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Impact of type of reduced-intensity conditioning regimen on the outcomes of allogeneic hematopoietic cell transplantation in classical Hodgkin lymphoma.

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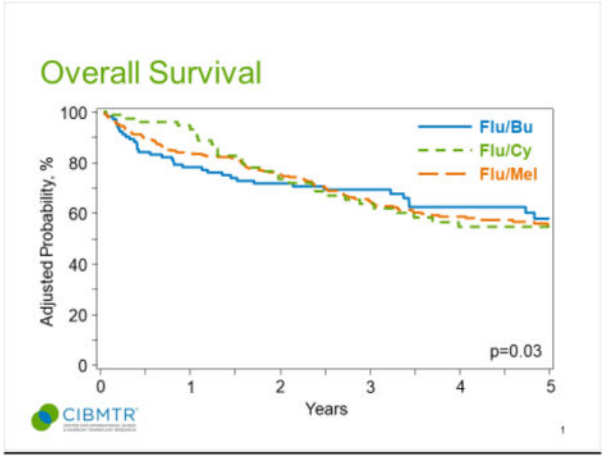
Abstract

Reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT) is a curative option for select relapsed/refractory Hodgkin lymphoma (HL) patients, however there is sparse data to support superiority of any particular conditioning regimen.

We analyzed 492 adult patients undergoing HLA-matched sibling or unrelated donor allo-HCT for HL between 2008–2016, utilizing RIC with either fludarabine/busulfan (Flu/Bu), fludarabine/melphalan (Flu/Mel140) or fludarabine/cyclophosphamide (Flu/Cy). Multivariable regression analysis was performed using a significance level of <0.01. There were no significant differences between regimens in risk for non-relapse mortality (NRM) (P=0.54), relapse/progression (P=0.02) or progression-free survival (PFS) (P=0.14). Flu/Cy conditioning was associated with decreased risk of mortality in the first 11months after allo-HCT (HR=0.28, 95%CI=0.10–0.73, p=0.009), but beyond 11months post allo-HCT it was associated with a significantly higher risk of mortality, (HR=2.46, 95%CI=0.1.32–4.61, P=0.005). 4-year adjusted overall survival (OS) was similar across regimens at 62% for Flu/Bu, 59% for Flu/Mel140 and 55% for Flu/Cy (P=0.64), respectively.

These data confirm the choice of RIC for allo-HCT in HL does not influence risk of relapse, NRM or PFS. Although no OS benefit was seen between Flu/Bu and Flu/Mel 140; Flu/Cy was associated with a significantly higher risk of mortality beyond 11months from allo-HCT (possibly due to late NRM events).

Graphical Abstarct



Keywords

reduced-intensity conditioning; allogeneic hematopoietic cell transplant; classical Hodgkin lymphoma

INTRODUCTION

The majority of classical Hodgkin lymphoma (HL) patients have excellent prognosis with conventional frontline therapies. However patients with relapsed or refractory disease have less favorable outcomes. A substantial proportion of relapsed patients with chemosensitive disease are successfully salvaged with an autologous hematopoietic cell transplantation (HCT), but up to 40–50% of patients will relapse after autografting and have very poor outcomes, with a 5-year overall survival (OS) of ~30%.(1–3) Allogeneic HCT (allo-HCT) is a potentially curative approach for these patients with 5-year OS ranging from 30–50%.(4–8) While allo-HCT with myeloablative conditioning (MAC) can provide durable disease control in patients with HL, these higher intensity approaches have been associated with higher rates of non-relapse mortality (NRM) in most,(9–11) but not all studies(12), and have never been shown to provide an OS benefit (12).

Reduced-intensity conditioning (RIC) regimens have extended the use of allo-HCT to **patients** who relapse after autologous HCT, older patients and those with significant comorbidities.(13–16) While a handful of retrospective studies have compared different RIC or non-myeloablative (NMA) conditioning platforms in lymphoma patients (17, 18), these analyses were not limited to the diagnosis of HL. Unlike non-Hodgkin lymphomas (NHL), where the median age of recipients at allo-HCT is usually in the late 50s(19, 20), the median age of HL patients at allo-HCT is typically in the mid 30s.(6, 12) It is possible that these much younger HL patients may be able to tolerate more dose-intense RIC regimens better than older NHL patients, and potentially may derive a survival benefit with such approaches. Using the Center for International Blood and Marrow Transplant Research (CIBMTR) database we evaluated the outcomes of the three most commonly used RIC/NMA regimens for HL.

