288 MINIMAL MORTALITY FROM VENO-OCCulsive DISEASE FOLLOWING BSUFLIN-based PREPARATIVE REGIMENS: A LARGE SINGLE INSTITUTION EXPERIENCE
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Hepatic veno-occlusive disease (VOD) is a frequently cited life threatening limitation of busulfan containing regimens. Reported incidence ranges from 5% to >50% and mortality rates can be substantial. Using a prospectively maintained database, a retrospective analysis was conducted to identify patients undergoing autologous or myeloablative allogeneic stem cell transplant with busulfan/cyclophosphamide or busulfan/cyclophosphamide/etoposide as the preparative regimen at a single institution from 1993–2007. The objective was to estimate the mortality from VOD. 1508 transplant patients (1037 autologous and 471 allogeneic) were identified with 1 to 15 years of follow up. The autologous group had VOD as the primary cause of death in only 3 patients (0.7% of deaths, 0.3% total population). In this group the most common cause of death was relapse (32% of total population, 74.9% of total deaths). The cumulative incidence of non relapse mortality (NRM) was 4.6% (95% CI 3.0–6.8%) being most common. Liver related mortality was not a significant factor in either subset of patients. This is the largest single institution analysis on the mortality risk of VOD following busulfan-based preparation. Unlike some previous reports, lethal VOD was infrequent following busulfan-based preparation and not a significant cause of mortality. When both autologous and allogeneic transplant groups were combined, VOD was the primary cause of death in <1% of patients. In conclusion, in a large single institution with significant experience administering busulfan-based preparative regimens for stem cell transplant VOD as a primary cause of death is extremely low.

289 DIFFERENTIAL MECHANISMS FOR CD4+ AND CD8+ MEDIATED INFLAMMATION IN THE DEVELOPMENT OF EXPERIMENTAL IDIOPATHIC PNEUMONIA SYNDROME
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Idiopathic pneumonia syndrome (IPS) is a frequently fatal complication following allogeneic BMT (allo-BMT). The pathophysiology of IPS involves both soluble and cellular effectors. We examined the role of cytolytic T lymphocyte (CTL) effector function in the development of IPS using well-established murine BMT models. In initial experiments, lethally irradiated B6D2F1 (F1) recipient mice received BMT from either allogeneic (B6) or syngeneic (F1) donors. Mice were then analyzed for the development of IPS and for donor T cell chimerism, cytokine phenotype, and CTL activity in the lungs at specified points after BMT. At week six, allo-BMT recipients developed significant lung injury compared to syngeneic controls. Donor CD4+ and CD8+ T cells use both FasL and TNFα but not IL-4 or IL-5. Furthermore, mRNA expression revealed that lungs from allo-BMT recipients expressed high levels of perforin, FasL and Fas within the first 2 weeks compared to syngeneic controls. Immunohistochemistry and FACS analysis confirmed that protein levels of Fas were also increased in the lungs after allo-BMT. Significant CTL activity (chromium release assay) mediated by both perforin and FasL, was present as early as week 2 after BMT. Next, F1 animals received allo-BMT from either wild type (WT) B6 donors or from B6 mice deficient in either perforin (p–/–) or FasL (gld). Reduced intensity conditioning (RIC) with FLU/MEL followed by hematopoietic stem cell transplantation (HSCT) may result in donor CD4+ and CD8+ T cells and TNFα levels. Further studies using strain combinations wherein donor and host mice differed at either MHC class I (CD8+ mediated IPS) or MHC class II (CD4+ mediated IPS), and additional donor mice lacking TNFα revealed that CD4+ cells use both FasL and TNFα whereas CD8+ T cells appear to use TNFα exclusively during the evolution of IPS. We conclude that CTL activity is present in the lungs of mice with IPS and that differential pathways for cell-mediated cytotoxicity are used by CD4+ and CD8+ T cells in this setting. These data confirm a role for cellular effector mechanisms in IPS and may provide insight toward developing novel strategies for treating this serious complication of allo-BMT.

