Outcome of Allogeneic Transplantation for Mature T-cell Lymphomas: Impact of Donor Source and Disease Characteristics

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Abstract:
Mature T-cell lymphomas constitute the most common indication of allogeneic hematopoietic cell transplantation (allo-HCT) in lymphomas. Large studies evaluating contemporary outcomes of allo-HCT in mature T-cell lymphomas, relative to commonly used donor sources are not available. Included in this registry study were adult patients who had undergone allo-HCT for anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL), or peripheral T-cell lymphoma–NOS (PTCL–NOS) between 2008 and 2018. HCT platforms compared were post-transplant cyclophosphamide-based haploidential (haplo)– HCT, matched sibling donor (MSD) HCT, diseased-related donor (MUD) HCT without T-cell depletion (MUD TCD–), and MUD HCT without TCD (MUD TCD+). Co-primary endpoints were overall survival (OS) and progression-free survival (PFS); secondary endpoints included non-relapse mortality (NRM), and relapse/progression incidence (RI). 1942 patients were eligible (haplo-HCT 237; MSD 911; MUD-TCD+ 468; MUD TCD- 326). Cohorts were comparable for baseline characteristics except for patients with decreased performance status (PS) and marrow graft recipients in the haplo-HCT group. On univariate and multivariate comparisons, OS and PFS, RI, and NRM were not significantly different between haplo-HCT, MSD, MUD-TCD+, and MUD-TCD–cohorts, with 3-year OS and PFS of 60%, 63%, 59%, and 64%; and 50%, 50%, 48%, and 52%, respectively. Significant predictors of inferior OS and PFS on multivariate analysis were active disease status at HCT and decreased PS. AITL was associated with significantly reduced relapse risk and better PFS compared to PTCL–NOS. Allo-HCT can provide durable PFS in patients with mature T-cell lymphoma outcomes. Of haplo-HCT were comparable to that of matched donor allo-HCT.

Conflict of interest: COI declared – see note

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Clinical trial registration information (if any):
Figure 1

1A. Chronic GVHD

Cumulative Incidence, %

|          | 0   | 1   | 2   |
|----------|-----|-----|-----|
| Haplo    | 226 | 89  | 53  |
| HLA sibling | 770 | 314 | 184 |
| MU no ATG | 296 | 81  | 43  |
| MU w/ ATG | 395 | 172 | 109 |

p < 0.001

1B. Non-Relapse Mortality

|          | 0   | 1   | 2   | 3   |
|----------|-----|-----|-----|-----|
| Haplo    | 237 | 117 | 73  | 53  |
| HLA sibling | 911 | 482 | 351 | 278 |
| MU no ATG | 326 | 181 | 148 | 117 |
| MU w/ ATG | 468 | 234 | 164 | 126 |

p = 0.49

1C. Relapse

|          | 0   | 1   | 2   | 3   |
|----------|-----|-----|-----|-----|
| Haplo    | 237 | 117 | 73  | 53  |
| HLA sibling | 911 | 482 | 351 | 278 |
| MU no ATG | 326 | 181 | 148 | 117 |
| MU w/ ATG | 468 | 234 | 164 | 126 |

p = 0.7

1D. Progression-Free Survival

|          | 0   | 1   | 2   | 3   |
|----------|-----|-----|-----|-----|
| Haplo    | 235 | 117 | 73  | 53  |
| HLA sibling | 909 | 482 | 351 | 278 |
| MU no ATG | 325 | 181 | 148 | 117 |
| MU w/ ATG | 465 | 234 | 164 | 126 |

p = 0.8

1E. Overall Survival

|          | 0   | 1   | 2   | 3   |
|----------|-----|-----|-----|-----|
| Haplo    | 235 | 140 | 89  | 64  |
| HLA sibling | 900 | 593 | 451 | 353 |
| MU no ATG | 326 | 223 | 181 | 141 |
| MU w/ ATG | 465 | 279 | 201 | 152 |

p = 0.3

1F. GRFS

|          | 0   | 1   | 2   | 3   |
|----------|-----|-----|-----|-----|
| Haplo    | 179 | 69  | 64  | 53  |
| HLA sibling | 665 | 263 | 168 | 168 |
| MU no ATG | 210 | 72  | 52  | 52  |
| MU w/ ATG | 378 | 152 | 105 | 105 |

p = 0.02
Outcome of Allogeneic Transplantation for Mature T-cell Lymphomas: Impact of Donor Source and Disease Characteristics.

Short Title: Allogeneic HCT for mature T-NHL.

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Key Words: T-cell NHL, haploidentical transplantation, allogeneic transplantation, angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma, anaplastic large cell lymphoma.
Key Points:
Three-year OS of T-cell lymphoma patients getting haplo-HCT, MSD, MUD-TCD+, and MUD-TCD- alloHCT is 60%, 63%, 59%, and 64%, respectively.
Three-year PFS of T-cell lymphoma patients getting haplo-HCT, MSD, MUD-TCD+, and MUD-TCD- alloHCT is 50%, 50%, 48%, and 52%, respectively.

