was done in all patients and 5 patients had 1-3 courses of DLI. On follow up of the 43 patients with MC, 24 achieved complete chimerism, 10 had stable mixed chimerism and 9 had rejection (mostly level 3 MC). Two patients developed mild graft versus host disease after DLI.

Conclusion: Occurrence of mixed chimerism is common after allogeneic HSCT for thalassaemia after Fludarabine/Treosulfan/Thiotepa conditioning. Rapid tapering of immunosuppression and judicious use of DLI helps in reducing the risk of secondary graft rejection. Closer monitoring of chimerism after HSCT needs to be done when such conditioning regimens are used.

406

Enlarged Spleen Prior to Allogeneic Transplantation for Myelofibrosis Is Associated with Poor Engraftment and Increased Non-Relapse Mortality

Usama Gergis [1], Koen van Besien [1,2], Tsiporah B. Shore [3], Sebastian Mayer [4], Eric Feldman [5], Gail Roboz [1], Ellen Ritchie [1], Richard Silver [6], Hanhan Wang [1], Xi Kathy Zhou [1], Emil Kuriakose [1]. *[1] Weill Cornell Medical College, New York, NY; [2] Cornell, New York, NY; [3] Cornell Medical Center Hematology/Oncology, The New York Hospital, New York, NY; [4] Department of Medicine, Weill Cornell Medical Center, New York, NY; [5] Leukemia, Weill Cornell Medical Center, New York, NY; [6] Weill Cornell Medical college, New York, NY*

Introduction: Allogeneic stem cell transplantation (SCT) is potentially curative for patients with Myelofibrosis (MF). However, treatment failure is common and often associated with slow engraftment or graft failure, risk factors for which are poorly defined.

Patients: From 2000 to 2014, 30 adult patients (median age, 49 (range 18-68) underwent SCT for primary or secondary MF at WCMC/NYP. All patients received PBSC from matched related (MRD-14) or matched unrelated donors (MUD-16). Most patients received fludarabine and melphalan (n=22) conditioning. ATG or alemtuzumab were used for patients who underwent MUD SCT. Only a minority of patients had low risk disease by DIPPS (26.7%) or Lille (20%) risk scores. Twenty patients had splenomegaly, 6 by physical exam and 14 by imaging studies (median 24.5 Cm, range 16.2-34).

Results: After a median follow-up of 49.5 months (range 3 to 154 months), the 4-year OS and RFS are 44% (95%CI: 29%-67%) and 37% (95%CI: 23%-61%) respectively. Neutrophil engraftment by day 18 occurred in 63% of patients. Platelets were engrafted by day 25 in 41% of patients. We used a Fine and Gray's proportional subdistribution hazard model. Splenomegaly was associated with delayed neutrophil engraftment (SHR=0.42, 95% CI=0.21, 0.83, p=0.01), delayed platelet engraftment (SHR=0.18, 95%CI= 0.07, 0.48, p<0.001) and non-relapse mortality (NRM) (SHR=3.24, 95%CI=0.94, 11.2, p=0.06). Elevated LDH was associated with delayed platelet engraftment (SHR=0.39, 95% CI=0.16, 0.94, p=0.04) and NRM (SHR=2.82, 95%CI= 1.08, 7.35, p=0.03). MUD grafts were marginally associated with delayed neutrophil engraftment (SHR=0.55, 95% CI= 0.27, 1.12, p<0.10) but not platelet engraftment or NRM.

Conclusion: Splenomegaly contributed to delayed neutrophil and platelet engraftment and NRM. Splenectomy should be considered for patients with splenomegaly in need of transplantation. Elevated LDH was associated with delayed platelets engraftment and NRM and might indicate more aggressive disease.