290 PHASE I-II STUDY OF CLOFARABINE-MELPHALAN-ALEMTUZUMAB CONDITIONING FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN PATIENTS WITH ADVANCED HEMATOLOGIC MALIGNANCES: UNEXPECTED RENAL TOXICITY

Fludarabine Melphalan-alemtuzumab (Flu-Mel-Camp) conditioning has high recurrence rates. Clofarabine (Clo), a second generation nucleoside analog, might enhance disease control. We report an ongoing phase I-II study of Clo-Mel-Camp conditioning. GVHD prophylaxis used tacrolimus. For the phase I, one pt was enrolled per level, until the first DLT or until 2 had gr 3 toxicity. Level 1 was: Clo 10 mg/m2/day on d -7 to -3 and Mel 100 mg/m2/day on d -2. Clo was increased by 10 mg per cohort until 40 mg/m2/d. Then Mel by 20 mg until 140 mg/m2. 12 pts were accrued in the phase I. 4 died from TRM: 2 of early sepsis unrelated to Clo toxicity; 1 from multi-organ failure and possible regimen related toxicity (RRT); and 1 at d159 from sepsis. The phase II dose was Clo 40 mg/m2/ day x 5 d and Mel 140 mg/m2. 3 pts in the phase I and 21 pts in the phase II portion received this dose. Median age 33 (20–70); 17 Myeloid, 1 CLL, 15 NHL; 26 high or intermediate risk, 5 relapse after alloHCT, 7 after auto HCT. HCT-CI was ≥ 3 in 12 and ECOG PS ≥ = 1 in 13. 18 had sib and 15 MUD donors. All evaluable pts engrafted. Median d 30 donor chimerism was 95% (14–100) with no late graft failures. There were 3 deaths from TRM in the phase II: 2 from RRT and 1 from GVHD. Grade 3–4 renal toxicity occurred between day -7 and day +7 in 8 of 24 (33.3%) pts receiving full dose Clo and Mel. Only 1 has recovered. No grade 3 renal toxicity occurred between day -7 and day +7 among 112 pts on Flu-Mel-Camp(P < 0.000). In addition grade 2 renal failure occurred in 8 pts, reversible in 5. Other toxicities included: gr 2–3 reversible ALT elevation in 17 pts; gr 2 reversible bilateral elevation in 2 pts; gr 2–3 hand–foot syndrome in 10 pts; gr 3 mucositis and pulmonary hemorrhage in 1 pt. With median follow-up of 173 days (12–487), 3 of 12 in the phase I, and 16 of 21 pts in the phase II portion remain in remission. Estimated day 180 progression-free survival is 53% (95% CI: 34–72) with no failures beyond day 160. Conclusions: Clo-Mel-Camp induces durable engraftment. Response and duration of response are encouraging. Common toxicities are elevation of transaminases, hand foot syndrome and grade 2–4 renal failure. There were seven TRM, all in pts with high risk disease, prior transplant and/or multiple comorbidities. Three TRM were attributed to Clo toxicity and occurred in the context of early onset grade 3–4 renal failure. Because of this, the Clo dose will be reduced to 30 mg/m2/day x 5 days.

291 TOTAL MARROW AND LYMPH NODE RADIATION THERAPY (TML) WITH FLUDARABINE (FLU) AND MELPHALAN (MEL) IS WELL TOLERATED AND MAY RESULT IN IMPROVED OUTCOME IN PATIENTS (PTS) WITH ADVANCED HEMATOLOGIC MALIGNANCIES
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Reduced intensity conditioning (RIC) with FLU/MEL followed by hematopoietic stem cell transplantation (HSCT) may result in reduced toxicity compared to myeloablative conditioning (MAC). A prospective, multi-institutional, phase I-II trial evaluated the safety and feasibility of total body irradiation (TBI), 100 cGy, followed by Fludarabine/Plerixafor (Flu/P) with Mel-depleted hematopoietic grafts. 133 adults (pts) with hematologic malignancies (HMA) were treated between 1999–2007. TBI included: 132 pts with 100 cGy; 1 pt with 200 cGy. 98% of pts were treated with Flu/P, 1% with Flu alone. Mean age 63±12, 52% men, 82% myeloablative, 16% autologous. Median follow-up 22 months. TBI was well-tolerated, mostly grade 1–2 with no late toxicity. 76% of pts engrafted, and 90% were in CR at 12 months. Most common grade 3–4 non-hematologic toxicity was neutropenic fever (52%). A total of 67% of pts developed grade 3–4 mucositis with grade 4–5 requiring hospitalization in 2% of pts. In conclusion, the feasibility of Flu/P with Mel-depleted grafts was demonstrated in pts with advanced HMA.
long-term survival in pts with hematologic malignancies and compromised organ function (COF); however, pts with advanced disease do poorly with RIC alone (Giralt, Biol. Blood Marrow Transplant, 13:884, 2007). In an attempt to improve the anti-tumor efficacy of RIC, while maintaining a low-toxicity profile, we added TMLI to FLU/MEL. We hypothesize that Flu/Mel with 1200 cGy of TBI delivered using 1-MV linac therapy is safe, tolerable, and may improve outcome in pts with COF and advanced hematologic malignancies.