Abstract
Mature T-cell lymphomas constitute the most common indication of allogeneic hematopoietic cell transplantation (allo-HCT) in lymphomas. Large studies evaluating contemporary outcomes of allo-HCT in mature T-cell lymphomas, relative to commonly used donor sources are not available. Included in this registry study were adult patients who had undergone allo-HCT for anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma (AITL), or peripheral T-cell lymphoma-NOS (PTCL-NOS) between 2008 and 2018. HCT platforms compared were post-transplant cyclophosphamide-based haploidentical (haplo-) HCT, matched sibling donor (MSD) HCT, matched unrelated donor HCT with in-vivo T-cell depletion (MUD TCD+), and MUD HCT without TCD (MUD TCD-). Co-primary endpoints were overall survival (OS) and progression-free survival (PFS); secondary endpoints included non-relapse mortality (NRM), and relapse/progression incidence (RI). 1942 patients were eligible (haplo-HCT 237; MSD 911; MUD-TCD+ 468; MUD TCD- 326). Cohorts were comparable for baseline characteristics except higher proportions of patients with decreased performance status (PS) and marrow graft recipients in the haplo-HCT group. On univariate and multivariate comparisons, OS and PFS, RI, and NRM were not significantly different between haplo-HCT, MSD, MUD-TCD+, and MUD-TCD- cohorts, with 3-year OS and PFS of 60%, 63%, 59%, and 64%; and 50%, 50%, 48%, and 52%, respectively. Significant predictors of inferior OS and PFS on multivariate analysis were active disease status at HCT and decreased PS. AITL was associated with significantly reduced relapse risk and better PFS compared to PTCL-NOS. Allo-HCT can provide durable PFS in patients with mature T-cell lymphoma. Outcomes of haplo-HCT were comparable to that of matched donor allo-HCT.
INTRODUCTION

Mature T-cell lymphomas are a heterogeneous group of (NHL) with varied morphological and clinical features,\textsuperscript{1,2} and an overall prognosis that is generally worse than their B-cell counterparts.\textsuperscript{2} The most common subtypes of mature T-cell lymphoma are peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL).\textsuperscript{3} While the addition of brentuximab vedotin to anthracycline-based frontline therapies has improved the outcomes of CD30+ T-cell NHL (especially ALCL),\textsuperscript{4} the results of first line treatments of PTCL-NOS and AITL remain suboptimal.\textsuperscript{5-7} In the relapsed/refractory setting available pharmacological options typically do not provide long term disease control,\textsuperscript{8-10} and adoptive immunotherapy in the form of allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative option for all three subtypes.\textsuperscript{11-16} In fact, with the recent decline in allo-HCT utilization for diffuse large B-cell lymphoma, T-cell NHL now constitutes the most common indication of allo-HCT for lymphomas in the United States and Europe.\textsuperscript{17} Historically, application of this option (even in relatively younger patients) was limited by the lack of donor availability and high procedure-related mortality rates (~30-35% at 1-year).\textsuperscript{11-13} Large contemporary analyses evaluating outcomes of allo-HCT in mature T-cell NHL, especially relative to alternative donor sources are not available.

With the introduction of post-transplant cyclophosphamide (ptCY)-based immunosuppression, allo-HCT using haploidentical (haplo) related donors has emerged as a valuable alternative for patients without an available matched sibling (MSD) or matched unrelated donors (MUD).\textsuperscript{18} Similar to more common indications of allo-HCT,\textsuperscript{19-21} ptCY haplo-HCT seems to provide outcomes comparable to MSD/MUD transplants [using conventional calcineurin inhibitor (CNI)-based prophylaxis] in patients with lymphoma.\textsuperscript{22-26} However, these results derive from retrospective analyses of patient samples with the global diagnoses of Hodgkin lymphoma
and/or NHL. Owing to the increasing utilization of allo-HCT in T-cell NHL, we evaluated the contemporary outcomes of this modality, relative to established donor sources, in the three most common nodal variants of mature T-cell lymphomas (PTCL-NOS, AITL and ALCL).

MATERIALS AND METHODS

Data sources

The study was performed through collaboration between the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR). EBMT is a voluntary organization comprising more than 600 transplant centers mainly from Europe. Accreditation as a member center requires submission of minimal essential data (MED-A form) from all consecutive patients to a central registry. Accredited EBMT centers are subject to on-site audits and obtaining written informed consent prior to data registration following the Helsinki Declaration is mandatory for all centers.

CIBMTR is a working group of more than 380 transplantation centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin (MCW). 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. Patients provided written informed consent for research. The institutional review boards of the MCW and the National Marrow Donor Program approved this study.
Study design

This was a collaborative retrospective registry-based analysis. Eligible were adult (≥18 years) patients with PTCL-NOS, AITL and ALCL, who had undergone their first allo-HCT between 2008 and 2018. Eligible donors included MSD, 8/8 MUD (allele-level match at HLA-A, -B, -C and -DRB1), or haploidentical related donors. Recipients of haplo-HCT were limited to those receiving graft-versus-host disease (GVHD) prophylaxis with ptCY (± CNI and mycophenolate mofetil [MMF]). GVHD prophylaxis in MSD was limited to CNI-based approaches without antithymocyte globulin/alemtuzumab in-vivo T cell depletion (TCD), while MUD recipients received CNI-based prophylaxis either with or without in-vivo TCD. Patients receiving ex vivo graft manipulation (e.g., CD34 selection; N=77) were excluded to reduce study heterogeneity. CIBMTR cohort was limited to patients from U.S. and Canada only, to avoid duplicate inclusion of European patients reported to both registries.