PATIENTS AND METHODS

Data source

CIBMTR is a working group of more than 500 transplantation centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin. Participating centers are required to report all transplantations consecutively; patients are followed longitudinally, and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. The CIBMTR collects data at two levels, transplant essential data (TED) in all patients and more comprehensive data (CRF) in a subset of patients selected by a weighted randomization scheme. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the

performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Patients

Patients with HL aged ≥18 years undergoing their first NMA or RIC allo-HCT, between 2008 and 2016 and reported to CIBMTR were included in this analysis. Donors were limited to HLA-matched sibling (MSD) or 8/8 HLA-matched unrelated donors (MUD). Following 3 most commonly used RIC regimens were analyzed: fludarabine (median dose=150mg/m^2)/ i.v. busulfan (~6.4mg/kg) (Flu/Bu), fludarabine (median dose=125mg/m^2)/melphalan 140mg/m^2 (Flu/Mel140) or fludarabine (median dose=120mg/m^2)/cyclophosphamide (median dose=1200mg/m^2) (Flu/Cy). Patients receiving Flu/Cy/2Gray total body irradiation (n=15) were not included in this analysis. Graft-versus-host disease (GVHD) prophylaxis was restricted to calcineurin inhibitor (CNI)-based approaches. Graft source was limited to peripheral blood. Allo-HCT recipients could have received *in vivo* T-cell depletion with antithymocyte globulin (ATG) or alemtuzumab. Patients receiving *ex vivo* graft manipulation were not included.

Definitions & Study Endpoints

The intensity of allo-HCT conditioning regimens was categorized as NMA/RIC using consensus criteria.(21) Disease response at the time of HCT was determined using the International Working Group criteria in use during the era of this analysis.(22) The primary endpoint was OS; death from any cause was considered an event and surviving patients were censored at last follow up. Secondary outcomes included NRM, progression/relapse, and PFS. NRM was defined as death without evidence of lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a complete remission (CR); NRM was considered a competing risk. For PFS, a patient was considered a treatment failure at time of progression/ relapse or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up. Acute GVHD and chronic GVHD were graded using established clinical criteria.(23, 24) Probabilities of PFS and OS were calculated using the Kaplan–Meier estimates. Neutrophil recovery was defined as the first of 3 successive days with ANC ≥500/μL after post-transplantation nadir. Platelet recovery was considered to have occurred on the first of three consecutive days with platelet count 20,000/μL or higher, in the absence of platelet transfusion for 7 consecutive days. For neutrophil and platelet recovery, death without the event was considered a competing risk.

Statistical Analysis

The Flu/Bu cohort was compared against the Flu/Cy and Flu/Mel140 cohorts. Cumulative incidences of hematopoietic recovery, GVHD, relapse, and NRM were calculated to accommodate for competing risks. Associations among patient-, disease, and transplantation-related variables and outcomes of interest were evaluated using Cox proportional hazards regression for chronic GVHD, relapse, NRM, PFS, and OS and logistic regression for acute GVHD. Forward stepwise selection was used to identify covariates that

influenced outcomes. Covariates with a **p<0.01** were considered significant to account for multiple testing. The proportional hazards assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Interactions between the main effect and significant covariates were examined. Center effect was tested using the score test for chronic GVHD, relapse, NRM, PFS, and OS and the generalized linear mixed model for acute GVHD.(25) Results are expressed as odds ratio (OR) for acute GVHD and hazard ratio (HR) for chronic GVHD, relapse, NRM, PFS, and OS. The variables considered in multivariate analysis are shown in Table 1S of supplemental appendix. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics:

