Methods: A retrospective review of the patients who relapsed following an allogeneic HCT for a myeloid malignancy at Mayo Clinic in Arizona was performed. The BM sample closest in time prior to relapse was identified and the morphologic, flow cytometric, karyotypic, FISH, PCR and chimerism results were reviewed.

Results: Out of 187 patients with a myeloid malignancy, 40 (31 AML, 4 MPN blast crisis, 4 MDS, 1 CML) relapsed at a median of 113 days (range 22-820 days) after HCT. Thirty percent of the relapses occurred after a myeloablative HCT. Donor type was equally distributed between matched related and mismatched/matched unrelated donors. A cytogenetic and molecular marker with the diagnosis was identifiable in 22/40 and 6/40 patients respectively. 18/40 patients had residual disease present at HCT. 13/40 patients showed an early relapse within the first 90 days. In the remaining patients, time between the last BM and relapse ranged from 38-184 days (median 69). Abnormal results were found only in 9/27 patients in the preceding BM and included abnormal cytogenetic clone identical to diagnosis in 2 patients; abnormal RT-PCR for BCR/ABL in 1, cytogenetic abnormality in donor cell line in 3, and decreased chimerisms in unsorted marrow cells in 3 patients.

Conclusions: A 3-month monitoring schedule of BM evaluation using the currently available tools had low sensitivity to predict relapse. Findings that may justify intervention were rare (less than 10% of patients), and were restricted to abnormal cytogenetic and abnormal RT-PCR results. The clinical significance of cytogenetic abnormalities observed in donor cells is not clear. Our findings emphasize that until the optimal surveillance technique and schedule can be defined and standardized, more frequent use of pre-emptive therapy in patients at high risk of relapse may be of benefit.

Impact of Dose Intensification of FluBu2 to FluBu4 on Transplant Related Mortality, Relapse, and Survival After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia in Remission

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Reduced intensity conditioning (RIC) with fludarabine (Flu) and sub-myeloablative doses of busulfan (Bu) (<8 mg/kg) has low transplant related mortality (TRM) compared to myeloablative (MA) conditioning, and is increasingly utilized in older and medically infirm pts. Flu with MA Bu (>5mg/kg) using pharmacokinetic (PK) dosing also has low TRM, but randomized comparisons to RIC are lacking. Therefore, we compared RIC and MA FluBu dosing on TRM, relapse and survival in remission AML. We reviewed AML pts receiving allogeneic hematopoietic stem cell transplant (HSCT) in remission (CR1/CR2) at the University of Michigan from 2003-2011. RIC (FluBu2) was flu 40mg/m2 x 4 days with IV Bu 3.2 mg/kg x 2 days. FluBu2 included TLI/TBI (200cGy) in 39% of cases, and ATG in one case. MA (FluBu4) was flu 40mg/m2 x 4 days with IV Bu 3.2 mg/kg x 4 days with PK adjustment to a target Css of 600-900 mcg/L (Seattle PK lab). FluBu4 had no TBI/TLI/ATG. Pt <18 yrs, cords, prior HSCT and active AML were excluded. Cumulative incidence of GVHD, TRM and relapse were calculated with competing risks. A total of 122 pts (FluBu2=71; FluBu4=51) were identified. Most primary GVHD prophylaxis was tacrolimus + mycophenolate mofetil (89%), and tacrolimus + methotrexate (86%). FluBu2 pts were older (60 vs. 51; P < 0.01), but donor type, HLA match, and disease risk (cytogenetics / FLT3 ITD) were not significantly different. There was a trend towards higher (≥3) comorbidity index scores in FluBu2 (42% vs. 25%; P = 0.09). All FluBu4 pts engrafted; two graft failures occurred (3%) in FluBu2. TRM did not differ at day 100 (FluBu2=0% vs. FluBu4=2%; P = 0.3) or 1 yr (FluBu2=17% vs. FluBu4=10%; P = 0.3), but by 3 yrs there was a trend towards greater TRM in FluBu2 (FluBu2=24% vs. FluBu4=10%; P = 0.6). After adjusting for donor type, HLA match, age, and HCT-CI the trend for greater TRM in FluBu2 remained (HR: 3.5, P = 0.4, 95% CI: 1.1-11.0). Pts with HCT-CI ≥3 had similar TRM with FluBu2 (HR: 1.5, P = 0.6, 95% CI: 0.4-5.7). Acute GVHD grade II-IV was not significantly different between FluBu2 and FluBu4 (38% vs. 24%; P = 0.9). Chronic GVHD caused late deaths in 10% of FluBu2, and in 4% of FluBu4. There was no significant difference in relapse at 3 yrs (FluBu2=43% vs FluBu4=36%; P = 0.5). Overall survival (OS) favored FluBu4 compared to FluBu2 (OS: 62% vs. 39%; P = 0.02). This difference in OS was greater in intermediate risk AML (74% vs 50%; P = 0.07), compared to high risk AML (40% vs 28%, P = 0.3). FluBu4 pts had a non-significant OS advantage after multivariate analysis including donor type, HLA match, and disease risk (HR: 1.75, P = 0.6, 95% CI: 1.0-3.1). In summary, MA conditioning with FluBu4 did not increase TRM compared to RIC with FluBu2. The potential survival benefit of FluBu4 in remission AML requires prospective validation.

Association of Mannose Binding Lectin (MBL) Levels and Invasive Fungal Disease (IFD) in Hematologic Malignancy Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT) or Receiving Chemotherapy

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Background: IFD is a major cause of morbidity and mortality after intensive chemotherapy and HSCT in patients with hematologic malignancies. MBL is a member of the C-type lectin superfamily of microbe pattern recognition molecules. Several studies have suggested an association of MBL levels below 1,000 ng/ml with a variety of infectious complications in cancer therapy, but there are conflicting data. The aim of this study was to investigate the association between low MBL levels and the development of IFD in patients with hematologic malignancies undergoing chemotherapy or HSCT.