Definitions

The intensity of alloHCT conditioning regimens was categorized as myeloablative (MAC) or non-myeloablative/reduced-intensity conditioning (NMC/RIC) using consensus criteria.\(^{27}\) Disease response at the time of HCT was determined using the International Working Group criteria in use during the era of this analysis.\(^{28-30}\)

Study Endpoints

The co-primary endpoints were overall survival (OS) and progression-free survival (PFS). Death from any cause was considered an event for OS and surviving patients were censored at last follow up. For PFS, a patient was considered a treatment failure at the time of progression/relapse or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up. Secondary outcomes included non-relapse mortality (NRM) and progression/relapse. NRM was defined as death without evidence of prior
lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a CR; NRM was considered a competing risk. Acute GVHD and chronic GVHD were graded using established clinical criteria.\textsuperscript{31,32} GVHD-free, relapse-free survival (GRFS) was calculated using the modification proposed by Ruggeri et al. for registry-based studies.\textsuperscript{33} Probabilities of GRFS, PFS and OS were calculated using the Kaplan–Meier estimates. Neutrophil recovery was defined as the first of 3 successive days with ANC $\geq 500/\mu L$ 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 haplo-HCT cohort was compared against the MSD, MUD with TCD (MUD TCD+) and MUD without TCD (MUD TCD-) cohorts. Patient-, disease- and transplant-related variables were compared between the four cohorts using the Chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Cumulative incidences of hematopoietic recovery, acute and chronic 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 acute GVHD, chronic GVHD, relapse, NRM, PFS, and OS. All potential prognostic factors for outcomes and characteristics that differed between the groups were included in multivariate models (stratified on data source: CIBMTR vs. EBMT), namely: donor source, disease status at HCT, patient age, patient gender, cell source, conditioning regimen intensity, prior autologous HCT, Karnofsky performance score and histology. The proportional hazards assumption for Cox regression was
tested by adding a time-dependent covariate for each risk factor and each outcome. Covariates violating the proportional hazards assumption were added as time-dependent covariates in the Cox regression model. Interactions between the main effect and significant covariates were examined. All tests were two sided. The type I error rate was fixed at 0.05. Statistical analyses were performed with SPSS 26 (SPSS Inc, Chicago, IL), and R 3.6.1 (R Development Core Team, Vienna, Austria) software packages.

RESULTS

Patient and transplant characteristics
Altogether, 1942 eligible patients (haplo 237, MSD 911, MUD TCD+ 468, MUD TCD- 326) were included. Of these, 23 patients were part of a previous EBMT study addressing the outcome of allo-HCT in ALCL,$^{34}$ and 144 patients overlapped with a prior CIBMTR analysis on allo-HCT in AITL.$^{35}$ Of note, patients receiving haplo-HCT were excluded from both of these studies. There were no significant differences between the four cohorts in terms of patient gender, disease status at allo-HCT, HCT-comorbidity index (HCT-CI), median number of prior therapies, distribution of T-cell histologies and history of a prior autologous HCT. Compared to the MSD and MUD cohorts, patients in the haplo-HCT cohort more frequently had Karnofsky performance score (KPS) $\leq 90$ (42% vs. 32%-35%; $p=0.03$) and bone marrow as graft source (31% vs. 6%-7%; $p<0.001$). Use of RIC was more frequent in haplo-HCT (73%) and MUD TCD- (73%) cohorts compared with MSD (62%) and MUD TCD+ (67%; $p<0.001$) cohorts. Fewer patients in MSD cohort were 60 years or older (19%) compared with other cohorts (26%-29%). Details are given in Table 1. The completeness of patient follow up at 1-year, 2-years and 3-years was 94.5%, 86.5% and 79.2% respectively.

Hematopoietic Recovery
The day 28 cumulative incidence of neutrophil recovery was significantly lower in the haplo-HCT cohort (86%, 95%CI=81-90), compared with MSD (95%, 95%CI=94-97), MUD TCD+ (94%, 95%CI=91-96) and MUD TCD- cohorts (97%, 95%CI=94-98; p<0.001; Table 2, Supplemental Figure 1S). Similarly, the day 100 cumulative incidence of platelet recovery was significantly lower in the haplo-HCT cohort (80%, 95%CI=74-85), compared with MSD (96%, 95%CI=94-97), MUD TCD+ (93%, 95%CI=89-95) and MUD TCD- (96%, 95%CI=93-98; p<0.001; Table 2, Supplemental Figure 1S) cohorts.

**Graft-versus-host disease**

The day 100 cumulative incidences of acute GVHD grade 2-4 (grade 3-4) in the haplo-HCT, MSD, MUD TCD+ and MUD TCD- cohorts were 33% (9%), 31% (11%), 30% (10%) and 37% (18%), respectively (Table 2). On multivariate analysis, compared with haplo-HCT, the MUD TCD- cohort was associated with a significantly higher risk of grade 3-4 acute GVHD (hazard ratio [HR]=2.0, 95%CI=1.2-3.3; p=0.01) (Tables 3). The 1-year cumulative incidences of chronic GVHD in the haplo-HCT, MSD, MUD TCD+ and MUD TCD- cohorts were 28%, 41%, 35% and 54%, respectively (Table 2). On multivariate analysis, compared with haplo-HCT, the MSD (HR=1.7, 95%CI=1.3-2.2; p<0.001), MUD TCD+ (HR=1.4, 95%CI=1.0-1.9; p=0.047) and MUD TCD- (HR=2.4, 95%CI=1.8-3.2; p<0.001) cohorts were associated with a significantly higher risk of chronic GVHD (Tables 3, Figure 1A).

