Tuesday, March 28th

16:30-18:00

Oral 12: Conditioning regimens

Thiotepa-Busulfan-Fludarabine compared to Busulfan-Fludarabine as conditioning regimen for matched sibling and unrelated donor transplant in patients with acute myeloid leukemia in first complete remission. A study from the Acute Leukemia Working Party (ALWP) of the European society for Blood and Marrow Transplantation (EBMT)

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Abstract

Background Intravenous (iv) Busulfan plus fludarabine (BF) is a widely used conditioning regimen for matched sibling (MSD) and unrelated donor (URD) transplant (SCT) in AML. Thiotepa, busulfan and fludarabine (TBF) regimen was initially developed for cord blood and subsequently employed in haplo-SCT; however, there is limited evidence about its value in MSD and URD SCT in AML. Patients and methods We included adult AML patients (pts) who had received TBF or BF as conditioning regimen for MSD or URD SCT in CR1 between 2007 and 2015, reported to the EBMT. Pts who received oral busulfan, T-depleted grafts, or transplant from 8/10 or inferior HLA-matched donor were excluded. Myeloablative conditioning regimen (MAC) was defined by iv Busulfan dose ≥ 9.6 mg/kg (TBF-MAC and BF-MAC), while reduced-intensity conditioning (RIC) by iv Busulfan dose of 6.4 mg/kg (TBF-RIC and BF-RIC). A total of 2910 pts met the inclusion criteria (212 TBF and 2698 BF). 147 pts received TBF-MAC and 65 TBF-RIC, while 1459 received BF-MAC and 1239 BF-RIC regimen, respectively. Fifty-seven percent of the pts were transplanted from MSD, 34% from 10/10 URD and 9% from 9/10 URD, respectively. Results As compared to BF-MAC, TBF-MAC group included significantly younger pts (45 vs 50 years), which were transplanted more recently (2014 vs 2013), received more frequently URD transplant (49% vs 35%) from a male donor (69% vs 59%) and BM as stem cell source (34% vs 17%). Engraftment rate was 98% following both regimens. The 2-year NRM was significantly higher after TBF-MAC compared to BF-MAC (27% vs 16%, p=0.006), respectively. Incidence of grade II–IV aGVHD was 25% vs 24% (p=0.8), respectively. The 2-year cumulative incidence of cGVHD was similar following TBF-MAC (35%) compared to BF-MAC (40%, p=0.5). The 2-year RI was significantly lower in TBF-MAC (14%) compared to BF-MAC (27%, p=0.002), while LFS and OS were 59% vs 57% (p=0.5) and 62% vs 61% (p=0.9) in TBF-MAC vs BF-MAC, respectively. The 2-year refined GVHD-free, relapse-free survival (GRFS) was 52% in TBF-MAC and 41% in BF-MAC (p=0.2). Multivariate analysis confirmed significantly higher NRM (HR 2.7, p<10^-5) and lower RI (HR 0.47, p=0.005) for TBF-MAC, thus leading to similar LFS (p=0.6) and OS (p=0.3) as compared to BF-MAC. A propensity score (PS)-matched pair analysis conducted on 138 TBF-MAC vs 262 BF-MAC pts confirmed those results. Among pts who received a RIC
regimen, TBF group (TBF-RIC) included significantly more pts receiving BM graft (17% vs 5%), transplanted more recently (2014 vs 2012), with a combination of CMV positive donor (71% vs 53%) and recipient (87% vs 66%), as compared to BF-RIC. Engraftment rate was 96% following TBF-RIC and 99% after BF-RIC (p = 0.063). Incidence of 2-year NRM was 15% and 18% for TBF-RIC and BF-RIC, respectively (p = 0.6). Incidence of grade II-IV aGVHD was 22% in both protocols. Cumulative incidence of cGVHD at 2 years was 40% in TBF-RIC and 34% in BF-RIC (p = 0.95), while RI was 39% vs 30% (p = 0.6), respectively. Similarly, no difference was observed in terms of LFS (47% vs 52%, p = 0.4) and OS (60% vs 57%, p = 0.8). The 2-year refined GRFS was 38% in both groups. Multivariate analysis and PS-matched pair analysis on 61 TBF-RIC vs 118 BF-RIC pts confirmed those results. Conclusions These data suggest that in AML pts transplanted from MSD or URD-SCT in CR1, TBF-MAC provides better leukemia control but significantly higher NRM, thus leading to similar survival as compared to BF-MAC. RIC doses of TBF and BF resulted in analogous outcome.

