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Title
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Permalink
https://escholarship.org/uc/item/6947j5tz

Journal
Transplantation and Cellular Therapy, 25(7)

ISSN
2666-6375

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Publication Date
2019-07-01

DOI
10.1016/j.bbmt.2019.02.002

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Biol Blood Marrow Transplant. Author manuscript; available in PMC 2021 July 08.

Published in final edited form as:

Biol Blood Marrow Transplant. 2019 July ; 25(7): 1340–1346. doi:10.1016/j.bbmt.2019.02.002.

Impact of Donor Type and Melphalan Dose on Allogeneic Transplant Outcomes for Patients with Lymphoma

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Abstract

We analyzed 186 patients with lymphoma who received allogeneic stem cell transplant (ASCT) with fludarabine-melphalan (FM) conditioning and different donors [25 haploidentical (HD), 98 matched unrelated (MUD), and 63 matched related (MRD)] at our institution between 09/2009-01/2018. Patients received fludarabine 160 mg/m^2 (40 mg/m^2/day x 4 days) in combination with one dose of melphalan 140 mg/m^2 (FM140) or 100 mg/m2 (FM100). Engraftment was similar between the 3 groups (92%, 89%, and 98%, respectively; p=0.7). The 6-months cumulative incidence of grade III-IV aGVHD was 4%, 14% and 8% (p=NS), and 3-year chronic GVHD was 5%, 16% and 26% (p=NS) for HD, MUD and MRD groups, respectively. The 3-year non-relapse mortality and relapse were 31%, 32% and 10% (HD vs. MUD, p=0.9, HD vs. MRD, p=0.02), and 15%, 21% and 39% (HD vs. MUD, p=0.4, HD vs. MRD, p=0.04) for HD, MUD and MRD groups, respectively. At 3 years, PFS was 59%, 44% and 46% (p=NS), OS was 52%, 54% and 67% (p=NS) and GVHD-free, relapse-free survival (GRFS) 39%, 31%, 24% for HD, MUD transplants (p=NS). No differences in the 3-year PFS [57% vs. 43% (p=0.3)] and OS [64% vs. 58% (p=0.7)] were seen for patients receiving FM100 versus FM140. In conclusion, HD transplants have similar outcomes compared with HLA matched transplants in patients with lymphoma, and FM100 appears to be at least as effective conditioning as FM140 regimen.

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Authorship contribution

NYS contributed with some data collection and wrote the first draft of the manuscript. RMS performed the statistical analysis. GR, FM contribute with data collection. UP, CMH, OB, QB, AO, YN, AA, PK, SS, RM, PA, EJS, MHQ, IFK, LF, HL, NF, SP, JW, FH, REC contributed with treatmet of patients and interpretation of results. SOC contributed with study design, some data collection, interpretation of results and manuscript writing. All authors reviewed and approved the final version of the manuscript.

Conflict of interest: Authors do not have any relevant conflict of interest to declare.

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INTRODUCTION

Despite the recent advances in the treatment of patients with lymphoma, especially B-cell non-Hodgkin's lymphoma, many patients relapse and have poor outcome.[1–3] Allogeneic stem cell transplantation (ASCT) is a potentially curative strategy for these patients, at least in part due to a potent graft-versus-lymphoma (GVL) effect.[4,5] Most lymphoma patients are heavily pre-treated with multiple lines of chemotherapy before ASCT, and application of myeloablative conditioning regimens is usually associated with prohibitive non-relapse mortality (NRM).[4] Over the last decade, improved outcomes with the use of reduced-intensity (RIC)/non-myeloablative conditioning (NMA) and haploidentical donor transplants (HD-ASCT) performed with post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis[6] has renewed interest in this form of treatment, especially for patients with advanced Hodgkin's disease, who were found to have remarkably good results with transplantation,[7,8] while patients with non-Hodgkin's lymphoma are increasingly considered for ASCT.[9–11] These strategies have also extended safer transplantation to virtually all candidates, including to non-Caucasians, as most patients will have a child, parent or sibling as a potential donor for transplantation[12,13]. Recent literature comparing ASCT from haploidentical donors (HD) with matched unrelated (MUD) and matched related donors (MRD) in lymphoma has shown similar outcomes.[8,9,14–17] However, most of these retrospective studies have included multiple transplant conditioning regimens, which confounds the interpretation of results. Fludarabine (F) in combination with melphalan (M) 140mg/m^2 has been used as a standard of care conditioning regimen for patients with lymphoma receiving ASCT with HLA matched donors.[18] More recently, a modified version of this regimen has been developed by our group for haploidentical donor transplants.[19] Here, we aimed to assess the impact of donor type and melphalan dose on transplant outcomes for patients who received FM-based conditioning at our institution.