**Non-relapse mortality**

The 3-year cumulative incidences of NRM in the haplo-HCT, MSD, MUD TCD+ and MUD TCD- cohorts were 22%, 21%, 24%, and 23%, respectively (Table 2, Figure 1B). The risk of NRM was not significantly different between the four cohorts on multivariate analysis (Table 3). Resistant disease at HCT, age 40 years or older and KPS <90 were independently associated with a higher risk of NRM (Table 3).
**Disease control**

The 3-year cumulative incidence of relapse/progression was 28% (95%CI=22-35) in the haplo-HCT cohort, compared to 29%, 28%, and 25% for MSD, MUD TCD+ and MUD TCD- cohorts respectively (**Table 2, Figure 1C**). The risk of relapse/progression was not significantly different between the four cohorts on multivariate analysis (**Table 3**). Other factors independently associated with risk of relapse included disease status at HCT, female donor for male recipient, KPS and lymphoma subtype (**Table 3**). Across all four donor groups, the majority of relapse/progression events occurred within the first six months after allo-HCT, whilst events became rare beyond 2-years post HCT.

**Survival**

The median follow-up of survivors was 38 (1-134) months. The 3-year PFS in the haplo-HCT group was 50% (95%CI=52-66) compared to 50%, 48% and 52% for the MSD, MUD TCD+, and MUD TCD- cohorts, respectively (**Table 2, Figure 1D**). The 3-year OS in similar order was 60%, 63%, 59% and 64%, respectively (**Table 2, Figure 1F**). Multivariate analyses did not show a significant difference in OS and PFS between the four cohorts (**Table 3**). Disease status less than a complete remission, age ≥40 years and decreased KPS significantly reduced OS and PFS on multivariate analysis. In addition, PFS was significantly associated with AITL histology and donor-recipient gender mismatch (**Table 3**). **Table 4** summarizes allo-HCT univariates outcomes based on pre transplant remission status. The 3-year PFS of patients in complete remission, partial remission and of those with refractory/untreated relapse was 57%, 47% and 36% respectively (p<0.0001). The respective 3-year OS estimates were 68%, 59% and 49% (p<0.0001).
Two-year composite endpoint GRFS following haplo-HCT was 37% (95%CI=29-45%) compared to 36% (95%CI=32-40%) following MSD, 41% (95%CI=36-46%) following MUD TCD+ and 31% (95%CI=25-37%) following MUD TCD- (p=0.02) (Figure 1F).

**Subgroup analysis**

The information on number of therapy lines prior to allo-HCT was not available in 1177 patients (61%, explained in Table 1, footnote #2). Baseline characteristics and univariate outcomes of patients with data available on prior therapy lines are shown in Table S1 and S2). To adjust for confounding variables the impact of number of treatment lines prior to allo-HCT was examined in a separate exploratory multivariate model restricted to patients with available data (Table S3). More than 1 treatment line prior to allo-HCT was associated with a significantly higher risk of NRM (HR=1.8; p=0.02), but not relapse/progression or PFS. Patients receiving 3 or more treatment lines prior to allo-HCT also had a higher risk of overall mortality (HR=1.6, p=0.02).

**Causes of death**

The most common cause of death in all 4 cohorts was recurrent T-cell NHL (haplo 38%, MSD 36%, MUD TCD+ 30%, MUD TCD- 31%). Infections accounted for overall the second most common cause of death (19%), with numerically highest proportion in the MUD TCD+ group (22%), followed by haplo-HCT (20%), MUD TCD- (19%) and MSD (17%) (Table S4).

**DISCUSSION**

Allogeneic HCT is an effective form of adoptive immunotherapy for patients with high risk and/or relapsed/refractory T-cell NHL. Although mature T-cell neoplasms now constitute the most common lymphoma indication for allografting in the US and Europe,17 published studies on allo-HCT in T-cell lymphoma have been limited by small sample size and heterogeneity of underlying diagnoses, and largely refer to transplant series performed in the early 2000s.36
contrast, this joint analysis performed by the EBMT and the CIBMTR evaluates a 15-fold larger sample than the prior registry study,\textsuperscript{12} focuses on the three most important T-NHL entities, and covers a contemporary era with specific emphasis on haplo-HCT. Several important observations are made: (1) regardless of the donor source, allo-HCT provides unprecedented rates of survival outcomes (3-year OS 60-64% and PFS 48-52%), (2) disease recurrence appears to be a rare event for patients surviving 2-years relapse-free, (3) careful patient preparation (adequate disease control, patient fitness etc.) remain crucial factors impacting allo-HCT outcomes and (4) the efficacy of allo-HCT appears to be different between the three main T-NHL subsets, showing the lowest risk of relapse in AITL.

The current collaborative analysis highlights the remarkable improvements in the outcomes of allo-HCT for T-cell NHL, since the last CIBMTR analysis looking at a similar population.\textsuperscript{12} That study reporting allo-HCT outcomes in PTCL-NOS, AITL and ALCL (era 1996-2006) was notably restricted to younger patients (age ≤ 60 years) receiving HLA-matched allografts.\textsuperscript{12} In that analysis, the 3-year rates of PFS and OS were 37% and 46% respectively and NRM rates ranged from 27-34% depending on conditioning intensity. By contrast, in the current report reflecting the era 2008-2018, the 3-year NRM, PFS and OS are substantially better (approximately 20%, 50% and 60%, respectively) despite inclusion of alternative donor sources and a sizable proportion of patients being 60 years or older (465 patients [24%]). These improved outcomes are potentially due to advances in unrelated donor selection, transplant supportive care and management of post-transplant complications.