Disclosure of conflict of interest

None
OUTCOMES AFTER SINGLE CORD BLOOD AND UNMANIPULATED HAPLOIDENTICAL STEM CELL TRANSPLANTATION USING THIOTEPA-BUSULFAN-FLUDARABINE (TBF) AS MYELOABLATIVE CONDITIONING IN ADULT PATIENTS WITH ACUTE MYELOID LEUKEMIA IN COMPLETE REMISSION: A COMPARATIVE STUDY ON BEHALF OF EUROCORD AND THE ALWP OF THE EBMT

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Abstract

Introduction: Unrelated cord blood transplantation (UCBT) and unmanipulated haploidentical stem cell transplantation (Haplo) are valid alternative options to treat patients (pts) with AML in need of HSCT. TBF as myeloablative conditioning (MAC) in single UCBT (SUCBT) has been widely applied and its efficacy is well established. Recently, its use is substantially increasing in the Haplo setting. Materials and methods: We retrospectively compared results of SUCBT (n=133, 57 females and 76 males) and Haplo (n=184, 83 females and 101 males) after TBF-based MAC in adults with de novo AML in first (CR1) or second (CR2) complete remission. Pts were transplanted between 2007 and 2015 in 77 EBMT centres (15 performed both SUCBT and Haplo). None had prior HSCT. TBF MAC was defined as a regimen containing a total dose of intravenous Busulfan ≥9.6mg/Kg. Results: Median follow-up was 21 and 22 months in SCBT and Haplo, respectively. Haplo were performed more recently, 2014 vs 2011 for SUCBT (p<0.001). Most of the pts were transplanted in CR1 (76% and 70% in SUCBT and Haplo, respectively, p=0.2). Median time from diagnosis to transplant was longer for Haplo (6.6 vs 5.7 months, p=0.01). Median age was 41 (range 18-68) and 45 (range 18-66) years at SUCBT and Haplo (p=0.028), respectively. ATG was most frequently used in SUCBT (87% vs 29%; p<0.001). In Haplo, bone marrow was the main source (80%) and post-transplant cyclophosphamide (PT-Cy) was administrated in 70% of the pts. Neutrophil engraftment was achieved in 88% of SUCBT and 96% of Haplo (p=0.018). In univariate analysis, 2-years (2-y) relapse incidence (RI) was 11% for SUCBT and 16% for Haplo (p=0.44). Cumulative incidence (CI) of grade II-IV acute GVHD (aGVHD) at 100-days and chronic GVHD (cGVHD) at 2-y were 28% and 37% for SUCBT, and 26% and 34% for Haplo (p=0.88 and p=0.57), respectively. CI of 2-y NRM was higher in SUCBT (44% vs 22%, p<0.10). The 2-y probabilities of LFS and GRFS in SUCBT and Haplo were 44% vs 61% (p<0.001) and 31% vs 54% (p<0.001), respectively. Overall, 65 pts died after SUCBT and 52 after Haplo. Causes of death were relapse (SUCBT: 13%, Haplo: 27%), GVHD (SUCBT: 24%, Haplo: 20%), infections (SUCBT: 46%, Haplo: 35%), others (SUCBT: 17%, Haplo: 18%). OS at 2-y was higher for pts receiving Haplo (67% vs 48%, p=0.0005). No significant differences were found between pts given or not PT-Cy in the Haplo group. In multivariate analysis, NRM was significantly higher in SUCBT compared to Haplo (HR: 2.54, p=0.008, 95%CI: 1.27-5.06). SUCBT did worse in terms of LFS, GRFS and OS (LFS, HR: 1.75, p=0.044, 95%CI: 1.01-3.02; GRFS, HR: 1.72, p=0.027, 95%CI: 1.06-2.78; OS, HR: 1.75, p=0.05, 95%CI: 1.3-3.07). Type of donor was neither associated with RI, nor to grade II-IV aGVHD or cGVHD. Other factors associated with poorer outcomes were age at transplant, use of female donors in male pts and Karnofsky PS<90. No centre effect was found. These results were all confirmed using propensity score analysis. Conclusion: These findings indicate that TBF-based regimen
is effective and safe in the Haplo setting. In the current cohort, NRM, LFS, GRFS and OS were improved for Haplo compared to SUCBT. High NRM in SUCBT was mostly due to infections. Impact of older age and poorer Karnofsky PS suggest that TBF at reduced intensity could be considered in older or unfit pts to improve outcomes.

