Introduction: Disease relapse remains the primary obstacle to success after reduced intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation (HSCT) for patients with acute leukemia and MDS. The ideal RIC regimen has not been defined. Clofarabine is a nucleoside analogue with potent anti-leukemia activity and its inclusion in RIC HSCT could potentially lead to decreased rates of disease relapse.

Methods: We conducted a phase II clinical trial of reduced intensity busulfan (6.4 mg/kg IV total) with clofarabine (40 mg/m2 IV daily x 4 days) conditioning before allogeneic 8/8 HLA-matched related or unrelated donor HSCT. GVHD prophylaxis was with tacrolimus and methotrexate (5 mg/m^2 on days 1, 3, 6). The primary endpoint was donor neutrophil engraftment by day +40 after HSCT. Secondary endpoints included non-relapse mortality, rates of acute and chronic GVHD, PFS, and OS.

Results: 34 patients with AML (n=24), MDS (n=6), and ALL (n=4) were enrolled and underwent RIC HSCT. Patients with AML or ALL were in CR and patients with MDS had < 10% bone marrow blasts. The median age of patients was 63.5 (range 25, 74) and median HCT-CI score was 1 (range 0, 9). Engraftment with donor chimerism by day +40 was achieved in 33 of 34 patients with one patient dying before successful count recovery. Of the patients who engrafted and had chimerism data available (n=30), median donor chimerism measured at approximately day +30 after HSCT was 97% (range 85%, 100%) for all leukocytes and median 80% (50%, 100%) for the CD3$^+$ population. Of those who have been followed for at least 100 days after HSCT (n=28), the probability of NRM at day 100 was 6.4% and 1-year was 36% (95% CI, 15%, 57%). Causes of NRM included acute GVHD (n=4), infection (n=2), and multi-organ failure (n=2). Four of the six patients with MDS died of NRM, all of whom were older than 65 and had HCT-CI scores 4 or above. The other two non-relapse deaths were due to acute GVHD in the setting of early taper of tacrolimus, one for decreasing chimerism and the other for neurological complications. There were no cases of hepatic VOD. The 12-month cumulative incidence of disease relapse was 27% (95% CI, 12%, 44%). The 6-month cumulative incidence of acute GVHD was 35% (95% CI, 18%, 53%) and the 12-month cumulative incidence of chronic GVHD was 24% (95% CI, 9.2%, 43%). The 12-month probability of PFS was 38% (95% CI, 18%, 59%) and OS was 41% (95% CI, 19%, 62%).

Conclusion: Reduced intensity conditioning with busulfan and clofarabine engenders successful donor engraftment with acceptable rates of toxicity, NRM, and GVHD, although caution should be used in older patients with significant comorbidities. Longer follow-up and comparison of outcomes with fludarabine-based regimens will be important in defining the role of this RIC regimen.

335

The Impact of Mold Infections after Allogeneic Transplantation

Tracey L. Churay, Holly A. Justman, Nancy L. Skurka, Steven C. Goldstein, Attaphol Pawarode, John Magenau, Daniel R. Couriel. Adult Blood and Marrow Transplant Program, University of Michigan, Ann Arbor, MI

Introduction: Fungi are among the most common microbes encountered by mammalian hosts and a major cause of morbidity and mortality of allogeneic hematopoietic stem cell transplantation (HSCT). Both innate and adaptive immunity prevent invasive fungal infections (IFI), and are impaired after HSCT. Due to Candida prophylaxis, Aspergillus and other molds are emerging as one of the main causes of non-relapse mortality (NRM) after allogeneic HSCT. In this study, we retrospectively evaluated the incidence of IFI and their impact on the outcomes of allogeneic HSCT.

Methods: The data was obtained from University of Michigan Blood and Marrow Transplant Program database under an IRB-approved protocol. We included only proven and probable fungal infections, defined according EORTC/MSG criteria (CID 2008; June 15;46 (12):1813).

Results: A total of 50 IFI were diagnosed in 542 patients between 2007 and 2012, 76% (n=37) due to mold mostly represented by Aspergillus (n=24, 63%), followed by Zygomyces and Rhizopus. Only 3/37 infections were diagnosed in 2012, probably reflecting more consistent prophylaxis against mold during this period. The CI of mold infections was 6.6% (95% CI 5-10%) and 10.4% (95% CI 8-14%) at 1 and 2 years respectively, with a median time to infection of 194 days (9-644). The median prednisone dose was 15 mg at the time of diagnosis, with a median duration of therapy of 124 days (0-1757). Mold infections were significantly more common in patients with a history of acute GVHD (aGVHD, CI at 1y 10.3% vs. 0.2%, HR=6.2, p=0.0001), but not in those with chronic GVHD (cGVHD, CI at 1y 5.4 vs. 7.7%, HR=0.7, p=0.2). The case fatality rate of mold infections was high at 83.3%, and they were associated with a substantial increase in NRM both in aGVHD (70 vs. 34% at 2 ys, HR=2.6, 1.68-4.1) and cGVHD (43% vs. 15% at 2y, HR=4, 2.2-7.5). After adjusting for other HSCT-related factors, mold infections persisted as an independent risk factor for NRM for patients with both aGVHD (HR=2.78, 1.7-4.4) and cGVHD (HR=4, 2-7).

Conclusions: Mold infections are emerging as a major cause of infection-related mortality, with a very high case fatality rate and a significant impact on NRM in patients with aGVHD and cGVHD. Our data further supports the need for anti-mold prophylaxis in high-risk populations.

336

Early Human Herpesvirus Type 6 Reactivation in Umbilical Cord Blood Allogeneic Stem Cell Transplantation

Frank Cirrone [1], Cindy Ippoliti [2], Koen van Besien [3]. [1] Pharmacy, NewYork-Presbyterian Hospital, New York, NY; [2] Pharmacy, NYP/Cornell, NY, NY; [3] University of Chicago, Chicago, IL

Human Herpesvirus Type 6 (HHV-6) reactivation occurs in 38%-67% of hematopoietic stem cell transplant (HSCT) recipients —usually within the first month post-transplant. Studies have shown that HHV-6 reactivation after allogeneic HSCT delays engraftment, has myelosuppressive effects, and potentially increases the risk of developing acute graft-versus-host disease (aGVHD). An increased incidence of HHV-6 reactivation in umbilical cord blood (UCB) HSCTs has been previously described.

In June 2012, Weill Cornell Medical Center began performing allogeneic HSCTs with haploidentical stem cells followed by UCB (Haplo-Cord). No published studies have examined HHV-6 reactivation and its sequelae in Haplo-Cord HSCTs.

The purpose of this study was to retrospectively assess for risk factors and sequelae of HHV-6 reactivation in UCB HSCTs. The objectives were to determine the impact of early HHV-6 reactivation (within 60 days of transplant) on overall survival and incidence of aGVHD at 100 days post-transplantation.

Fifty-seven adult transplants between August 2010 and June 2013 utilizing UCB with $\geq$ 1 HHV-6 PCR level reported were included: 29 double UCB HSCTs, 26 Haplo-Cord HSCTs, and 2 single UCB HSCTs.

HHV-6 reactivation occurred in 35/57 (61.4%). No baseline factors (age, ASBMT RFI disease classification, conditioning