The outcomes of the haplo-HCT cohort of the current analysis (n=237), also validate results of prior retrospective reports limited by small sample sizes (comprising 20-35 patients only), broad variety of T-cell NHL subtypes investigated, and restriction to single center analyses and/or certain types of conditioning and graft sources (n≤35).\textsuperscript{37-40} Thus, the current study is the first one
showing comparable outcomes of haplo-HCT to matched donor transplants across the three main T-cell lymphoma subsets on a reasonable patient number in a multicenter setting. Based on the current analysis we cannot speculate about scenarios where haplo-HCT might be preferable over matched donor HCT and vice versa. However, in a recent cross-sectional EBMT study on predictors of haplo-HCT outcomes in lymphoma, chemorefractoriness at transplantation and primary diagnosis emerged as the only significant independent risk factors for survival.41

The timing of allo-HCT in T-cell NHL is controversial (in first remission vs. for relapsed/refractory disease). A French/German randomized study compared allo-HCT versus autologous HCT in younger patients with nodal T-cell lymphoma as part of first-line therapy.15 Roughly half of the patients randomized to allo-HCT (23/49) did not undergo allotransplantation, largely because of disease progression and donor unavailability. Among the 67 patients undergoing HCT no difference in survival outcomes was seen. At this time the American Society for Transplantation and Cellular Therapy guidelines do not recommend allo-HCT in first complete remission for nodal mature T-cell NHL.42 Notably, although our study suggests that survival after allo-HCT decreases with increasing number of pretreatment lines, this effect reached statistical significance only in case of 3 or more lines of therapy, but not if 1 vs. 2 prior lines of treatment were compared. However, the design of our study does not permit valid conclusions on the impact of early versus delayed allo-HCT on the natural course of T-cell NHL.

In the current analysis for the first time, it was possible to compare allo-HCT outcomes of the main T-NHL subsets on an informative sample size. Relative to PTCL-NOS, patients with AITL had significantly lower risk of relapse and better PFS (Table 3). This is in keeping with preliminary data suggesting that AITL appears to be exquisitely sensitive to GVL effects43, and with a previous CIBMTR study showing excellent survival of patients with AITL after RIC allo-
HCT (4-year survival=70%) and no relapses beyond two years.\textsuperscript{35} ALCL patients on the other hand had a significantly higher risk of relapse, relative to PTCL-NOS (Table 3), which is in accordance with a previous small EBMT series also containing mismatched unrelated donors, where a 40% 3-year relapse incidence was observed.\textsuperscript{34} The benefits of intensifying conditioning intensity in lymphoma patients are debatable. Similar to previous studies on allo-HCT in other NHL subtypes,\textsuperscript{22,44-49} the current study does not show an advantage of high intensity conditioning regimens for the first time also for mature nodal T-cell NHL in a large dataset.

Disease status at HCT was an independent outcome predictor in our analysis. Although being in CR at transplant was most favorable, patients in PR experienced 3-year PFS and OS of approximately 47% and 58% and seem to suggest that alloHCT can provide durable disease control in a sizeable subset of responding patients not in CR. Outcomes are not as encouraging in resistant disease, but with 36% PFS and 49% OS at 3 years still appear very reasonable for patients with refractory T-cell NHL.

Unlike their B-cell counterparts, chimeric receptor modified (CAR) T-cell therapies for T-cell lymphoma are in early phases of development. Inherent challenges of CARs for T-cell malignancies include fratricide by self-targeting of antigens on the CARs themselves and high risk of life-threatening infections due to potential T-cell aplasia. Several antigens under active investigations include CD5, CD7, CD30, CD3, CD4 and T-cell receptor β-chain constant region among others.\textsuperscript{17} Coming years will define the safety and efficacy profile of CAR platforms in T-cell malignancies. Until then, allo-HCT remains a standard-of-care option for the management of relapsed/refractory mature T-cell NHL.

When interpreting the results of the present analysis some important shortcomings inherent to the design of the study need to be taken into consideration. There are significant differences to
consider between the haplo patients and the other groups. Haplo-HCT cohort had more patients with KPS < 90, and more frequent use of BM grafts and RIC. Most importantly GVHD prophylaxis was inherently different amongst groups. Application of the ptCY platform to MUD transplants may question the equivalence of haplo-HCT and matched donor transplantation. 

This analysis is underpowered to detect small differences between the cohorts. The typical limitations of a registry analysis have to be taken into account, e.g., selection bias (i.e. applicable only to fitter patients in remission able to undergo HCT), lack of central review of histology, unavailability of ALK status in a third of ALCL patients (Table 2, footnote #3), and missing information on other confounders that could not be compensated in the present analysis, such as center practices and patient selection. In addition, during the era of this analysis the registries did not collect information on imaging modalities used for response assessment (CAT scan or positron emission tomography scan) or captured data regarding post relapse therapies.

In summary, this study shows that in the modern era, adoptive immunotherapy by allo-HCT can provide high rates of durable disease control in high-risk nodal mature T-cell lymphomas, with NRM rates that compare favorably against historical data. Outcomes across various commonly used donor sources in the contemporary era are comparable. Early evaluation by transplant physicians should be considered in all patients with refractory or relapsed nodal mature T-cell lymphomas.
DATA SHARING STATEMENT

For data sharing, contact the corresponding author: mhamadani@mcw.edu.