**Disclosure of conflict of interest**

The authors declare no conflict of interest to disclose.
Reduced-intensity vs reduced-toxicity myeloablative fludarabine/busulfan-based conditioning regimens for allografted non-Hodgkin lymphoma adult patients: a retrospective study on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire.

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Abstract

Introduction: Allogeneic stem cell transplantation is a potentially curative treatment for patients with high-risk non-Hodgkin lymphoma (NHL). Fludarabine/busulfan based conditioning regimens are widely used in Europe for this purpose. Busulfan dose intensity discriminates between reduced intensity (FB2) and reduced-toxicity myeloablative (FB3/FB4) conditioning regimens. While some data have been recently published showing some advantages of higher busulfan dose intensity for myeloid malignancies, there is no such data available in the lymphoid setting. Methods: This was a large retrospective study conducted on behalf of the SFGM-TC including all adults allografted in France between January 2004 and December 2014 for NHL (n=378). Clinical data were obtained through ProMiSe (Project Manager Internet Server), an internet-based system shared by all French transplantation centers. We aim to compare various outcomes between those who received FB2 (n=277) or FB3/FB4 (n=101) as conditioning regimens. Results: Both groups were comparable for the following variables: median follow-up (FB2: 24.9 vs FB3/4: 23 months), gender (male 61% vs 53%), disease type (low-grade lymphoma 25% vs 21%, mantle-cell lymphoma 17% vs 13%, high-grade lymphoma 25% vs 21%, T cell lymphoma 32% vs 45%), disease status at transplant (complete remission/very good partial response 64% vs 62%, partial response 28% vs 31%, active disease 8% vs 7%), donor type (sibling 43% vs 49.5%, matched unrelated 56% vs 47), median number of previous courses of treatment (2 vs 2, p=0.44), stem cell source (peripheral blood 96% vs 95%). FB2 patients were significantly older (median 57.3 vs 53.1 years, p=0.07), have been transplanted more recently (median year of transplant: 2011 vs 2010, p=0.001) and have been more previously autografted (69% vs 50.5%, p=0.001). FB3/4 patients have been allotransplanted earlier during the evolution of their disease (median time between diagnosis and allograft 18.2 vs 33.8 months, p<0.0001). The majority of patients (n=353, 98.4%) received ATG as GVHD prophylaxis. In univariate analysis, 2-years OS (FB2 66.5% vs 60.3%, p=0.33), LFS (FB2 57.9% vs 49.8%, p=0.26), R1 (FB2 23% vs 29.1%, p=0.32) and NRM (FB2 19% vs 21.1%, p=0.91) were similar between both groups. Cumulative incidence of grade 3-4 acute (FB2 11.2% vs 18%, p=0.08) and extensive chronic (FB2: 17.3% vs 10.7%, p=0.18) GVHD were also comparable as well as 2-year GRFS (FB2: 44.4% vs 42.8%, p=0.38). In multivariate analysis there was a trend for worse outcome using
FB3/FB4 regimens (OS: HR 1.46, 95%CI: 0.96-2.23, p=0.07; LFS: HR: 1.43, 95%CI: 0.99-2.06, p=0.05; RI: HR 1.54; 95%CI: 0.95-2.48, p=0.07). These results were also confirmed using a propensity score-matching strategy including 184 FB2 and 98 FB3/4 patients. Conclusion: This large retrospective study showed that reduced toxicity myeloablative fludarabine/busulfan regimens did not improve outcomes of adults allografted for NHL. FB2 conditioning regimen still should be considered as the standard of care conditioning regimen in this setting. To validate these results, prospective studies are needed, like the French prospective trial currently ongoing for myeloid diseases (NCT01985061). Also, new conditioning regimens and post-allograft strategies should be tested to improve outcomes of patients.