Patients and Methods: Pts, ≥50 years of age or COF with advanced disease status defined as high-risk remission and marrow blasts ≥10%, were eligible. The RIC consisted of FLU 25 mg/m²/d x 5 days, MEL 140 mg/m² for one day, and TMLI delivered at 150 cGy/fraction in 8 fractions over 4 days.

Results: There were 16 evaluable pts (median age: 50.8 yr range 24.3–65.7 yr). The diagnoses were: AML (n = 10), ALL (n = 1), NHL (n = 2), multiple myeloma (n = 1). At the time of HSTCT 9 patients (56%) had advanced disease: 1st or 2nd relapse (n = 3), induction failure (n = 5) and progressive disease (n = 1). Seven pts (44%) were in complete remission. Mobilized peripheral blood stem cells from HLA-identical siblings (n = 7) or matched unrelated donor (n = 9) were used in all cases. Transplant-related toxicities by day +30 included: nausea grade 2 (n = 4) grade 3 (n = 12), emesis grade 2 (n = 6) and grade 3 (n = 4), mucositis grade 2 (n = 2) and grade 3 (n = 14) and anorexia grade 2 (n = 6) and grade 3 (n = 4). Myeloid and platelet engraftment occurred at a median of 15 (range: 10–19 days) and 16 (range:10–19 days) days post transplant, respectively. Acute GvHD grade II–IV occurred in 38.5% of patients (grade II (31%) and grade III in 7.5%) and extensive chronic GvHD in 3 patients (19%). Five patients expired; 2 of relapsed disease, 1 with a secondary malignancy, and 2 of transplant related mortality. At a median of 12 month overall survival (OS) and disease-free survival (DFS) are 81% (95% CI, 51%–91%), and 59% (95% CI, 23%–82%), respectively.

Conclusion: The addition of TMLI at a dose to RIC with FLU/MEL appears to be tolerable and safe. The low rate of relapse and improved OS and DFS compared to historical data are promising. A study is ongoing to further assess efficacy in pts with hematologic malignancies who are not eligible for RIC due to disease burden.

292 CYCLOSPORINE, MYCOPHENOLATE MOFETIL AND METHOTREXATE AS POST GRAFTING IMMUNOSUPPRESSION AFTER NONMYELOABLATIVE ALLOGENIC STEM CELL TRANSPLANTATIONS CONDITIONED WITH FLUDARABINE AND LOW-DOSE TOTAL BODY IRRADIATION


Introduction: Nonmyeloablative (NM) hematopoietic cell transplantation (HCT) has extended the potential curative treatment option of allografting to patients in whom it was previously contraindicated due to advanced age or comorbidity. Graft-versus-host disease (GvHD), however, remains one of the major impediments to long term remission. Recently, our group has introduced a modified post grafting immunosuppression by adding methotrexate (MTX) onto the standard mycophenolate mofetil (MMF)/cyclosporine (CSP) protocol for NMHCT recipients, with significant reduction in severe GvHD and non relapse mortality (NRM), thereby conferring favorable survival in patients receiving NMHCT. The current study is initiated to assess the feasibility and efficacy of similar approach in the setting of single institution with additional patient accrual.

Patients and Methods: Twenty-seven patients (median age, 47 years) with hematologic diseases, who were poor candidates for a conventional myeloablative transplantation, receiving NM conditioning with fludarabine 90 mg/m² and total body irradiation (TBI) 200-cGy, followed by filgrastim-mobilized peripheral blood stem cells (PBSC) from HLA identical (n = 26), or matched unrelated (n = 1) donors. Diagnosis include leukemia/MDS (n = 17), lymphoma (n = 2), ALL (n = 1), myeloma (n = 5) and CML (n = 2). All patients were given CSP, MMF and short course of MTX as post-grafting immunosuppression.