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| Table 1. Patient characteristics* |
|----------------------------------|
|                                  | Haplo-HCT | MSD-HCT | MUD-TCD+ | MUD-TCD- | P value |
| No. of patients                  | 237       | 911     | 468      | 326      |         |
| Data source (%):                |           |         |          |          | < 0.001 |
| CIBMTR                          | 104 (44)  | 324 (36)| 156 (33) | 209 (64) |          |
| EBMT                            | 133 (56)  | 587 (64)| 312 (67) | 117 (36) |          |
| Median Patient age – (range):   |           |         |          |          | 0.004    |
| 60-69                           | 51 (18-77)| 164 (18)| 126 (27) | 89 (27)  |          |
| ≥ 70                            | 11 (5)    | 8 (1)   | 10 (2)   | 6 (2)    |          |
| Male sex (%)                    |           |         |          |          | 0.98     |
| ≥ 70                            | 84 (35)   | 322 (35)| 165 (35) | 119 (37) |          |
| KPS ≥ 90 (%)                    |           |         |          |          | 0.03     |
| Not reported                    | 10        | 47      | 24       | 5        |          |
| Cell source (%)                 |           |         |          |          | < 0.001  |
| Bone marrow                     | 74 (31)   | 61 (7)  | 26 (6)   | 23 (7)   |          |
| Peripheral blood                | 163 (69)  | 850 (93)| 442 (94)| 303 (93) |          |
| Conditioning intensity (%)      |           |         |          |          | <0.001   |
| Myeloablative                   | 65 (27)   | 345 (38)| 154 (34)| 86 (27)  |          |
| Reduced-intensity               | 172 (73)  | 552 (62)| 306 (67)| 239 (73) |          |
| Missing                         | 0         | 14      | 8        | 1        |          |
| Disease status (%)              |           |         |          |          | 0.84     |
| CR                              | 120 (51)  | 451 (51)| 238 (52)| 161 (51)|          |
| PR                              | 74 (32)   | 252 (29)| 124 (27)| 96 (30) |          |
| Resistant/Untreated             | 39 (17)   | 177 (20)| 93 (20) | 60 (19) |          |
| Missing                         | 4         | 31      | 13       | 9        |          |
| HCT-CI ≥3 (%)                   | 52 (28)   | 191 (30)| 105 (35)| 95 (37) | 0.08     |
| Missing¹                        | 52        | 280     | 164      | 72       |          |
| Number of chemo lines           |           |         |          |          |         |
| Median [IQR]                    | 2 [1.8-3] | 2 [1-3] | 2 [1-3] | 2 [2-3] | 0.34     |
| 1 line (%)²                    | 31 (23)   | 89 (26) | 57 (29) | 19 (20) |          |
| 2 lines (%)²                   | 47 (35)   | 109 (32)| 62 (32) | 32 (34) |          |
| 3 or more lines (%)²           | 58 (43)   | 143 (42)| 76 (39) | 42 (45) |          |
| Missing³                        | 101       | 570     | 273      | 233      |          |
| Female Donor/ Male Recipient - no. (%) | 61 (26) | 254 (28) | 52 (11) | 45 (14) | <0.001 |
| Histology (%)                  |           |         |          |          | 0.14     |
| AITL                            | 68 (29)   | 270 (30)| 155 (33)| 101 (31)|          |
| ALCLe                          | 58 (24)   | 170 (19)| 82 (18) | 75 (23) |          |
| PTCL                            | 111 (47)  | 471 (51)| 231 (49)| 150 (46)|          |
| Prior autologous HCT (%)        | 78 (33)   | 336 (37)| 195 (42)| 132 (41)| 0.09     |
|                      | Haplo-HCT | MSD-HCT | MUD-TCD+ | MUD-TCD- | P value |
|----------------------|-----------|---------|----------|----------|---------|
| No. of patients      | 237       | 911     | 468      | 326      |         |
| Follow-up –          | 24 (1-113)| 43 (1-128)| 35 (1-132)| 49 (1-134)|         |
| median (range) [IQR] | [13-48]   | [17-72] | [13-63] | [24-72] |         |

Values in parentheses represent percentages if not indicated otherwise

**Abbreviations:** AITL=angioimmunoblastic T-cell lymphoma, ALCL=anaplastic large cell lymphoma, Haplo=haploidentical, HCT=hematopoietic cell transplantation, HCT-CI=hematopoietic cell transplant-comorbidity index, IQR= interquartile range, KPS=Karnofsky performance score, MSD=matched MUD=matched unrelated donor, in-vivo T-cell depletion=TCD+, without TCD=TCD-, PTCL=peripheral T-cell lymphoma.