Disclosure of conflict of interest

No
The outcome of BEAC conditioning regimen prior to autologous stem cell transplant in non-Hodgkin lymphoma (NHL) and comparison with BEAM conditioning: a Lymphoma Working Party-EBMT study.

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Abstract

Introduction: High dose therapy and autologous stem cell transplant (ASCT) is considered the standard consolidation therapy in several lymphoma subtypes. The optimal conditioning therapy for ASCT has not been established and most centres currently use the BEAM regimen (BCNU, VP-16, ara-C, melphalan). A recent shortage of melphalan has prompted transplant centres to use alternative conditioning regimens. The BEAC regimen (BEAM with melphalan substituted by cyclophosphamide) has previously been described and is, therefore, a reasonable alternative. However, there have been concerns raised about the toxicity of BEAC conditioning, particularly in relation to cardiac complications and multiple organ failure (MOF). Methods: We conducted a retrospective analysis of the EBMT database. Inclusion criteria were the following: BEAC or BEAM conditioning prior to ASCT; age≥18; histological diagnosis of follicular lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma or peripheral T cell lymphoma; no prior transplant; peripheral blood stem cells; date of transplant 2007–2016. Planned tandem SCTs were excluded. 21722 patients (424 BEAC, 21298 BEAM) were identified fulfilling these criteria. Basic patient and transplant related details were obtained from the Med A submissions to the EBMT database. 383 BEAC conditioned patients with adequate essential data were matched with BEAM conditioned patients (ratio of 1:2) using the following matching criteria: age at SCT, gender, disease status at SCT, performance status at SCT, NHL subtype, year of SCT. The matched cohorts were compared in terms of non-relapse mortality (NRM), relapse (RR), progression free survival (PFS) and overall survival (OS). Results: A total of 383 patients received BEAC conditioning regimen prior to ASCT at 29 different centres. Only 11 centres had used the BEAC conditioning 5 or more times and 1 centre performed 149 of the transplants. The number of BEAC conditioned ASCT ranged from 23 to 70 per year over the study period. There was a marked variation in the use of BEAC by country, with the majority of cases performed in 5 countries (Sweden 171, Finland 77, Israel 63, Portugal 43, Italy 34). The characteristics of the BEAC and the matched BEAM cohorts are given in Table I. With a median follow up of 28 months for the BEAC group, 25 patients have died from NRM events (6 infection, 5 MOF, 2 infection + cardiac toxicity, 1 infection + pulmonary toxicity, 1 cardiac toxicity, 6 secondary malignancies, 4 unknown). In the matched BEAM cohort there were 34 NRM events (9 infection, 4 MOF, 1 infection + VOD, 2 infection + pulmonary toxicity, 4 cardiac toxicity, 5 secondary malignancies, 5 other causes, 4 unknown). At 1 year the cumulative incidence of NRM was 4% in the BEAC conditioned patients and 3% in the BEAM group (p=NS). The 2-year RR was 32% with BEAC and 33% with BEAM (p=NS). At 2 years the PFS was and OS were 63% and 78% for BEAC and 63% and 77% for BEAM conditioned patients (p=NS for PFS and OS). Conclusions: In this retrospective study the toxicity observed with BEAC conditioning as measured by NRM was similar to that seen with BEAM. The concerns regarding cardiac toxicity and MOF were not confirmed with 32% and 23% of NRM deaths in the BEAC and BEAM cohorts, respectively, being related to these toxicities. In addition, there were no significant differences between the two groups in terms of other outcomes, suggesting that BEAC is a safe conditioning regimen.
Table I Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>BEAC (n=383)</th>
<th>BEAM (n=766)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at SCT, median (range)</td>
<td>57.6 (19-73)</td>
<td>57.9 (18-76)</td>
</tr>
<tr>
<td>Gender, n (%) Male</td>
<td>253 (66.1)</td>
<td>506 (66.1)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>130 (33.9)</td>
</tr>
<tr>
<td>Months from diagnosis-SCT, median (range)</td>
<td>11.5 (2.3-226)</td>
<td>11.7 (0.9-237)</td>
</tr>
<tr>
<td>Lymphoma subtype n, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>159 (41.5)</td>
<td>318 (41.5)</td>
</tr>
<tr>
<td>Follicular Lymphoma</td>
<td>74 (19.3)</td>
<td>148 (19.3)</td>
</tr>
<tr>
<td>Mantle Cell Lymphoma</td>
<td>121 (31.6)</td>
<td>242 (31.6)</td>
</tr>
<tr>
<td>Peripheral T Cell</td>
<td>29 (7.6)</td>
<td>58 (7.6)</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>351 (91.6)</td>
<td>702 (91.6)</td>
</tr>
<tr>
<td>Poor</td>
<td>6 (1.6)</td>
<td>12 (1.6)</td>
</tr>
<tr>
<td>Not known</td>
<td>26 (6.8)</td>
<td>52 (6.8)</td>
</tr>
<tr>
<td>Disease status at SCT, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1/VGPR1/PR1</td>
<td>196 (51.2%)</td>
<td>392 (51.2%)</td>
</tr>
<tr>
<td>CR/VGPR/PR&gt;1</td>
<td>92 (24.0)</td>
<td>184 (24.0)</td>
</tr>
<tr>
<td>CR unknown</td>
<td>27 (7.1)</td>
<td>54 (7.1)</td>
</tr>
<tr>
<td>PR unknown</td>
<td>15 (3.9)</td>
<td>30 (3.9)</td>
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<tr>
<td>Primary Refractory</td>
<td>7 (1.8)</td>
<td>14 (1.8)</td>
</tr>
<tr>
<td>Relapse/Progression</td>
<td>46 (12.0)</td>
<td>92 (12.0)</td>
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Disclosure of conflict of interest
None
HAPLOIDENTICAL BONE MARROW TRANSPLANT WITH A MODIFIED POST-TRANSPLANT CYCLOPHOSPHAMIDE (PT-CY) REGIMEN, IN ACUTE LEUKEMIA PATIENTS: A MULTICENTER STUDY

