Poster Session II

ALLOGENEIC TRANSPLANTS

270

IDENTIFICATION OF AN AUC OF 7603 UMOL*MIN/HR PER DAY X 4 DAYS AS THE MAXIMUM TOLERATED DOSE (MTD) OF IV CONTINUOUS INFUSION (CI) BUSULFAN (BU) WITH FIXED DOSE FLUDARABINE (FLU) IN A PHARMACOKINETICALLY-BASED DOSE PHASE I STUDY IN PATIENTS (PTS) WITH HEMATOLOGIC MALIGNANCIES UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

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We previously demonstrated the benefit of using a test-dose of IV Busulfan to predict systemic exposure in patients with hematologic malignancies undergoing allogeneic stem cell transplant (Walko et al, J Clin Oncol, ASCO, 24, : 16502, 2006). We now report on this approach in 30 pts receiving a 90-hr CI of Bu in a dose-escalation study.

Methods: Pts received a 0.8 mg/kg test dose over 2 hours and PK sampling at 0, 2.5, 4, 5, and 6 hours one week prior to initiation of full-dose treatment. Conditioning consisted of 30 mg/m2 Flu qd × 5 and targeted Bu to achieve an AUC of 4800 (9 pts), 5760 (6 pts), 6912 (8 pts), 7603 (3 pts) or 8363 (2 pts) umol*min/hr/d on days -7 to -3. PK sampling occurred at hours 0, 12, 16, 18, 48, 60, 72, and 89.5. All pts received tacrolimus and IV alemtuzumab in doses of 30mg for matched related donors (MRD) or 60mg for matched unrelated donors (MUD) for prevention of GVHD.

Results: 30 pts (14 MRD, 16 MUD) ages 18–55 (median 37) with high-risk AML (11), ALL (7), MDS (4), or other (8) were enrolled. All engrafted with a median of 13 days to ANC 〉 500 and 14 days to platelet count 〉 20K with no late graft failures. There were 9 treatment related deaths. Seven were from infection: pneumonia (1) and biliary sepsis (1) prior to day 100, and aspergillus (2), nocardia (1), biliary sepsis (1), and hemorrhagic cystitis (1) after day 100. One death was from late VOD and liver failure (d 201), and one from leukoencephalopathy (d 196). Grade 4 toxicities included 3 cases of mucositis (2 at dose level 5, AUC 8363, and 1 at level 2), and 1 liver failure at level 2. Grade 3 toxicities included mucositis (8), hepatitis (3) pneumonia (2) and seizures (1). 11 pts developed grade 2, two grade 3, and one grade 4 aGVHD. Two pts developed extensive and two developed limited cGVHD. 11 pts (37%) relapsed at a median of 117 days (range 17–652) post-transplant. PFS at 18 months was 36%. The MTD was level 4 with a target AUC of 7603 umol*min/hr per day × 4 days. Dose limiting toxicity was grade 4 mucositis in 2/2 pts at dose level 5 with an actual mean AUC of 8600 umol*min/hr per day × 4 days.

Conclusion: This approach permits accurate delivery of a 55% increase in target systemic exposure to IV Bu compared to the standard AUC of 4800 umol*min/hr per day x 4 days, is well-tolerated, and will be studied in a Phase II trial with ATG and MTX as GVH prophylaxis in an attempt to reduce the rate of deaths from late infections and relapse.

271

A STRATEGY FOR DISTINGUISHING SNP IDENTITY IN MULTIPLE-DONORS INVOLVED IN HAPLOIDENTICAL BONE MARROW TRANSPLANTATION

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Chimerism is an important index in hematopoietic cell transplantation (HCT). Determination of chimerism can be challenging in cases of multiple-donors, such as second allogeneic HCT, double-cord blood transplantation, or novel cell therapies. Commonly used methods used to estimate chimerism include cytogenetic analysis in sex disparate transplantations and molecular analysis of polymorphic tandem repeat sequences; however, these techniques are either restricted by gender or inefficient sensitivity. Single nucleotide polymorphisms (SNPs) are the most common source of human genetic diveristy, providing a virtually unlimited resource of molecular markers that can be used to distinguish individuals. In principle, real-time PCR-based assays can be used to assess SNPs, and such assays demonstrate a substantially higher sensitivity (0.001%), but the specificity is unclear due to a low level signal from mismatched sequences. In this study, we cloned 14 pairs of SNPs selected from the SNP HapMap database and examined the specificity and sensitivity of their detection by real-time PCR. We also explored the efficacy of using SNP assays to measure chimerism. Each PCR reaction includes two primer/fluorescent probe pairs to allow genotyping of the two possible variants at the SNP site in a target template sequence. We found that both the polymorphic nucleotide as well as the sequence immediately adjacent to the polymophism influences the ability to distinguish a signal between the target and mismatched sequences. Moreover, the specific fluorescent reporter probe can affect the difference in signal intensity between the target and mismatched sequences which determines the specificity of the assay. By optimal selection of the polymorphic sequences and fluorescent reporter, the real-time PCR SNP assay of chimerism can attain a sensitivity of 0.1%–0.5% with nearly 100% specificity. This strategy will be applied in upcoming clinical trials of bone marrow cell therapy.

XC and TJH contributed equally to this work

272

IMPACT OF CYTOGENETICS AND MARROW REMISSION STATUS ON DISEASE PROGRESSION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) OR MYELODYSPLASTIC SYNDROME (MDS) UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

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Our aim was to determine the impact of cytogenetics and remission status on outcome of AML or MDS pts treated with allogeneic stem cell transplantation (alloSCT) conditioned with busulfan (Bu) based regimens. We reviewed retrospectively all pts who received alloSCT at MD Anderson Cancer Center for AML or MDS between 1990 and 2007 conditioned with Bu (1 mg/kg IV q 6h ×4 days) and cyclophosphamide (60 mg/kg IV × 2 days), Bu and fludarabine (Flu) in myeloablative (Bu 130 mg/m2 ×4 days and Flu 40 mg/m2 ×4 days) or reduced intensity doses. Pts in first or subsequent remission and those achieving morphologic remission after initial induction treatment but without platelet recovery to >100,000/mcl (marrow remission) were included in the analysis. Pts were categorized according to the Dana-Farber cytogenetics classification. Cox's regression analysis was used to evaluate prognostic factors for disease progression, overall survival (OS) and progression free survival (PFS). Among 265 pts (median age 45 [5–69]) diagnoses were AML (n = 217), MDS (n = 17) and AML evolving from MDS (n = 31). Disease status at alloSCT was; first complete remission (CR) (n = 129), advanced remission (beyond first CR) (n = 93) and marrow remission (n = 43). Majority of the donors were matched related (n = 152) or matched unrelated (n = 94). Stem cell source was bone marrow (n = 108), peripheral blood (n = 153) or cord blood (n = 4). Median follow-up time of surviving pts was 39 months (1.6–189). The 3 years actuarial probability of OS was 55% and PFS 49%. On univariate analysis, adverse cytogenetics were associated with higher disease progression rate ($p<0.05$). There was also a trend for worse OS ($p = 0.09$) and PFS ($p = 0.098$) for adverse cytogenetics. In addition pts in "marrow remission" compared to those who were in CR with full platelet recovery prior to transplant had a significantly higher rate of disease progression ($p = 0.001$) and poorer 3 years OS (37% vs 59%, $p = 0.001$) and PFS (30% vs 53%, $p = 0.001$). Outcomes were comparable for pts in first and advanced remissions. Pts with de novo AML had more favorable OS ($p = 0.02$)