PATIENTS AND METHODS

Study design and patients

This retrospective study evaluated all consecutively treated patients with a diagnosis of lymphoma or chronic lymphocytic leukemia (CLL) who received their first allogeneic transplant with FM-based conditioning regimen from September 2009 to January 2018 at the University of Texas M. D. Anderson Cancer Center (UTMDACC). Donor preference was in order a MRD, a 10/10 MUD followed by a HD. A HD was used when no MUD was available or when the transplant was urgently needed. All patients provided written informed consent for transplantation according to the Declaration of Helsinki. Patients were treated on a clinical trial or according to the current standard of care institutional practice. The UTMDACC Institutional Review Board approved this retrospective study.

Conditioning regimen and transplantation

Patients received fludarabine 160 mg/m^2 administered in four daily IV doses (40 mg/m^2/day) in combination with melphalan 140 mg/m^2 (FM140) or 100 mg/m2 (FM100). For the purpose of this study patients receiving FM140 were considered to have received

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myeloablative conditioning (MAC) and those who received FM100 non-myeloablative conditioning (NMA). FM100 regimen was primarily used to treat older patients or patients with significant comorbidities, because of concerns for toxicity. Thiotepa at a dose of 5 mg/kg or 2 Gy total body irradiation (TBI) was added for HD-ASCT to facilitate engraftment. Additionally, patients with CD20-positive disease receive rituximab 375 mg/m2 on days −13, −6, +1, and +8.[20] Most HD transplants received bone marrow (BM) graft whereas MRD and MUD transplants received predominantly peripheral blood stem cells (PBSC). Standard infectious prophylaxis was applied to all transplant recipients with pentamidine or Bactrim, voriconazole, posaconazole or fluconazole and acyclovir or valgancyclovir, as previously described.[21]

Graft-versus-host disease (GVHD) prophylaxis

Transplants performed with an HLA matched donor received mini-methotrexate and tacrolimus (tacro). In addition, all MUD transplant recipients received anti-thymocyte globulin (ATG) for a total dose of 5 mg/kg. Haploidentical transplants received PTCy at 50 mg/kg on days +3 and + 4 followed by mycophenolate mofetil (MMF) and tacro starting from day +5 and continued until 3 months and 6 months post-transplant, respectively, followed by a weekly taper. The goal for tacrolimus level was 8 ng/ml (therapeutic level between 5 and 15 ng/ml), which was maintained for at least six months after transplantation and tapered weekly after that if there were no signs or symptoms of GVHD. All patients received granulocyte-colony stimulating factor (G-CSF) starting day +6 until engraftment [absolute neutrophil count (ANC) >1000/μL].

Outcome endpoints and definitions

The primary outcome was progression-free survival while secondary outcomes included engraftment rate, relapse, non-relapse mortality (NRM), the incidence of acute and chronic GVHD, overall survival (OS), and GVHD-free, relapse-free survival (GRFS). Engraftment was defined as achieving an ANC $\geq 0.5 \times 10^9$/L for three consecutive days before day 28 post-transplant. Platelet recovery was defined as achieving a platelet count ≥20,000/μL unsupported by platelet transfusions for seven days. NRM events were defined as death without evidence of persistence or relapse of the disease. OS was estimated from the time of transplant to the last date of follow-up. GRFS was estimated as the time from transplant to disease relapse, the onset of severe acute GVHD and/or extensive cGVHD, or to death of any cause. Toxicities were graded according to the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE), version 5.

Statistical Analysis

Actuarial OS, PFS, and GRFS were estimated based on the Kaplan-Meier method. The cumulative incidence of GVHD, NRM, and disease progression was estimated accounting for competing risks. Competing risks included: disease progression and death of any cause for GVHD; death with persistent disease and disease progression for NRM; and death with persistent disease and NRM for disease progression. Predictors of OS, PFS, and GRFS were evaluated using Cox's proportional hazards regression on univariate and multivariate analysis when indicated. Fine and Gray regression analysis was used to evaluate predictors of GVHD, NRM, and disease progression on univariate and multivariate analysis.

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Characteristics were compared using a chi-square test for categorical variables, and Wilcoxon-rank test for continuous variables. Statistical significance was defined at the 0.05 level. Statistical analyses were performed using primarily STATA 14.0 (StataCorp (2015). Statistical Software: Release 14. College Station, TX: StataCorp LP.)

RESULTS

Patient's characteristics

A total of 186 pts (25 HD, 98 MUD, and 63 MRD) were analyzed. Table 1 describes the patient and transplant-related characteristics. The number of ASCT performed according to histological subtypes were as follows: Non-Hodgkin lymphoma (n=93), Hodgkin lymphoma (HL) (n=58) and CLL/small lymphocytic lymphoma (n=35). The histology for patients with NHL were: diffuse large B-cell lymphoma (n=23), mycosis fungoides/sezary syndrome (n=20), follicular lymphoma (n=7), composite/discordant lymphoma (n=7), mantle cell lymphoma (n=6), large cell anaplastic lymphoma (n=4), hepatosplenic gamma-delta lymphoma (n=3), extra nodal marginal zone lymphoma (n=1), and other rare histology (n=22).