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Abstract

Introduction: In last decade haploidentical bone marrow transplantation (HAPLO-BMT) with post-transplant cyclophosphamide (PT-CY) is being increasingly used in patients with acute myeloid leukemia (AML) who lack a suitable HLA-matched donor. The Baltimore regimen included PT-CY 50 mg/kg on days +3 and +4, with a calcineurin inhibitor and mycophenolate (MMF) starting on day +5 after transplant after a non myeloablative conditioning regimen. We modified the original Baltimore regimen and are now reporting a multicenter retrospective analysis in 142 AML patients. All patients received cyclosporine (CsA) starting on day 0, MMF starting on day +1, and PT-CY 50 mg/kg on days +3 and +5. Patients and conditioning regimen. All patients received unmanipulated haploidentical marrow between year 2010 and 2016. Clinical characteristics were: 73/69 M/F, median age 50 years (17-74); low ELN risk group (3%) intermediate risk (34%) and high risk (63%); FLT3-ITD positivity (22%); first complete remission (CR1) (46%), second CR (CR2) (21%) and active disease (33%). The median dose of TNC infused was 3.1x10^6/kg (range 0.8-6.5). All patients received a myeloablative regimen: either thiopeta (10 mg/kg), busulfan (3.2 mg/kgx3), fludarabine (50 mg/m^2x3) (TBF) in 114 patients (median age 55 years), or full dose TBI in 28 patients (median age 37 years). Busulfan was capped at 2 days in patients over 60 years. The median follow up for surviving patients was 532 days (100-1893). Results: 133 patients (94%) engrafted; the median time to neutrophil 0.5x10^9/L was day 18 (range 13-56), while to platelets 20x10^9/L was 24 days (range 9-90). The 100 day cumulative incidence (CI) of grade II-IV and III-IV aGVHD was 17.1% and 3.1%. The CI of moderate and severe cGVHD was of 16.3% at 3 years. The CI of transplant related mortality (TRM) at 5 years was 18%; the CI of relapse related death (RRD) was 32%. Causes of death were relapse (n=26), infections (n=14), graft failure (n=3), multi-organ failure (n=2), chronic GvHD (n=2), and interstitial pneumonia (n=2). Patients in CR1, CR2, or with active disease, had an actuarial 5 year overall survival (OS) of 67%, 62% and 23%, respectively (p<0.0001); a CI of TRM at 5 years of 13%, 20% and 31% (p=0.03) respectively and a RRD of 12% for CR1 and CR2, and 47% for active disease (p<0.00001). The OS according to risk groups was 76%, for intermediate risk and 44% for high risk patients (p=0.007). Survival free of GvHD and relapse (GRFS) at 3 years, was 68% for CR1+CR2 patients and 17% for pts with advanced disease (fig.1). We found that older patients receiving grafts from older donors had a higher TRM (57%) only if the disease was advanced. In multivariate analysis, active disease at transplant was the only negative predictor of survival. Despite older age of patients given TBF (10 year difference), survival was comparable to the TBI regimen; the OS of 22 patients aged 60 and over, receiving TBF, grafted in CR1 or CR2, was 73%. Conclusion: This study shows that our modified PT-CY regimen, with CyA given before PT-CY, and one day rest between the two CY doses, can be successfully applied in a multicenter setting of unmanipulated HAPLO-BMT for AML. We demonstrated a very low incidence of severe GvHD and an excellent outcome in terms of TRM, RRD and survival for CR1,CR2 patients also in patients over 60. Relapse remains a problem in patients with active disease and may require post-transplant interventions.
Reference