Patients	Characteristics
Age	
Median (Range)	49 (18-68)
Sex	
Male	20 (67%)
Female	10 (33%)
Disease Risk at HSCT	
Lille	
Low	6 (20%)
Intermediate	15 (50%)
High	9 (30%)
DIPPS	
Low	2 (6%)
Intermediate-1	6 (20%)
Intermediate-2	17 (57%)
High	5 (17%)
JAK 2 Kinase	
Positive	11 (37%)
Negative	11 (37%)
Unknown	8 (24)
Spleen	
Enlarged	18 (60%)
Normal	4 (13%)
Removed	8 (27%)
Albumin [1]	
Median	3.9
Min	2.6
Max	4.9
LDH [2]	
Median	487
Min	126
Max	1304
ECOG	
0	5
1	17
2	4
Unknown	4

[1] Albumin normal value: 3.5-4.8 g/dl
[2] LDH normal value: 98-192 IU/L

407

Assessment of Additional Consolidation Chemotherapy Effects in Patients with Acute Myeloid Leukemia before Allogeneic Stem Cell Transplantation

Ardeshir Ghavamzadeh, K. Ali Moghaddam, M. Vaezi, Y. Zafari, R. Maheriazar, A. Mousavi, B. Bahar, M. Jahani. *Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran*

Objectives: To assess the effects of additional consolidation therapy in acute myeloid leukemia (AML) patients before allogeneic hematopoietic stem cell transplantation (HSCT).

Methods: Seventy-two AML patients (range: 18-55 years) who transplanted in CR1 after being treated with a standard chemotherapy (7+3) regimen were randomly divided into two groups. Thirty-six patients in group A directly underwent transplantation and 36 in group B received chemotherapy regimen (5+2) prior to allogeneic HSCT. All patients received fully HLA-matched transplants.

Results: The median age at transplantation was 38.3 in group A and 37.2 in group B. The male to female ratio was 21:15 and 23:13 in groups A and B, respectively. The median time to neutrophil and platelet recovery was 8 and 27 days in group A, while it was 9 and 19 days in group B, respectively (P: 0.77, 0.01). Acute graft-versus-host disease (GvHD) was more frequent in group A (26 vs. 23) patients(P:0.44). Chronic

GvHD was more frequent in group A(18 versus16) patients(P: 0.37). Five relapses were observed in group A and 9 relapses occurred in group B (P: 0.23). The main causes of death in both groups were relapse (50%) and aGvHD (22.2%). The median follow-up time was 24 months. Disease–free survival (DFS) was 47 in group A and 37 months (P: 0.34) in groups B. The study showed overall survival (OS) of 45 and 34 months (P: 0.71) in groups A and B, respectively.

Conclusion: Even without considering the costs of treatment, it is recommended that AML patients directly undergo transplantation after being treated with a standard chemotherapy regimen (7+3) because no differences in DFS, OS, GvHD were observed between the two groups.

408

A Phase 2 Study of the Hedgehog Pathway Smoothened Inhibitor PF-04449913 to Reduce Relapse in High Risk Acute Leukemia and MDS Patients Following Allogeneic Stem Cell Transplantation

Jonathan A. Gutman, Emily Denoncourt, Derek Schatz, Clayton Smith, Daniel Aaron Pollyea. *University of Colorado, Aurora, CO*

Relapse is the most common cause of allogeneic stem cell transplantation (SCT) failure. Non-cycling, chemoresistant leukemic stem cells (LSCs) are thought to contribute to disease relapse and have been shown to be dependent on signaling through the Hedgehog (Hh) pathway. Targeting this pathway represents a rational approach to the eliminate LSCs to prevent relapse. PF-04449913 (Pfizer) is a small molecule inhibitor of the transmembrane G protein-coupled Smoothened (SMO) receptor, a key mediator of the Hh pathway. PF-04449913 demonstrates single-agent activity in relapsed leukemias.

We designed an open label, Phase 2 study employing PF-04449913 in acute leukemia and MDS patients following SCT. Eligibility requirements include enrollment within 28-50 days of SCT, engraftment, and high risk of relapse. High relapse risk is defined for myeloablative conditioning regimens in acute leukemia as the presence of persistent morphologic disease or minimal residual disease (MRD) at the time of transplant as measured by flow cytometry, cytogenetics, or FISH, and, for MDS, persistent disease at the time of transplant with poor risk cytogenetics. For non-myeloablative transplants, patients with a relapse risk score >0, as defined by the Fred Hutchinson Cancer Research Center scoring system, are also included. Patients receive consecutive 28-day cycles of PF-04449913 at 100 mg/day for up to one year or until toxicity or relapse. Twenty-eight patients are required for an 80% power to detect an estimated one year relapse free survival improvement from a null hypothesis of 30% to 53%.