Four hundred and ninety-two adult HL patients underwent a first allo-HCT using either a MSD or MUD between 2008–2016. The study population was divided in 3 cohorts for analysis: Flu/Bu (n=102), Flu/Mel140 (n=318) and Flu/Cy (n=72). Baseline patient-, disease-, and transplantation-related characteristics are shown in Table 1. The 3 groups were comparable with respect to patient age, gender, race, Karnofsky performance score (KPS), median time from diagnosis to allo-HCT, donor type and history of prior autologous HCT. The HCT-comorbidity index (HCT-CI) of ≥3 was more frequent in the Flu/Bu cohort compared to Flu/Mel140 and Flu/Cy; 55% vs 32% vs 31% respectively (p<0.001). ATG or alemtuzumab use with conditioning regimen was more frequent in Flu/Bu (36%) and Flu/Mel140 (27%) cohorts compared to Flu/Cy (7%; p<0.001). CNI and methotrexate-based GVHD prophylaxis was less frequent in the Flu/Cy cohort, while CNI and mycophenolate mofetil-based prophylaxis was less commonly used in the Flu/Mel140 group. The median follow up of survivors was 47 (range 3–101) months, 49 (range 3–121) months and 60 (range 3–97) months in the Flu/Bu, Flu/Mel140 and the Flu/Cy groups respectively.

Hematopoietic Recovery:

The day 30 cumulative incidence of neutrophil recovery for the Flu/Bu patients was 100% (95%CI=100–100) compared 97% (95%CI=95–99) for the Flu/Mel140 group and 99% (95%CI=95–100) for the Flu/Cy group (*P*=0.01). The day 100 cumulative incidence of platelet recovery in the same order was 100% (95%CI=100–100), 97% (95%CI=95–99) and 99% (95%CI=95–100) (*P*=0.01); Table 2), respectively.

Graft-vs-Host-Disease:

On univariate analysis, the day 180 cumulative incidence grade 2–4 acute GVHD was 46% (95%CI=36–56) with Flu/Bu, 34% (95%CI=29–40) with Flu/Mel140 and 26% (95%CI=16–37) with Flu/Cy (P=0.02; Table 2). Grade 3–4 acute GVHD in the same order was 16% (95%CI=10–24), 15% (95%CI=11–19), and 12% (95%CI=6–21) respectively (P=0.77). On multivariate analysis, the risk of grade 3–4 acute GVHD was not significantly different across the three conditioning cohorts (P=0.79; Table 3)

The 1-year cumulative incidence of chronic GVHD on univariate analysis was 50% (95%CI=41–60), 49% (95%CI=43–54), and 43 (95%CI=31–54) for Flu/Bu, Flu/Mel140 and Flu/Cy cohorts, respectively (P=0.56). On multivariate analysis, after adjusting for ATG/alemtuzumab use, the risk of chronic GVHD was not significantly different across the three conditioning cohorts (P=0.12; Table 3, Fig1a). GVHD-free, relapse-free survival is shown in Table 2.

Non-relapse Mortality and Relapse:

The adjusted cumulative incidence of NRM at 1-year in the Flu/Bu, Flu/Mel140 and Flu/Cy cohorts was 10% (95%CI=4–16) vs. 10% (95%CI=7–14) vs. 3% (95%CI= 0–7), respectively (*P*=0.02) (Table 2). On multivariable analysis, after adjusting for patient age and donor type, no significant difference was seen between the three groups in terms of NRM risk (P=0.54; Table 3, Fig 1b, for details of multivariate analysis refer to Table 2S).

The adjusted probability of relapse/progression at 4-years for the Flu/Bu, Flu/Mel140 and Flu/Cy cohorts was 57% (95%CI=47–67), 47% (95%CI=41–53) and 65% (95%CI=53–76), respectively (p=0.01; Table 2). On multivariate analysis after adjusting for remission status at the time of HCT, relative to Flu/Bu conditioning the risk of relapse following Flu/Mel140 conditioning (HR=0.73; 95%CI=0.53–1.00; P=0.05), or Flu/Cy conditioning (HR=1.13; 95%CI=0.76–1.66; P=0.55) was not significantly different (Table 3, Fig 1c). Additional factors predictive of relapse/progression risk included disease status and are shown in Table 2S.