There were no significant differences in characteristics between the 3 donor groups in terms of age, International Prognostic Index (IPI) score, comorbidities, disease status at the time of transplant, number of prior lines of chemotherapy and response to salvage chemotherapy regimens, except that a higher proportion of patients in the HD group received NMA regimen, 64% compared with 11% for MUD and 10% MRD transplants, and a BM graft, 84% compared with 35% for MUD and 2% for MRD transplants. Patients receiving a HD (77%) had more advanced stage disease (Stage III-IV) on initial presentation compared with 66% for MUD and 51% for MRD transplants (Table 1). However, there was no statistical difference in the disease risk-index (DRI) distribution between the three groups as shown in Table 2 ($p = 0.5$).

Hematopoietic recovery

The proportion of neutrophil engraftment was similar in HD (reference), MUD and MRD groups [92%, 89% ($p=0.7$), and 98% ($p=0.3$), respectively]. Median time to neutrophil recovery was 18, 12 ($p<0.001$), and 12 ($p<0.001$) days, and median time to platelet recovery was 26, 14 ($p<0.001$) and 12 ($p<0.001$) days, for the corresponding groups, respectively. The median peripheral blood T-cells and myeloid chimerism was 100% donor on days 30 and day 90 for all three donor groups.

Acute and cGVHD

The cumulative incidence of grade II-IV aGVHD at 6 months post-transplant was 29% in HD [95% confidence interval (CI): 16–55, reference], 36% in MUD (CI: 28–47, $p=0.4$) and 35% in MRD transplants (CI: 25–49, $p=0.5$), while the corresponding incidence of grade III-IV aGVHD at 6 months was 4% in HD (CI: 1 – 28, reference), 14% in MUD (CI: 8 – 23, $p=0.2$) and 8% in MRD transplants (CI: 3 – 18, $p=0.5$). The incidence of chronic GVHD at 3 years was 5% in HD (CI: 1 – 36, reference) compared to 16% (CI: 10 – 26, $p=0.2$) and 26% (CI: 17 – 40, $p=0.09$) in MUD and MRD transplants, respectively.

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Relapse and NRM

In univariable analysis, the rates of disease relapse at 3 years were 15% (CI: 55 – 42), 21% (CI: 14 – 31) and 39% (CI: 29 – 54) for HD, MUD and MRD group, respectively (HD vs. MUD, p=0.4, HD vs. MRD, p=0.04) (Table 3, Supplementary Table 1). Multivariate analysis (MVA) was not indicated for disease progression, as donor type was the only significant predictor of rate of progression. In comparison to HD, MUD had a comparable rate (HR=1.6, p=0.4) while MRD had a significantly higher (HR=3.4, p=0.04) rate of disease progression.

In univariable analysis, the rates of NRM at 3 years were 31% (CI: 16–58), 32% (CI: 24–43) and 10% (CI: 4–20) for HD, MUD and MRD groups, respectively (HD vs. MUD, p=0.9, HD vs. MRD, p=0.02) (Table 3, Supplementary Table 1). In MVA, in comparison to HD, MRD transplants had significantly lower NRM (HR: 0.3, CI: 0.1–0.8, p=0.02), while no difference was observed with MUD transplants (HR: 1.1, CI: 0.5–2.4, p=0.8). Age >50 years was the only other significant variable associated with higher NRM (HR: 1.9, CI: 1.1 – 3.5, p=0.03) in MVA.

Survival

The median follow-up among all surviving patients was 57 months (range 3–101). Among different donor groups, the median follow-up was 34 months (range, 3 – 74) for HD, 62 months (range, 3 – 100) for MUD and 54 months (range, 6 – 101) for MRD transplants. At last follow-up, 107 (57%) patients were still alive. In univariable analysis, PFS at 3 years was 49% (CI: 26 – 69), 44% (CI: 34–54) and 46% (CI: 33 – 58) for HD, MUD and MRD group, respectively (HD vs. MUD, p=0.6, HD vs. MRD, p=0.8) (Table 3, Supplementary Table 1). MVA revealed no difference in PFS rate between the three donor groups. Patients with HL (HR: 0.5, CI: 0.3 – 0.9, p=0.01) had better PFS, while those receiving >3 prior lines of chemotherapy (HR: 1.8, CI: 1.2 – 2.6, p=0.01) had worse PFS. None of the other factors evaluated were associated with PFS. In univariate analysis, OS at 3 years was 52% (CI: 28 – 71), 54% (CI: 44 – 64) and 67% (CI: 54 – 77) for HD, MUD and MRD transplants, respectively (HD vs. MUD, p = 0.9, HD vs. MRD, p=0.2) (Table 3, Supplementary Table 1). In MVA, there were no significant predictors of OS.

The 3-year GRFS rate tended to be higher (45%, CI: 22 – 65, reference) in the HD compared with MUD (34%, CI: 25 – 43, p=0.3) and MRD (29%, CI: 18 – 41, p=0.2) groups (Figure 2), yet these differences did not reach statistical difference.