Results: The median times to neutrophil (500/mL) and platelet recovery (100,000/mL) were 20 and 11 days, respectively. Methotrexate was moderate with neutrophil counts not declining below 500/mL in 5 (19%) patients, and with more than half of the patients not requiring any blood or platelet transfusion. Non-relapse mortality was low with no transplant related death occurring within the first 1 year. Overall, 11 (20%) patients had grade 2–4 acute GvHD, with only 5 (9%) patients experiencing grade 3–4 acute GvHD. Acute GvHD was diagnosed at median day +98 (range, days +33 to +138). Extensive chronic GvHD was observed in 2 of 24 evaluable patients (8.3%). Relapse-related death occurred in 6 (21%) patients. At median follow-up of 40 months (range, 20–57 months), the 4-year probability of overall and progression-free survival were 61% and 42%, respectively.

Conclusions: The addition of MTX onto the CSP and MMF as post grafting immunosuppression offers the possibility of further optimization of GvHD control in patients receiving NMHCT, with encouraging survival.

293 ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT) FOR PATIENTS IN THE 6TH AND 7TH DECADES OF LIFE WITH AML OR MDS USING MYELOABLATIVE, REDUCED TOXICITY IV BUSULFAN/FLUDARABINE (BUFLU) CONDITIONING REGIMEN

Poster: S. Giralt, L. Anderson, B., Pelusino, M., Rondon, G., Qazi-Ratib, M., Giralt, S., de Padua Silva, L.J., Huang, G., Kebriaei, P., Zhang, W., Saliba, R., Champlin, R., de Lima, M.: UT MD Anderson Cancer Center, Houston, TX; 2 University of Pisa, Pisa, Italy

AML and MDS are moderately sensitive to the graft-versus-leukemia effect, therefore making the preparative regimen dose intensity an important part of the treatment plan. For patients older than age 55, the optimal conditioning regimen prior to HSTCT remains to be determined. Because of the high rates of morbidity and mortality associated with HSTCT in the elderly, many patients older than 50–55 years are excluded from treatment with myeloablative conditioning regimens. Herein, we report promising findings using intravenous (IV) BuFlu myeloablative conditioning regimen in patients older than age 54 years with AML or MDS.

Methods: A cohort of 74 patients age 53 years with AML (n = 60) with high or intermediate risk cytogenetics or MDS (n = 14) with a high IPSS were transplanted in first complete remission (CR1) or with disease beyond CR1. The preparative regimen consisted of IV Flu 40 mg/m² and IV Bu 130 mg/m² given once daily over 3 hours on pre-transplant days -6 to -3. Graft-versus-host disease (GvHD) prophylaxis was accomplished with use of Tacrolimus and methotrexate.

Results: Median age was 58 years (range 55–60); 18 patients (24%) were older than 59 years. Fifty-four percent of patients were in CR1, CR2, and with active disease at time of HSTCT, respectively. Thirty-two percent of the patients have relapsed (n = 22), GVHD (n = 5), and infection (n = 24). Myeloid and platelet engraftment occurred at a median of 15 (range: 10–19 days) and 16 (range:10–19 days) days post transplant, respectively. Acute GvHD grade II–IV occurred in 38.5% of patients (grade II (31%) and grade III in 7.5%) and extensive chronic GvHD in 3 patients (19%). Five patients expired; 2 of relapsed disease, 1 with a secondary malignancy, and 2 of transplant related mortality. At a median of 12 month overall survival (OS) and disease-free survival (DFS) are 81% (95% CI, 51%–91%), and 59% (95% CI, 23%–82%), respectively.

Conclusion: Our results show low TRM rates for selected patients in the 6th and 7th decades of life with high-risk AML and MDS who received BuFlu. Furthermore, long-term follow up indicates that responses with this regimen are stable in a significant proportion of patients. We conclude that age in itself should not be the primary reason to exclude patients from receiving myeloablative transplants.

Cumulative Incidence of Transplant-Related Mortality (TRM) by Pre-Transplant Disease Status

<table>
<thead>
<tr>
<th>Pre-Transplant Disease Status</th>
<th>TRM</th>
<th>30-Days</th>
<th>100-Days</th>
<th>1-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>None</td>
<td>4%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>ALL CR (n = 40)</td>
<td>None</td>
<td>5%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>CR1 (n = 24)</td>
<td>None</td>
<td>4%</td>
<td>15%</td>
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<tr>
<td>Persistent Disease (n = 24)</td>
<td>None</td>
<td>3%</td>
<td>27%</td>
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