Progression-free Survival:

The adjusted probability of PFS at 4-years for the Flu/Bu, Flu/Mel140 and Flu/Cy cohorts was 29% (95%CI=20–38), 37% (95%CI=31–43) and 25% (95%CI=14–35), respectively (p=0.07; Table 2). On multivariate analysis after adjusting for remission status at the time of HCT, relative to Flu/Bu conditioning the risk of therapy failure (inverse of PFS) following Flu/Mel140 conditioning (HR=0.82; 95%CI=0.62–1.08; P=0.16), or Flu/Cy conditioning (HR=1.06; 95%CI=0.76–1.66; P=0.74) was not significantly different (Table 3, Fig 1d). Patients in partial remission at allo-HCT (HR=1.93; P<0.001) and those with resistant disease (HR=2.90; P<0.001) also had higher risk of therapy-failure (Table 2S).

Overall Survival:

The adjusted probability of OS at 4-years for the Flu/Bu, Flu/Mel140 and Flu/Cy cohorts was 62% (95%CI=52–73), 59% (95%CI=53–65) and 55% (95%CI=42–67), respectively (p=0.64; Table 2). On multivariate analysis, the proportional hazards assumption for Cox regression model for OS was violated. Thus, a piecewise proportional hazards model was built, where the best cutoff of 11months (post allo-HCT) was selected based on the maximum likelihood method. Relative to Flu/Bu, the Flu/Cy conditioning was associated with a decreased risk of mortality in the first 11months after allo-HCT (HR=0.28, 95%CI=0.10–0.73, p=0.009), but beyond 11months post allo-HCT, Flu/Cy was associated with a significantly higher risk of mortality, (HR=2.46, 95%CI=0.1.32–4.61, p=0.005; TABLE 3, Fig 1e). No difference in mortality risk was seen between Flu/Bu and Flu/Mel140

cohorts. Patients in partial remission at allo-HCT (HR=1.73; P=0.001) and those with resistant disease (HR=2.08; P<0.001) also had higher risk of mortality (Table 2S).

No center effect was seen for any outcomes. The p-values for relapse, NRM, PFS, and OS are 0.89, 0.19, 0.47 and 0.78, respectively.

Causes of Death:

Relapse was the leading cause of death for all groups, accounting for 19 (51%) of Flu/Bu, 50 (39%) of Flu/Mel140 and 18 (53%) of Flu/Cy cohort deaths. Infections accounted for 3%, 13% and 12% of deaths in Flu/Bu, Flu/Mel140 and Flu/Cy cohorts. GVHD was the main cause of death in 5% of Flu/Bu, 8% of Flu/Mel140 and 3% of the Flu/Cy group. Detailed information about causes of death is shown in Table 3S.

DISCUSSION

Allogeneic HCT is a frequently considered treatment option in heavily pretreated HL patients, including those relapsing after a prior autologous HCT. Previous data comparing MAC versus RIC **allo-HCT** for HL, have not shown a superiority of MAC approaches over the lower intensity options.(9, 10, 12) In this manuscript we report the outcomes of patients undergoing RIC HCT specifically for HL, a patient population that is demonstrably younger at the time of allo-HCT compared to other lymphoma patients and in which the merits of various RIC platforms are not known. The main findings of our study are as follows: (1) the most commonly used RIC regimen in allo-HCT for HL is Flu/Mel140 which was compared to Flu/Bu and Flu/Cy, the next most frequently used regimens; (2) the choice of conditioning regimen did not confer any benefit in terms of the risk of relapse, decrease in NRM or improvement in PFS; and (3) Flu/Cy was associated with a significantly higher risk of mortality in patients beyond 11 months from allo-HCT.