Disclosure of conflict of interest

None
Melphalan 140mg/m2 demonstrates identical clinical outcomes to melphalan 200mg/m2 amongst patients undergoing autologous transplant for multiple myeloma: a multicentre UK study

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Abstract

Introduction Dose-attenuated melphalan (MEL140) is used as a conditioning regimen for autologous stem cell transplant (ASCT) in older patients with multiple myeloma (MM), and in those with renal impairment or other substantial comorbidities, in order to minimise the risk of TRM and toxicities. Previous studies have compared MEL100 to MEL200, demonstrating that low-dose melphalan compromises progression-free survival. However, multicentre studies have not investigated the efficacy of MEL140, despite its widespread use. Patients & methods Patients transplanted at University Hospitals Birmingham (2000-12; n=421)), Leeds Teaching Hospitals (2003-14; n=266) and Barts Health NHS Trust (2010-13; n=129), UK were included. MEL140 was used in all 3 centres for patients aged over 65 years, PS 2 or eGFR<50mL/min/1.73m². The study was confined to first, single ASCT only and patients were identified from data submitted to the EBMT registry. For continuous variables, data represent medians, with Mann-Whitney U test for statistical significance. Categorical variables were assessed using the Chi-square test. The logrank test was used to define significance in the Kaplan-Meier survival analyses. Results A total of 816 patients underwent ASCT during the study period, of which 144 (17.6%) received MEL140. Patients receiving MEL140 were older (66 vs. 58 years; p<0.001), had a lower eGFR (59.0 vs. 84.8 mL/min/1.73m²; p<0.001), were more likely to have an intermediate or high risk haematopoietic cell transplantation-specific comorbidity index (HCT-CI) score (43.1% vs. 20.8%; p<0.001) and had a higher ISS stage (52.5% stage III vs. 22.9%; p<0.001) compared to patients who received MEL200. Nonetheless, Kaplan-Meier survival analysis showed no significant difference in DFS or overall survival between MEL140 and MEL200 (Figure 1). Cox regression analysis, incorporating age, gender, eGFR, year of transplant and melphalan dose, confirmed that both DFS and overall survival were equivalent in MEL140, compared to MEL200 patients (HR=0.99 (95% CI: 0.72-1.36); p=0.95 and HR=1.16 (95% CI: 0.80-1.67); p=0.44 respectively). TRM was similar in both patient groups (3 (2.7%) in MEL140 and 12 (2.2%) in MEL200; p=0.761). There was significant variation in MEL140 usage amongst transplant centres (10.8% in Leeds vs. 21.1% in Birmingham vs. 26.4% in Barts; p<0.001) and this was not explained by regional differences in age, renal impairment or HCT-CI score. Figure 1. Kaplan-Meier survival graphs showing DFS (left) and overall survival (right) for all patients that underwent ASCT. Conclusion This study demonstrates equivalent clinical outcomes between MEL140 and MEL200 conditioning regimens for ASCT in MM, despite higher patient age, greater renal impairment, higher comorbidity score and higher ISS stage in the MEL140 group. This indicates that patients receiving MEL140 are being treated appropriately and raises the possibility that more patients currently regarded transplant-ineligible, could benefit from reduced-dose melphalan. The variation in MEL140 usage amongst transplant centres is indicative of the deficiency in the evidence base, and highlights the need for guideline development and implementation.