1. HCT-CI missing: EBMT does not collect this variable for MED-A patients.
2. Missing number ignored for calculating percentages.
3. Lines of therapy missing: CIBMTR does not collect this variable for the TED level patients
4. ALCLs included 116 ALK positive cases, 143 ALK negatives and 126 cases where ALK status was not known.
### Table 2. Univariate outcomes.

| Outcomes                  | Haplo-HCT (N = 235) | MSD-HCT (N = 909) | MUD-TCD+ (N = 465) | MUD-TCD- (N = 325) | P Value  |
|---------------------------|---------------------|-------------------|--------------------|--------------------|----------|
| **Neutrophil recovery**   |                     |                   |                    |                    | <0.001   |
| 28-day                    | 230                 | 883               | 453                | 322                |          |
|                           | 86% (81-90)         | 95% (94-97)       | 94% (91-96)        | 97% (94-98)        |          |
| **Platelet recovery**     |                     |                   |                    |                    | <0.001   |
| 100-day                   | 219                 | 737               | 378                | 284                |          |
|                           | 80% (74-85)         | 96% (94-97)       | 93% (89-95)        | 96% (93-98)        |          |
| **II-IV aGVHD**           |                     |                   |                    |                    | 0.03     |
| 100-day                   | 225                 | 837               | 429                | 305                |          |
|                           | 33% (27-39)         | 31% (28-34)       | 30% (26-35)        | 37% (32-42)        |          |
| **III-IV aGVHD**          |                     |                   |                    |                    | 0.002    |
| 100-day                   | 225                 | 837               | 429                | 305                |          |
|                           | 9% (6-13)           | 11% (9-13)        | 10% (8-13)         | 18% (14-23)        |          |
| **Chronic GVHD**          |                     |                   |                    |                    | <0.001   |
| 1-year                    | 226                 | 770               | 395                | 296                |          |
|                           | 28% (22-34)         | 41% (37-44)       | 35% (30-40)        | 54% (48-59)        |          |
|                           | 11% (7-16)          | 8% (7-10)         | 10% (8-13)         | 8% (6-12)          |          |
| 2-year                    | 237                 | 911               | 468                | 326                | 0.49     |
|                           | 32% (25-38)         | 50% (47-54)       | 41% (36-46)        | 64% (58-70)        |          |
| **Non-relapse mortality** |                     |                   |                    |                    |          |
| 100-day                   | 337                 | 911               | 468                | 326                | 0.73     |
|                           | 11% (7-16)          | 8% (7-10)         | 10% (8-13)         | 8% (6-12)          |          |
| 1-year                    | 237                 | 911               | 468                | 326                | 0.80     |
|                           | 22% (17-28)         | 25% (22-27)       | 23% (19-27)        | 23% (19-28)        |          |
| 2-year                    | 27% (21-33)         | 29% (25-32)       | 26% (22-31)        | 25% (20-30)        |          |
| 3-year                    | 28% (22-35)         | 29% (26-32)       | 28% (24-33)        | 25% (21-30)        |          |
| **Relapse**               | 237                 | 911               | 468                | 326                |          |
| 1-year                    | 22% (17-28)         | 25% (22-27)       | 23% (19-27)        | 23% (19-28)        |          |
| 2-year                    | 27% (21-33)         | 29% (25-32)       | 26% (22-31)        | 25% (20-30)        |          |
| 3-year                    | 28% (22-35)         | 29% (26-32)       | 28% (24-33)        | 25% (21-30)        |          |
| **Progression-free survival** | 235               | 909               | 465                | 325                | 0.80     |
| 1-year                    | 22% (17-28)         | 25% (22-27)       | 23% (19-27)        | 23% (19-28)        |          |
| 2-year                    | 27% (21-33)         | 29% (25-32)       | 26% (22-31)        | 25% (20-30)        |          |
| 3-year                    | 28% (22-35)         | 29% (26-32)       | 28% (24-33)        | 25% (21-30)        |          |
| **Overall survival**      |                     |                   |                    |                    | 0.30     |
| 1-year                    | 237                 | 911               | 468                | 326                |          |
|                           | 70% (63-75)         | 74% (71-77)       | 70% (65-74)        | 74% (69-78)        |          |
| 3-year                    | 60% (52-66)         | 63% (59-66)       | 59% (54-64)        | 64% (58-69)        |          |
| **GRFS**                  |                     |                   |                    |                    | 0.02     |
| 1-year                    | 179                 | 665               | 378                | 210                |          |
|                           | 46% (38-53)         | 46% (42-50)       | 50% (44-55)        | 38% (32-45)        |          |
| 2-year                    | 37% (29-45)         | 36% (32-40)       | 41% (36-46)        | 31% (25-37)        |          |