Causes of death for all donor groups are provided in Supplementary Table 2.

Comparison of FM100 versus FM140

FM100 conditioning regimen was more likely to be utilized in older individuals (median age 57 vs. 46 years, p<0.01) and in patients receiving an HD (64% vs. 11%, p<0.01). Consequently, patients receiving FM100 were also more likely to have BM grafts as a source of stem cells (55% vs. 25%, p=0.01). In univariate analysis, FM100 regimen had similar outcomes compared to FM140 regimen with regards to PFS (HR=0.7, p=0.3), relapse rate (HR=0.4, p=0.1) and NRM (HR=0.9, p=0.8). The 3-year PFS for patients receiving FM100

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and FM140 conditioning regimen was 57% vs. 43% (p=0.3) and the corresponding 3-year OS was 64% vs 58% (p=0.7).

DISCUSSION

Here, we describe the impact of donor type and melphalan doses on outcomes in lymphoma patients who underwent FM-based conditioning regimen and ASCT at our institution. This analysis shows that survival after HD transplants was comparable to MUD and MRD transplants.

In comparison to MRD transplants, HD had lower relapse rates, but higher NRM, which appears to offset the benefit and yielded similar survival. The rates of cGVHD were significantly lower in patients receiving HD transplants, while other outcomes were similar between HD and MUD transplants. In addition, we showed that non-myeloablative FM100 regimen, although used for significantly older patients or those with comorbidities, was non-inferior in terms of survival when compared with the more intense, close to the myeloablative FM140 regimen, and, notably, FM140 regimen did not lead to a lower relapse rate.

FM-based conditioning regimen remains one of the most commonly employed conditioning regimens for allogeneic transplantation for lymphoma.[22] More recently, our group began using lower doses of melphalan (FM100) for older individuals and observed comparable outcomes between FM100 and FM140 for patients with acute leukemia and multiple myeloma.[23,24] Here, we had similar results in patients with lymphoma. Previously, a phase II trial evaluated the FM100 regimen in 26 lymphoma patients, and 77% (20/26) of patients had progressive disease at the time of ASCT.[25] The 5-yr OS and NRM rates were 40.4% and 21.2% with no adverse effect on engraftment. In our study, despite having a higher proportion of older patients or with significant comorbidities, the survival in FM100 cohort (3-yr OS 64%) was comparable to FM140 group (3-yr OS 58%), confirming our initial observations,[18] and raising the question if FM100 conditioning should replace FM140 for all lymphoma patients to decrease NRM in younger patients further, and possibly improve survival.

Recently, the Center for International Blood and Marrow Transplant Research (CIBMTR) published two large retrospective series comparing outcomes of HD-ASCT with MUD and MRD transplants in lymphoma patients.[9,17] The first report compared 185 HD-ASCT patients with PTCy approach to 807 MRD ASCT patients with calcineurin-based GVHD prophylaxis.[17] There were no differences in post-transplantation outcomes between the two groups, but HD transplants led to a significantly lower risk of cGVHD. In our cohort, as seen previously,[20] the use of FM/TBI regimen in comparison to Flu/Cy/TBI in the above-mentioned series was associated with higher NRM (34% vs. 15%) but lower relapse rate (15% vs. 40%) in HD transplant, resulting in similar PFS (48% vs. 49%). These results suggest that younger and fit patients should be offered FM100/TBI regimen due to lower risk of relapse, while older patients or those with significant co-morbidities might benefit more from Flu/Cy/TBI regimen, which has the lowest NRM.

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In the second report,[9] 732 MUD ASCT patients were compared to 185 HD-ASCT (PTCy) and showed comparable outcomes between two donor groups except for significantly lower rates of acute and chronic GVHD with HD transplants. Multiple studies comparing HD transplants with PTCy to MUD transplants performed with standard calcineurin-based GVHD prophylaxis have consistently shown better GVHD control and a plateau in overall survival after two years owing to decreased mortality from chronic GVHD in HD transplant groups. These observations suggest that patients receiving an HLA-matched donor transplant could also benefit from PTCy-based GVHD prophylaxis. The ongoing BMT CTN trial 1203 evaluating PTCy as GVHD prophylaxis in allogeneic transplants will help us understand the impact of PTCy in this setting. In addition, given the ease of donor availability in HD transplants and comparable outcomes to MUD transplants, patients, especially those who require urgent disease control (those who failed to respond to chemotherapy, achieved partial response or failed CAR T cell therapy) should proceed immediately to a HD transplant. This could bring more patients to transplantation and gives an opportunity for a cure to these patients who otherwise are bound to have dismal outcomes. This approach appears to be reflected in that fact that the number of haploidentical transplants worldwide continues to increase, as compared with MUD transplants who appear to have plateaued in past several years.[12]

Another interesting observation in our analysis was an impressive 3-yr overall survival of 78% in patients with HL despite most patients having the advanced disease in our cohort. Although numbers in our study are small to make firm conclusions, it is possible that a lower relapse rate is seen with HD transplants for HL patients, as has been reported by other investigators.[7,8] Limitations of this study are related to a relatively small number of patients and heterogeneity in disease type, even though the same conditioning regimen was used in all patients. However, we confirm similar outcomes between haploidentical donors and HLA matched donor transplants in a group of patients treated with the same conditioning regimen, and suggest that PTCy-based GVHD prophylaxis should be extended to all donor types and that reduced doses of melphalan should probably be used in all patients.