To date 13 patients have enrolled including 9 AML, 3 ALL, and 1 MDS (7 myeloablative and 6 non-myeloablative). Median follow up is 176 days. Three patients (one of whom relapsed) required dose reductions to 50 mg due to muscle cramps and dysgeusia, and one patient discontinued due to muscle cramps. No other significant toxicities were attributed to the drug. Three patients relapsed including one morphologic, one MRD, and one with graft failure (developing prior to enrollment on study) with subsequent relapse. One patient died of GVHD, and 12 remain alive. One patient has completed the study and 7 remain on study with a median of 6 cycles completed (range 1-10). Preliminary data suggests that PF-04449913 is well tolerated early post-SCT and may reduce relapse rates.

409

Pilot Clinical Trial of Lymphocyte-Selective Pentostatin Plus Cyclophosphamide Conditioning, High Dose Sirolimus and Pre-Emptive DLI with Rapamycin-Resistant Donor CD4+ T Cells

David Halverson [1], Miriam Mossoba [2], Brenna Hansen [1], Bazetta Blacklock Schuver [1], Seth M. Steinberg [3], Fran Hakim [4], Syed Abbas Ali [5], Roger Kurlander [6], Juan Gea-Banacloche [1], Dennis Hickstein [1], Steven Z. Pavletic [4], Hanh Khuu [7], David F. Stroncek [8], Michael R. Bishop [9], Ronald Gress [10], Daniel Fowler [4].

*[1] Experimental Transplantation and Immunology Branch, NCI, Bethesda, MD; [2] ETIB, NCI, Bethesda, MD; [3] Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [4] Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [5] *, Little Rock, AR; [6] Clinical Center, NIH, Bethesda, MD; [7] Department of Transfusion Medicine, NIH, Bethesda, MD; [8] Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD; [9] University of Chicago, Chicago, IL; [10] * Co-Senior Experimental Transplantation and Immunology Branch/NCI/NIH, Bethesda, MD*

We recently found that early pre-emptiveDLI with donor CD4+ T-Cells cultured in rapamycin (T-Rapa) allowed allo-engraftment after low-intensity fludarabine plus cyclophosphamide (Cy) host conditioning (Blood, 2013). To evaluate further reductions in conditioning intensity, we conducted a pilot clinical trial of allogeneic HSCT using a novel regimen of pentostatin and low-dose, daily cyclophosphamide (PC) in patients with refractory renal cell carcinoma (RCC, n=10; Table 1). After PC conditioning, patients received high dose sirolimus, a T-replete matched related

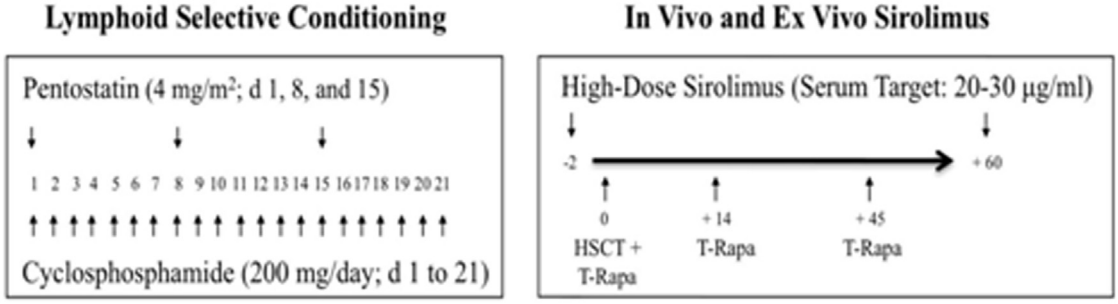

Figure.