Reference

Disclosure of conflict of interest

None
Sequential conditioning with Thiopeta in T-cell replete HLA-haploidentical hematopoietic stem cell transplantation for the treatment of refractory hematological malignancies: comparison with matched related and unrelated donors

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Abstract

Introduction The results of conventional allogeneic stem cell transplantation (SCT) in refractory hematological malignancies are poor. Sequential strategies, such as FLAMSA, have shown promising results in refractory acute myeloid leukemia (AML), but have not been validated in the haploidentical (Haplo) setting. We developed a new sequential approach combining chemotherapy with broad anti-tumor activity, followed by reduced-intensity conditioning (RIC) regimen for the treatment of wide spectrum refractory hematologic malignancies. Patients and methods Seventy-two patients (median age, 54 years) with refractory hematological malignancies (44 AML, 7 ALL, 8 MDS, 5 CMML, 2 MPN and 6 lymphomas) were included in this retrospective multicenter study. The Karnofsky score was <90% in 39 patients (54%). The comorbidity index was ≥2 in 41 patients (59%).graft source was PBSCs in 65 patients (90%). Twenty-seven patients received Haplo and were compared to 16 patients with matched related donor (MRD) and 29 patients with unrelated donor (UD) who received the same regimen. TEC-RIC regimen consisted in total dose Thiopeta of 10 mg/kg, Etoposide 400 mg/m², Cyclophosphamide (Cy) 1600 mg/m² (day-15 to -10), and after 3 days rest, Fludarabine 150 mg/m², iv Busulfan 6.4 mg/kg and Thymoglobuline 5 mg/Kg (day-6 to -2). For patients older than 60 years and/or with comorbidities, Thiopeta, Etoposide and Cy total doses were reduced to 5 mg/kg, 300 mg/m², and 1200 mg/m², respectively. GVHD prophylaxis consisted of Cyclosporine and Mycophenolate Mofetil. High dose post-transplant Cy (PT-Cy) was added in case of Haplo. Results Median follow-up was 14 months (range, 3.5 - 37). Neutrophil recovery was delayed in Haplo (median 18.5 days; range, 13-32) compared to MRD (median 13 days; range, 10-17) and UD (median 14 days; range, 10-47) (p=0.001). The cumulative incidence of grade II-IV and grade III-IV acute GVHD was 11.1% and 3.7% in Haplo, 12.5% and 0% in MRD, 41.4% and 31% in UD patients (p=0.031 and p=0.003, respectively). Chronic GVHD developed in 8/20 evaluable Haplo patients (including 1 severe form), 6/13 MRD patients (1 severe form) and 11/19 UD patients (3 severe forms) (p=0.528). At day+30, 69 patients were evaluable for response and 66 patients (95.7%) were in CR. At last follow-up, 21 patients relapsed, 28 died and 44 are still alive. Cumulative incidence of 1-year NRM was 16.7% in Haplo, 20.5% in MRD, and 31.3% in UD, respectively (p=0.362). The 1-year OS and EFS were 73.6% and 60.8% in Haplo, 61.1% and 48.2% in MRD, 49.9% and 41.4% in UD, respectively (p=0.20 and p=0.08). Thirteen patients (including 6 Haplo) received prophylactic DLI (pDLI). In order to enhance the GVL effect, azacitidine was administered to 3 patients and sorafenib to one patient in combination with pDLI. After a median follow-up of 16.5 months post-pDLI, 12/13 patients were alive. Conclusion TEC-RIC sequential conditioning regimen seems to be a safe and valid platform in Haplo setting with PT-CY for patients with wide-spectrum refractory hematological diseases. In comparison with MRD and UD allo-SCT, toxicities were not increased and survival was not inferior in Haplo. Thus, there seem to be no benefit in searching for UD when a Haplo donor is easily...
and quickly available. Two prospective multicenter studies based on this new sequential approach including early post-transplant immuno-intervention are currently being scheduled.