In conclusion, our study adds to the growing literature from multiple centers and registries, lending support to the feasibility of HD transplants as an attractive alternative to HLA matched donor transplants for patients with lymphoma and perhaps, a preferential use of HD for urgent patients who cannot wait for a MUD. Stratification for treatment of patients with lymphoma, at least for HD transplants, might be needed based on conditioning intensity: younger and more fit patients who can tolerate a more intense regimen might benefit from FM100/TBI regimen due to a lower rate of relapse, while older patients or with comorbidities might benefit from a lower intensity conditioning like Flu/Cy/TBI regimen, which has been assocaited with the lowest NRM (8). FM140-based conditioning does not appear to provide any added benefit for any group of patients. Future randomized studies could provide insight into which of the reduced-intensity regimens is superior for patients with lymphoma. Moreover, these results, in conjunction with the recent literature, also suggest that reduced-intensity conditioning allogeneic transplantation in conjunction perhaps with immunotherapy or maintenance therapy should replace more intense conditioning for patients with lymphoma.

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Supplementary Material

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HIGHLIGHTS

- Haploidentical transplants with PTCy have similar long-term survival comparing with HLA matched donor transplants
- FM100 regimen had similar survival with FM140 regimen for patients with lymphoma, although used primarily for older patients.

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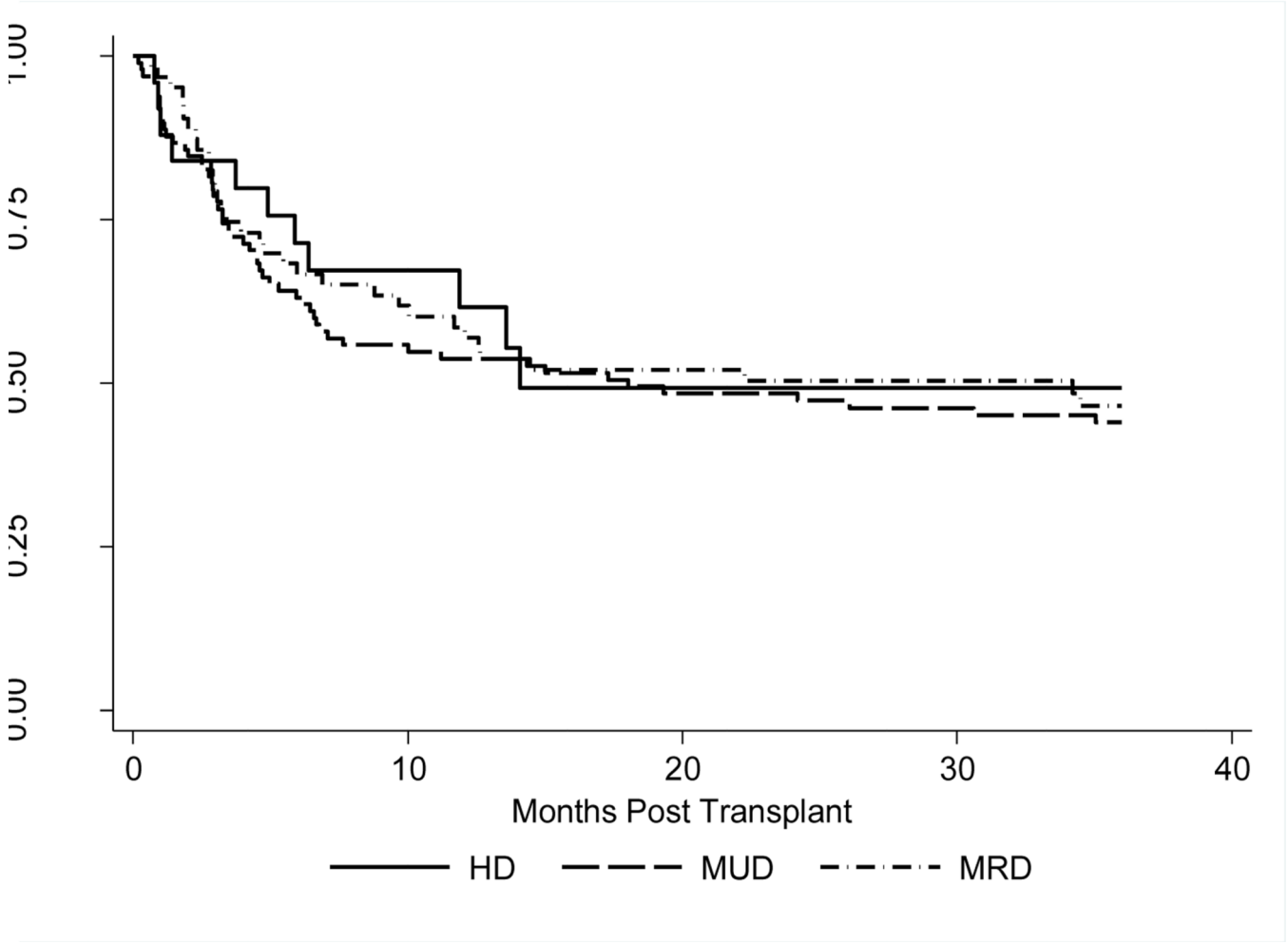
A.