**Abbreviations**: GVHD=graft-versus-host disease, GRFS=GVHD-free, relapse-free survival, Haplo=haploidentical, HCT=hematopoietic cell transplantation, MSD=matched MUD=matched unrelated donor, in-vivo T-cell depletion=TCD+, without TCD=TCD-, N=number; Prob=probability.
| Covariates          | Reference Group (bold) | OS         | PFS         | Relapse     | NRM         | Acute GVHD 3-4 | Chronic GVHD |
|---------------------|------------------------|------------|-------------|-------------|-------------|----------------|---------------|
| **Type of donor**   |                        |            |             |             |             |                |               |
| MSD                 | Haplo-HCT              | 0.9(0.7-1) | 1.0(0.8-1)  | 1.0(0.8-1)  | 0.9(0.7-1)  | 1.2(0.8-2)    | 1.7(1.3-2)    |
| MUD TCD+            | 0.9(0.7-1.3)           | 0.7(0.8-1) | 1.1(0.8-1.5)| 1.0(0.7-1.4)| 1.0(0.5-1.7)| 1.0(1.9-1)    | 1.4(1.1-2)    |
| MUD TCD-            | 0.9(0.7-1.2)           | 0.4(0.7-1) | 0.9(0.6-1.2)| 1.0(0.7-1.5)| 2.0(1.2-3.3)| 2.4(1.8-3.2)  | <0.001        |
| **Disease status**  |                        |            |             |             |             |                |               |
| PR                  | CR                     | 1.4(1.1-1.6)| 1.4(1.2-1.7)| 1.7(1.4-2.1)| 1.2(0.9-1.5)| 1.2(0.9-1.7)  | 1.1(0.9-1.3)  |
|                     | Resistant/Unt          | 1.8(1.4-2.1)| <0.001      | <0.001      | 1.5(1.2-2)  | 0.01           | 0.25          |
| **Age Patient**     | 18-39                  | 1.3(1.1-1.7)| 1.2(1-1.5)  | 1.0(0.8-1.3)| 1.6(1.2-2.3)| 1.2(0.8-1.8)  | 1.3(1.1-1.6)  |
|                     | 60 and more            | 1.7(1.3-2.2)| <0.001      | 1.0(0.7-1.3)| 2.1(1.5-3.1)| <0.001         | 1.3(1.1-1.7)  |
| **Gender**          | Female vs Male         | 0.9(0.7-1) | 0.9(0.8-1)  | 0.9(0.7-1)  | 0.9(0.7-1.2)| 0.7(0.5-0.9)  | 1.0(0.8-1.2)  |
|                     |                         | 0.09       | 0.15        | 0.60        | 0.01        |                |               |
| **Female D to Male R** | Yes vs No             | 1.1(0.9-1.3)| 1.2(1.4)    | 1.3(1.6)    | 1.1(0.9-1.5)| 0.9(0.6-1.3)  | 1.4(1.1-1.7)  |
|                     |                         | 0.50       | 0.045       | 0.38        | 0.64        |                |               |
| **Cell source**     | PB vs BM               | 0.9(0.7-1.2)| 0.9(0.7-1.1)| 0.8(0.6-1.2)| 0.8(0.6-1.2)| 1.1(0.6-1.8)  | 0.9(0.7-1.2)  |
|                     | Conditioning           | 1.0(0-1.2) | 1.1(0.9-1.2)| 1.2(0.9-1.4)| 1.0(0.8-1.2)| 1.0(0.8-1.4)  | 1.0(0-1.2)    |
|                     | RIC vs MAC             | 0.63       | 0.47        | 0.15        | 0.80        | 0.87           | 0.9(0-1.2)    |
| **Prior auto HCT**  | Yes vs No              | 1.0(0-1.2) | 1.1(0.9-1.2)| 1.0(0.8-1.2)| 1.1(0.9-1.4)| 0.8(0.6-1)    | 0.9(0-1.2)    |
|                     | <90 vs ≥90             | 1.5(1-3.1) | <0.001      | 1.3(1.2-1.5)| 1.3(1-1.5)  | 1.2(0.9-1.6)  | 0.9(0.8-1.1)  |
| **Histology**       | PTCL                   | 0.9(0.8-1.2)| 1.1(0.9-1.3)| 1.3(1-1.6)  | 0.8(0.6-1.1)| 1.5(1-2.2)    | 1.1(0.9-1.4)  |
|                     | AITL                   | 0.9(0.7-1) | 0.7(0.6-0.9)| <0.001      | 0.9(0-1.2)  | 1.1(0.8-1.5)  | 1.0(0.8-1.2)  |

**Abbreviations:** AITL=angioimmunoblastic T-cell lymphoma, ALCL=anaplastic large cell lymphoma, auto=autologous, CR=complete remission, D=donor, Haplo=haploidentical, GVHD=graft-versus-host disease, HCT=hematopoietic cell transplantation, HR=hazard ratio, KPS=Karnofsky performance score, MAC=myeloablative conditioning, MSD=matched MUD=matched unrelated donor, in-vivo T-cell depletion=TCD+, without TCD=TCD-. PTCL=peripheral T-cell lymphoma, PR=partial remission, R=recipient, RIC=reduced intensity conditioning, Unt=untreated, 95%CI=95% confidence interval. (Significant p-values shown in red)
Table 4. Univariate outcomes according to pre allogeneic transplant remission status.

|                  | Overall Survival | Progression-free Survival | Relapse/Progression | Non relapse mortality |
|------------------|------------------|----------------------------|---------------------|-----------------------|
| **At 1 year**    |                  |                            |                     |                       |
| Complete Remission| 79% [76-82]      | 68% [65-71]                | 17% [15-20]         | 15% [13-17.]          |
| Partial Remission| 70% [66-74]      | 55% [51-59]                | 29% [25-33]         | 16% [13-19]           |
| Resistant/Untreated| 61% [55-65]     | 45% [39-50]                | 34% [29-39]         | 21% [17-26]           |
| P value          | <0.0001          | <0.0001                    | <0.0001             | 0.13                  |
| **At 3 year**    |                  |                            |                     |                       |
| Complete Remission| 68% [65-71]      | 57% [53-60]                | 22% [19-25]         | 21% [19-24]           |
| Partial Remission| 59% [54-63]      | 47% [42-51]                | 33% [29-37]         | 20% [17-24]           |
| Resistant/Untreated| 49% [44-55]     | 36% [31-41]                | 39% [33-44]         | 25% [21-30]           |
| P value          | <0.0001          | <0.0001                    | <0.0001             | 0.13                  |
Figure legend:
Figure 1. Transplantation outcomes: 1a: cumulative incidence of chronic GVHD; 1b: Cumulative incidence of non-relapse mortality; 1c: Cumulative incidence of relapse; 1d: Progression-free survival; 1e: Overall survival; 1f: GVHD-free, relapse-free survival (GRFS).