Sureda et al., (13) compared RIC to MAC in HL for the lymphoma working party of the European Society for Blood and Marrow Transplantation (EBMT) and showed a significantly decreased incidence of NRM and improved OS in the RIC group. Of note, the in the most recent EBMT study on difference in NRM rates between MAC and RIC approaches was seen.(12) While prior EBMT and CIBMTR registry studies have reported outcomes of HL patients undergoing RIC allo-HCT, none of these studies compared different RIC regimens.(26, 27) The EBMT analysis reported 3-year OS was 29% and PFS of 25%, which is considerably lower than our current analysis, **though** the study included patients at an earlier time period (1995 and 2005). The CIBMTR study (27) showed a 2-year PFS of 20%, OS of 37%, and NRM of 33%. The outcomes in our current analysis across the 3 regimens studied at 4 years surpass those previously reported with PFS of 25–37%, OS of 55–62% and NRM of 12–17% respectively, but with similar relapse rate of 47–65% at 4 years. NRM of allo-HCT in young HL patients has dramatically improved but this fact is often under appreciated. The NRM rates our study are comparable to the NRM rates reported by other contemporaneous studies. (11). The recent CIBMTR analysis of alternative donor allo-HCT for HL noted a NRM for T cell–replete related donor haploidentical HCT of 11% (95% CI, 6 to 17) compared with 6% (95% CI, 4 to 8) in the MSD/CNI group.(6) Alvarez et al.(28), prospectively evaluated 40 patients who underwent

RIC allo-HCT utilizing Flu/Mel140 and demonstrated a 2-year OS of 52% and PFS of 34% with 1-year NRM of 25%. Peggs et al. (29) prospectively treated 49 patients with relapsed HL with Flu/Mel140 and reported 4-year OS and PFS of 55% and 39%. Of note, in our study there was a non-significant trend towards a lower relapse rate with the Flu/Mel140 relative to Flu/Bu (HR=0.73, 95%CI=0.53–1.00; Table 3).

The Flu/Cy arm in our study on multivariate analysis, was associated with decreased risk of mortality, compared to Flu/Bu in first 11 months after allo-HCT (OR 0.28, 95%CI 0.10–0.73, p=0.009), but beyond 11 months post allo-HCT it was associated with a significantly higher risk of mortality, (OR 2.46, 95%CI 0.1.32–4.61, p=0.005). To further investigate the reason for increased mortality in Flu/Cy patients beyond 11months, we evaluated NRM, relapse/progression, and PFS for the group before and after 11month cutoff. Comparing ≤11months vs. >11months the direction and magnitude of HR changes for NRM (HR=0.27 vs. 2.87), relapse/progression (HR=1.1 vs. 1.3) and PFS (HR=0.91 vs. 1.5) in Flu/Cy cohort suggest late NRM (as opposed to late relapses) as the main driver of increased late mortality risk. However, deciphering the exact reasons driving this higher late NRM and overall mortality using cause of death data reported to registry is limited, as previously published. (30)

The rate of acute and chronic GVHD was similar across arms after adjustment for ATG/alemtuzumab use in conditioning and GVHD prophylaxis. We did not see any increase in the rates of acute GVHD with the Flu/Mel cohort as has been reported by Kekre et al., when comparing Flu/Mel and Flu/Bu RIC regimens in patients with lymphoma. Their cohort included HL, as well as indolent and aggressive NHL and the patients had a higher median age at the time of allo-HCT.(18)

In contrast to NHL patients who tend to be much older at the time of allo-HCT (median age in 50s-60s), HL patients are typically younger (6); this holds true in this analysis with the median age of our cohort being 33 years old. These younger patients theoretically may tolerate more intense RIC approaches (e.g. Flu/Mel140) better. For example a recent study showed higher NRM and inferior OS with Flu/Mel140 (arguably a more intense RIC) compared to Flu/Bu in an older predominantly NHL population.(18) In the current analysis, likely owing to the much younger median age of HL patients, no significant difference in the NRM risk was seen between more intense RIC approach (Flu/Mel140) and less intense approaches (Flu/Bu, Flu/Cy).

