous HCT patients (n = 161)	Prophylaxis, allogeneic HCT patients (n = 184)	IC/Candidemia patients (n = 120)*	IA patients (n = 93)†
Days of micafungin, median	17.5	18.0	6.0	17.0	21.0	14.0	29.0
Creatinine (mg/dl), median (min-max)							
Baseline	0.70 (0.1-6.6)	0.6 (0.1-5.4)	0.40 (0.2-0.9)	0.70 (0.1-5.4)	0.60 (0.1-2.7)	0.98 (0.1-4.7)	0.90 (0.2-6.6)
Peak	0.86 (0.3-2.2)	0.70 (0.1-4.4)	0.70 (0.7-0.7)	0.75 (0.5-0.8)	0.70 (0.2-2.3)	0.98 (0.1-4.7)	1.00 (0.2-3.8)
EOT	0.71 (0.1-6.9)	0.70 (0.1-4.4)	0.40 (0.2-0.8)	0.70 (0.2-4.4)	0.70 (0.1-2.4)	0.91 (0.1-6.9)	1.00 (0.2-3.8)
Increase from <2 ULN at baseline to ≥2 ULN at EOT, n/N (%)	16/527 (3.0)	1/363 (0.3)	—	—	—	10/79 (12.7)	5/85 (5.9)
Bilirubin (mg/dl), median, (min-max)							
Baseline	0.80 (0-17.2)	0.70 (0.0-7.3)	0.80 (0.1-2.8)	0.60 (0-3.1)	0.70 (0.1-7.3)	1.20 (0.2-11.6)	1.10 (0.1-17.2)
Peak	1.10 (0.2-23.5)	1.10 (0.4-23.5)	0.80 (0.1-2.8)	1.25 (0.5-4.4)	1.10 (0.4-23.5)	1.32 (0.1-9.3)	1.30 (0.1-37.9)
EOT	0.80 (0.1-37.9)	0.70 (0.1-31.3)	0.60 (0.1-5.7)	0.60 (0.1-4.4)	0.90 (0.2-31.3)	1.17 (0.2-13.9)	1.30 (0.1-37.9)
Increase from <2.5 ULN at baseline to ≥2.5 ULN at EOT, n/N (%)	39/490 (8.0)	17/355 (4.8)	—	—	—	9/65 (13.8)	13/70(18.6)
ALT (U/L), median, (min-max)							
Baseline	27.0 (2-655)	26.5 (4-472)	30.0 (13-129)	23.0 (4-370)	28.0 (4-472)	31.5 (7-204)	27.0 (2-655)
Peak	30.0 (1-2151)	39.0 (7-389)	44.0 (13-96)	26.0 (13-33)	46.0 (7-389)	57.0 (17-88)	34.0 (3-194)
EOT	25.0 (1-2793)	24.0 (1-2793)	27.0 (8-167)	20.0 (4-383)	28.0 (1-2793)	30.0 (6-1119)	26.0 (3-313)
Increase from <2.5 ULN at baseline to ≥2.5 ULN at EOT, n/N (%)	35/455 (7.7)	17/315 (5.4)	—	—	—	8/68 (11.8)	10/72 (13.9)

ALT = Alanine aminotransferase; EOT = end of treatment; IA = invasive aspergillosis; IC/C = invasive candidiasis/candidemia; ULN = upper limits of normal.

*Comprised of 89 non-HCT patients, 16 autologous HCT patients, and 5 allogeneic HCT patients. Renal and hepatic function laboratory parameter data not available for these subgroups.

†Comprised of 57 non-HCT patients, 5 autologous HCT patients, and 31 allogeneic HCT patients. Renal and hepatic function laboratory parameter data not available for these subgroups.