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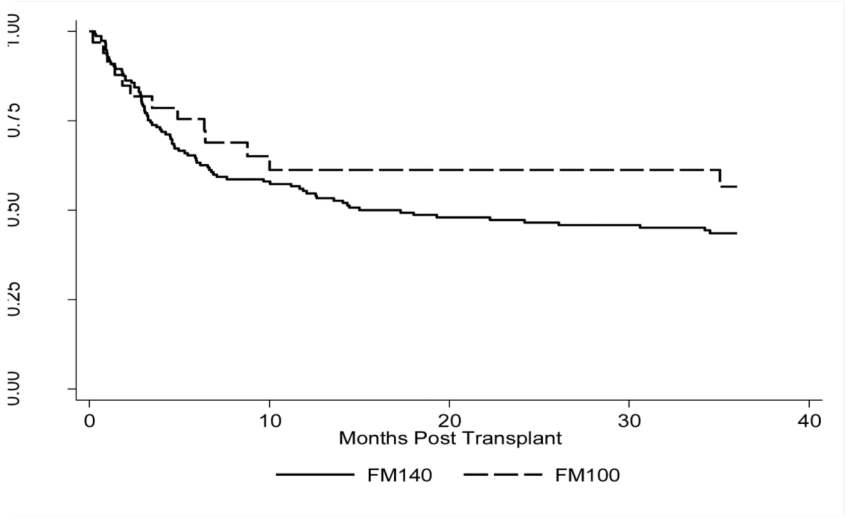
B.



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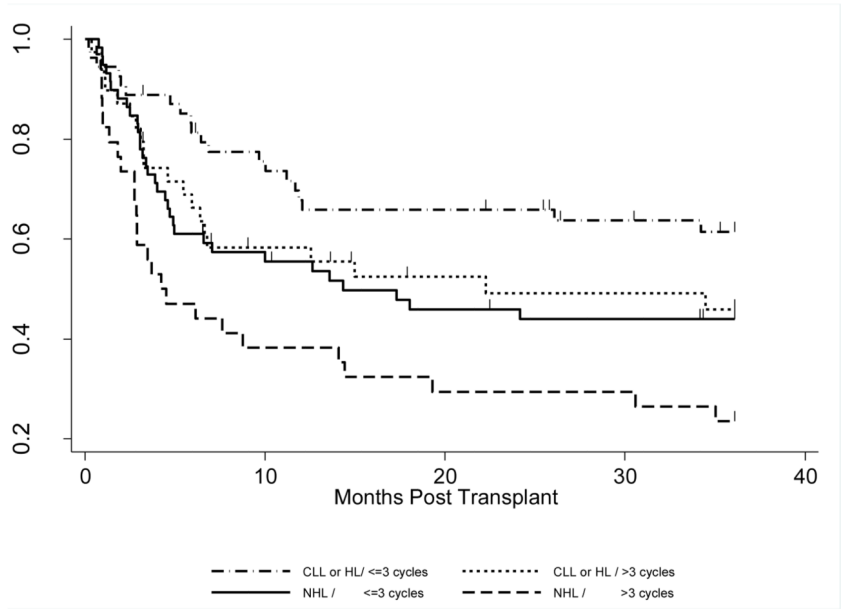

Figure 1.

Progression-free survival based on A) Donor type, B) Mephalan dose, C) Disease and number of chemotherapy cycles received.