Recent data suggest that patients with both pre allo-HCT and post allo-HCT exposure to checkpoint inhibitors (CPI) may have an increased risk of acute GVHD.(31–33) In the CIBMTR registry, detailed information about pre-transplant chemotherapy treatments is available only for patients reported at the CRF level (as described in the methods sections under the “Data Source” subheading). Only 24 subjects in the current report were reported at the CRF level, which precludes our ability to see if prior CPI exposure would interact with specific RIC platforms. Similar to other registry-based studies there are limitations inherent to this analysis. Our analysis cannot adjust for unknown factors that would have prompted a center to choose one RIC regimen over another. The nature of data captured in the CIBMTR registry does not allow us to adequately assess the number or type pf pre-transplant salvage

regimens, including CPI exposure. However, as opposed to GVHD prophylaxis approaches (e.g. post-transplant cyclophosphamide) (6, 34), no data are available to suggest superiority of one RIC platform over another in CPI exposed HL patients. We advise caution in extrapolating the results of the current analysis to HL patients undergoing haploidentical allo-HCT.(6, 7, 35, 36)

Our analysis shows that the choice of RIC conditioning regimen does not impact the risk of NRM, relapse, PFS or risk of GVHD in HL patients undergoing allo-HCT, with one potential exception. Flu/Cy appears to be associated with a higher delayed risk of late NRM and worse OS. Relapse remains the most common form of therapy failure after allo-HCT in HL. Continued efforts are essential to develop better strategies for disease control for this patient population in both pre- and post- HCT settings.(37)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

1. In classical HL patients, three common RIC regimens (Flu/Bu vs. Flu/Mel140 vs. Flu/Cy) had no difference in NRM, relapse and PFS.
2. RIC allogeneic HCT with Flu/Cy was associated with higher late overall mortality risk, relative to Flu/Bu.

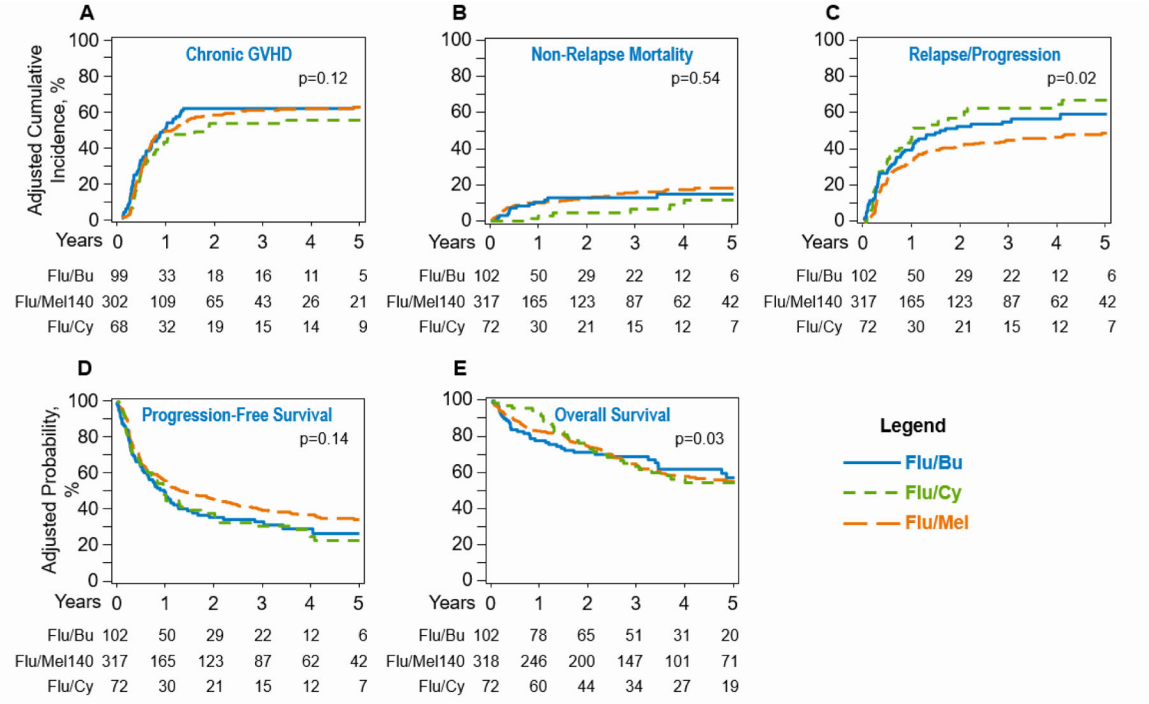

Fig 1.