Disclosure of conflict of interest

None
Comparable Outcomes after Allogeneic Stem-Cell Transplantation with Intravenous Busulfan or Treosulfan – based Reduced-Intensity and Reduced Toxicity Regimens in Acute Myeloid Leukemia. A Study on Behalf of the Acute Leukemia Working Party of EBMT.

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Abstract

Introduction: Allogeneic stem cell transplantation (SCT) with myeloablative conditioning (MAC) is associated with prohibitive rates of non-relapse mortality (NRM) in older and less medically fit patients with AML. Several reduced intensity conditioning (RIC) regimens and more recently the more dose-intensive reduced toxicity myeloablative (RTC) regimens were designed to replace MAC in this setting. There is no clear data on the comparative outcomes with the different regimens. Patient and Methods: The current study included 3561 patients with AML given a first allogeneic SCT from an HLA-matched sibling (n=1683) or a 10/10 matched unrelated donor (n=1878) in 2000-2014. Patients given fludarabine with either intravenous busulfan (ivBu), (FB, n=2990) or treosulfan (FT, n=571) were analyzed. Fludarabine and ivBu at 6.4 mg/kg (n=1457) or treosulfan at 30-36 gr/m2 (n=168) was considered RIC while fludarabine with ivBu at 9.6-12.8 mg/kg (n=1533) or treosulfan at 42 gr/m2 (n=403) was considered RTC regimen. Results: The median age of FB and FT recipients was 55.5 and 58.3 years, respectively (P<0.0001). The status at SCT was 72.5% CR1, 15.0% CR2 and 12.5% advanced disease in the FB group compared to 55.0%, 20.3% and 24.7% in the FT group, respectively (P<0.0001). More FT recipients had SCT from unrelated donors (64.8% Vs. 50.4%, P<0.0001) but less had in-vivo T-cell depletion (58.4%Vs 70.5%, P<0.0001). Cytogenetic subgroup distribution was similar between the groups. The 2-year relapse incidence (RI) was 32.7% and 35.5%, respectively (P=0.49). NRM was 17.6% and 19.4%, respectively (P=0.09). Leukemia-free survival (LFS) and overall survival (OS) were 49.5% and 54.8% after FB and 45.1% and 52.6% after FT, respectively (P=0.04, P=0.17). Acute GVHD grade II-IV and chronic GVHD were 23.1% and 35.7% after FB and 18.8% and 39.8% after FT, respectively (P=0.03, P=0.04). GVHD/ relapse-free survival (GRFS) was 36.5% and 31.5%, respectively (P=0.08). After adjusting for the differences in patient characteristics, there was no difference between FB and FT in RI, NRM, LFS, OS and GRFS. However, acute GVHD grade II-IV was higher after FB (HR, 1.49, P=0.0004). The same observations were seen when analyzing RIC or RTC separately, or when only patients in remission were analyzed. However, when analyzing only the 516 patients with advanced disease at SCT, 2-year OS was 29.7% and 43.0% after FB and FT (P=0.002) and this difference remained significant in the multivariate analysis (HR, 1.50, P=0.003). The factors associated with reduced OS among all patients were advanced age (HR 1.01, P<0.0001), secondary AML (HR 1.19, P=0.005), CR2 (HR 1.21, P=0.007) and advanced disease (HR 2.02, P<0.0001) and female donor to male recipient (HR 1.15, P=0.03). Conditioning type and intensity, donor type, CMV status and in vivo T-cell depletion were not significant. RI was lower and NRM was higher with RTC compared with RIC, but OS was similar. The same factors predicted GRFS, with the only difference been the positive role of in vivo T-cell depletion (HR 0.8, P=0.0002). Conclusion: RIC and RTC with ivBu or treosulfan is associated with similar outcomes. OS is primarily affected by disease factors such as disease status at SCT and secondary leukemia. Treosulfan- based conditioning is associated with a lower rate of acute GVHD, but similar rates of chronic GVHD, NRM and GRFS. Treosulfan conditioning may have some advantage in patients with advanced disease at SCT.

Disclosure of conflict of interest

None