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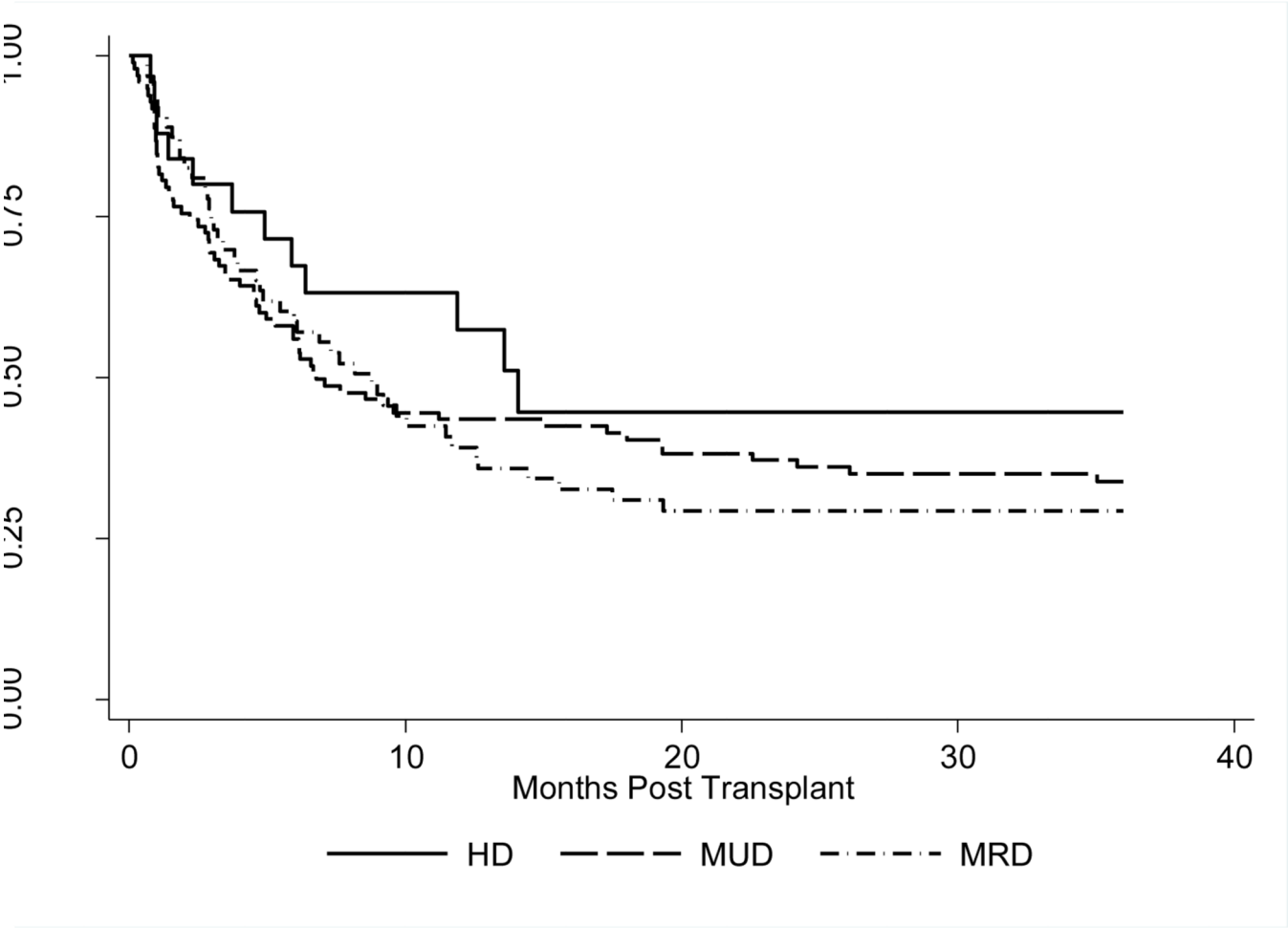

Figure 2.
GVHD-free, relapse-free survival based on donor type

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Table 1.

Patient's characteristics

	HD N=25	MUD N=98	MRD N=63	HD vs MUD (p-Value)	HD vs MRD (p-value)
Age at Transplant (median, range)	50 (20–65)	47 (20–71)	50 (18–72)	0.5	0.5
HCT-CI score					
Median score (range)	1(0–7)	2 (0–9)	2 (0–7)	0.7	0.3
>3	5 (20%)	20 (20%)	14 (22%)	0.6	0.5
Diagnosis					
CLL	5 (20%)	17 (17%)	13 (21%)		
HL	4 (16%)	33 (34%)	21 (33%)		
NHL	16(64%)	48 (49%)	29 (46%)	0.2	0.2
Stage at Diagnosis					
0	(0%)	1 (1%)	1 (2%)		
1	1 (4%)	6 (6%)	13 (21%)		
2	4 (16%)	23 (23%)	14 (22%)		
3	4 (16%)	13 (13%)	9 (14%)		
4	13 (52%)	46 (47%)	20 (32%)		
Unknown	2 (8%)	9 (9%)	6 (10%)		
Stage 3–4	17 (77%)	59 (66%)	29 (51%)	0.3	**0.03**
Disease Status					
Active	18 (72%)	76 (78%)	44 (70%)	0.6	0.8
Remission	7 (28%)	22 (22%)	19 (30%)		
Prior Response					
CR	9 (36%)	36 (37%)	28 (44%)		
PR	9(36%)	36 (37%)	18 (29%)		
SD	5(20%)	17 (17%)	14 (22%)		
PD	2(8%)	9 (9%)	3 (5%)		
CR/PR	7(72%)	72 (73%)	46 (73%)	0.9	0.9
Melphalan Dose					
100 mg/m2	16 (64%)	11 (11%)	6 (10%)	**<0.001**	**<0.001**
140 mg/m2	9 (36%)	87 (89%)	57 (90%)		
Cell source					
PB	4 (16%)	63 (64%)	62 (98%)		
BM	21 (84%)	35 (36%)	1 (2%)	**<0.001**	**<0.001**
Prior Chemo, median (range)	3 (1–8)	3 (0–9)	3 (0–13)		
>4	7 (28%)	21 (21%)	13 (21%)	0.5	0.5
Treatment					
Standard of Care	14 (56%)	58 (59%)	40 (63%)		