(A) Cumulative incidence of chronic graft-versus-host-disease (overall, P= 0.12). (B) Cumulative incidence of non-relapse mortality (overall, P = 0.54). (C) Cumulative incidence of relapse and/or progression in recipients of Flu/Bu, Flu/Cy and Flu/Mel140 transplantations (overall, P= 0.02). (D) Kaplan-Meier estimate of progression-free survival (PFS) (overall, P = 0.14). (E) Kaplan-Meier estimate of overall survival (OS) (overall, P = 0.03).

Table 1.

Baseline characteristics

	Flu/Bu	Flu/Mel140	Flu/Cy	P-value
Number of patients	**102**	**318**	**72**	
Median patient age, years(range)	33 (19–69)	33 (18–70)	33 (19–61)	0.18
Male gender	69 (68)	182 (57)	43 (60)	0.18
Patient race				0.33
Caucasian	94 (92)	272 (86)	60 (83)	
Other	8 (8)	44 (14)	12 (17)	
Missing	0	2 (<1)	0	
Karnofsky performance score ≥ 90	70 (69)	240 (75)	52 (72)	0.07
Missing	0	13 (4)	3 (4)	
HCT-CI				<0.001
0	25 (25)	134 (42)	35 (49)	
1–2	21 (21)	78 (25)	11 (15)	
≥ 3	56 (55)	102 (32)	22 (31)	
Missing	0	4 (1)	4 (6)	
Remission status at HCT				0.23
Complete remission	40 (39)	134 (42)	18 (25)	
Partial remission	42 (41)	136 (43)	36 (50)	
Resistant	18 (18)	39 (12)	16 (22)	
Missing/Unknown	2 (2)	9 (3)	2(3)	
Prior autologous HCT	91 (89)	271 (85)	60 (83)	
Median time from diagnosis to transplant, months	32 (4–201)	33 (3–276)	39 (13–250)	0.17
Donor type				0.06
Matched sibling donor	48 (47)	175 (55)	47 (65)	
Matched unrelated donor	54 (53)	143 (45)	25 (35)	
GVHD prophylaxis				<0.001
CNI + MMF +- other(s)	30 (29)	34 (11)	18 (25)	
CNI + MTX +- other(s)	58 (57)	202 (64)	35 (49)	
CNI + other(s)	14 (14)	82 (26)	19 (26)	
ATG/alemtuzumab use in conditioning	37 (36) *	87 (27) *	5 (7) *	<0.001
CMV status Donor/Recipient				0.75
+/−	18 (18)	40 (13)	10 (14)	
Other	82 (80)	274 (86)	62 (86)	
Missing	2 (2)	4 (1)	0	
Year of transplant				0.03 [a]
2008–2011	36 (35)	133 (42)	40 (56)	
2012–2016	66 (65)	185 (58)	32 (44)	
Median follow-up of survivors (range), months	47 (3–101)	49 (3–121)	60 (3–97)	

Hypothesis testing:

[a] Pearson chi-square test

Abbreviations: CNI=calcineurin inhibitor; CMV=Cytomegalovirus; Cy=cyclophosphamide; Flu=fludarabine; Bu=Busulfan; HCT-CI=hematopoietic cell transplant-comorbidity index; Mel=melphalan; MMF=mycophenolate mofetil; MTX=methotrexate

[*] The median total dose and type of ATG in each conditioning cohort was as following: Flu/Bu (Horse ATG=60mg/kg; Rabbit ATG=6mg/kg); Flu/Mel140 (Horse ATG=45mg/kg; Rabbit ATG=5mg/kg) and Flu/Cy (Horse ATG=45mg/kg; Rabbit ATG=5mg/kg). Median total alemtuzumab dose with Flu/Mel140 was 40mg.

Table 2.