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	HD N=25	MUD N=98	MRD N=63	HD vs MUD (p-Value)	HD vs MRD (p-value)
Protocol	11 (44%)	40 (41%)	23 (37%)	0.8	0.5
IPI for Lymphoma					
0	7 (44%)	22 (46%)	10 (34%)		
1	3 (19%)	13 (27%)	6 (21%)		
2	3 (19%)	4 (8%)	5 (17%)		
3	1 (6%)	1 (2%)	3 (10%)		
Unknown	2 (13%)	8 (17%)	5 (17%)		
>1	4 (29%)	5 (13%)	8 (33%)	0.1	0.8

Abbreviations: CLL – chronic lymphocytic leukemia; HCT-CI – hematopoietic cell transplant – comorbidity index; HAPLO – haploidentical; HL – Hodgkin lymphoma; IPI – International prognostic index; NHL – Non-Hodgkin lymphoma; MUD – matched unrelated donor, SIB: matched related donor sibling or relative.

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Table 2.

Disease Index Risk categories of patients by donor type

Donor Type		Disease Index Risk (DRI) category			Total (%)
		High	Intermediate	Low	
HD	**n %**	6 24.0%	8 32.0%	11 44.0%	25 100%
MUD	**n %**	11 11.22%	34 34.69%	53 54.08%	98 100%
MRD	**n %**	8 12.70%	25 39.68%	30 47.62%	63 100%
Total	**n %**	25 13.44%	67 36.02%	94 50.54%	186 100%

Abbreviations: HD – haploidentical donor, MUD – matched unrelated donor, MRD – matched related donor; n - number

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Table 3.

Univariable analysis for outcomes by donor type

Outcomes	HD (n=25)	MUD (n=98)	MRD (n=63)	P-value
Relapse Rate				HD (Reference) HD v MUD, 0.4 **HD v MRD, 0.04**
3-yr incidence	15 %	21 %	39 %	
95% CI	5 to 42	14 to 31	29 to 54	
NRM				HD (Reference) HD v MUD, 0.9 **HD v MRD, 0.02**
3-yr incidence	31 %	32 %	10 %	
95% CI	16 to 58	24 to 43	4 to 20	
PFS				HD (Reference) HD v MUD, 0.6 HD v MRD, 0.8
3-yr incidence	49 %	44 %	46 %	
95% CI	26 to 69	34 to 54	33 to 58	
OS				HD (Reference) HD v MUD, 0.9 HD v MRD, 0.2
3-yr incidence	52 %	54 %	67 %	
95% CI	28 to 71	44 to 64	54 to 77	
Acute GVHD Grade II - IV				
6-mo incidence	29 %	36v%	35 %	HD (Reference) HD v MUD, 0.4 HD v MRD, 0.5
95% CI	16 to 55	28 to 47	25 to 49	
Acute GVHD grade III - IV				
6-mo incidence	4 %	14 %	8 %	HD (Reference) HD v MUD, 0.2 HD v MRD, 0.5
95% CI	1 to 28	8 to 23	3 to 18	
Chronic GVHD				HD (Reference) HD v MUD, 0.2 **HD v MRD, 0.09**
3-yr incidence	5 %	16 %	26 %	
95% CI	1 to 36	10 to 26	17 to 42	
GRFS				HD (Reference) HD v MUD, 0.3 HD v MRD, 0.2
3-yr incidence	45 %	34 %	29 %	
95% CI	22 to 65	25 to 43	18 to 41	
PFS by disease type (3yr)				
NHL	42 % (15 to 67)	31 % (19 to 44)	41 % (24 to 58)	
HL	50 % (6 to 84)	60 % (42 to 75)	56 % (32 to 74)	
CLL	75 % (13 to 96)	50 % (24 to 71)	41 % (14 to 67)	
OS by disease type (3-yr)				
NHL	42 % (15 to 67)	42 % (28 to 55)	62 % (42 to 77)	
HL	67 % (5 to 94)	73 % (54to 85)	78 % (51 to 91)	
CLL	75 % (13 to 96)	56 % (29 to 76)	60 % (28 to 81)	

Abbreviations: cGVHD - chronic graft-versus-host disease; HD - Haploidentical donor; GRFS - GVHD – free, relapse-free survival; MRD - Matched related donor; MUD - match-unrelated donor; NRM - non-relapse mortality; OS - overall survival; PFS - progression-free survival.