Univariate and adjusted probabilities of outcomes of NMA/RIC patients receiving first allo-HCT for HL 2008–2016

	Flu/Bu (N = 102)		Flu/Mel 140 (N = 318)		Flu/Cy (N = 72)		
Outcomes	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**p-value**
Neutrophil recovery	100		312		71		
30 days		100 (100–100)%		97 (95–99)%		99 (95–100)%	0.010
Platelet recovery	100		310		67		
100-day		100 (100–100)%		97 (95–99)%		99 (95–100)%	0.010
Grade 2–4 acute GVHD	100		301		66		
180 days		46 (36–56)%		34 (29–40)%		26 (16–37)%	0.02
Grade 3–4 acute GVHD	99		301		65		
180 days		16 (10–24)%		15 (11–19)%		12 (6–21)%	0.77
Chronic GVHD	99		302		68		
1-year		50 (41–60)%		49 (43–54)%		43 (31–54)%	0.56
GRFS	99		301		65		
2-year		21 (14–30)%		25 (20–30)%		29 (18–41)%	0.45
Adjusted Non-relapse mortality	102		317		72		
1-year		10 (4–16)%		10 (7–14)%		3 (0–7)%	0.02
4-year		15 (7–23)%		17 (13–22)%		12 (3–21)%	0.51
Adjusted Relapse/Progression	102		317		72		
1-year		40 (30–49)%		34 (29–39)%		48 (38–59)%	0.05
4-year		57 (47–67)%		47 (41–53)%		65 (53–76)%	0.01
Adjusted Progression-free Survival	102		317		72		
1-year		50 (41–60)%		56 (51–61)%		48 (37–59)%	0.36
4-year		29 (20–38)%		37 (31–43)%		25 (14–35)%	0.07
Adjusted Overall survival	102		318		72		
1-year		78 (70–86)%		84 (79–88)%		93 (87–99)%	0.005
4-year		62 (52–73)%		59 (53–65)%		55 (42–67)%	0.64

Abbreviations: Eval=evaluable; GVHD=graft-versus-host disease; GRFS=GVHD-free, relapse-free survival; N=number; Prob=probability.

Table 3.

Main effect of multivariate analysis.

	N	HR	95% CI Lower Limit	95% CI Upper Limit	p-value
Grade 3–4 acute GVHD					
Conditioning regimen					
Flu/Bu	99	1			**0.79**
Flu/ Mel 140	301	0.89	0.48	1.66	
Flu/Cy	65	0.73	0.29	1.82	
Chronic GVHD					
Conditioning regimen					
Flu/Bu	100	1			**0.12**
Flu/ Mel 140	305	0.88	0.65	1.18	
Flu/Cy	69	0.65	0.43	0.99	
Chronic GVHD adjusted for significant covariate: ATG/alemtuzumab use in conditioning.					
Non-relapse mortality (NRM)					
Conditioning regimen					
Flu/Bu	102	1			**0.54**
Flu/ Mel 140	317	1.21	0.66	2.23	
Flu/Cy	72	0.83	0.34	2.05	
NRM adjusted for significant covariates: patient age and donor type.					
Progression/relapse					
Conditioning regimen					
Flu/Bu	102	1			**0.02**
Flu/ Mel 140	318	0.73	0.53	1.00	
Flu/Cy	72	1.13	0.76	1.66	
Progression/relapse adjusted for significant covariate: remission status at HCT.					
Progression free survival					
Conditioning regimen					
Flu/Bu	102	1			**0.14**
Flu/ Mel 140	318	0.82	0.62	1.08	
Flu/Cy	72	1.06	0.75	1.51	
Progression free survival adjusted for significant covariate: remission status at HCT.					
Overall Survival					
Conditioning regimen ≤ 11* months**					
Flu/Bu	102	1			**0.03**
Flu/ Mel 140	318	0.80	0.49	1.32	0.39
Flu/Cy	72	0.28	0.10	0.73	0.009
Conditioning regimen > 11 months* **					
Flu/Bu	78	1			**0.02**

	N	HR	95% CI Lower Limit	95% CI Upper Limit	p-value
Flu/ Mel 140	256	1.62	0.93	2.82	0.09
Flu/Cy	64	2.46	1.32	4.61	0.005
Overall survival adjusted for significant covariate: remission status at HCT.					

*** The 11-months was chosen as the cut-off OS based on the maximum likelihood value in the Cox model.