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Allogeneic Haematopoietic Cell Transplantation for Extranodal Natural Killer/T-cell Lymphoma, Nasal Type: A CIBMTR Analysis

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Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKL), is a rare entity characterized by extranodal involvement and association with Epstein–Barr virus (EBV). Treatment with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)-like therapies alone generally does not provide durable remissions(Tse & Kwong, 2013). While chemo-radiation (for limited stage disease) or L-asparaginase-containing regimens (for advanced stage disease) have improved outcomes, ~40-50% of patients experience progression/relapse(Tse & Kwong, 2016). The median survival of advanced stage or relapsed ENKL is poor at ~6-12 months(Suzuki, 2010, Au *et al*, 2009). The role of allogeneic haematopoietic cell transplantation (allo-HCT) has been explored in a few small retrospective studies, which almost exclusively were comprised of Asian patients (Table 1S). Studies evaluating allo-HCT for ENKL in a North American/European cohort are not available. Using the observational database of the Center for International Blood and Marrow Transplant Research (CIBMTR), we report here the largest analysis and the only study to include Caucasian patients.

Adult (≥18 years) ENKL patients undergoing allo-HCT between 2000 and 2014 were included. Central biopsy report review by expert haematopathologist was required for inclusion (details of methods, study definitions and statistical analysis are provided in Supplemental Appendix). The baseline patient-, disease- and transplantation-characteristics of 82 ENKL patients undergoing allo-HCT are described in Table I. The median age at the time of allo-HCT was 44years (range: 20-70); 66% were male and 78% had Karnofsky performance score of ≥80%. Recipients were predominantly Caucasian (66%), 19% were of Asian ethnicity. The disease status at the time of HCT was complete remission (CR), partial remission (PR) and chemorefractory disease in 45% 30% and 12%, respectively. The majority of patients received peripheral blood grafts (89%) from matched related donors (61%). Reduced-intensity (RIC) or myeloablative conditioning (MAC) was used in 59% and 38% of cases, respectively.

Table 2S describes post-transplantation outcomes. With a median follow-up of 36 months (range: 1-121), the cumulative incidence of non-relapse mortality (NRM) and relapse at 3 years were 30% (95%confidence interval [CI]: 20-40) and 42% (95%CI: 32-53), respectively (Figure 1A-B). The corresponding 3-year progression-free (PFS) and overall survival (OS) were 28% (95%CI:19-39) and 34% (95%CI:24-45), respectively (Figure 1C-D). No disease relapse was noted beyond the 2-year mark. At last follow-up 52 patients had died, with lymphoma relapse/progression being the most common cause of death (n=22) (Table 5S). Results of

univariate analysis to identify factors predicting outcomes are described in Table 3S. We also built a univariate Cox proportional hazards model for each covariate (Table 4S). Recipient race (Caucasian vs. Asian) did not significantly impact PFS (Hazard ratio [HR]=0.92, 95%CI: 0.47-1.80, *p*=0.81) or OS (HR=1.17, 95%CI: 0.59-2.32, *p*=0.65). NK-prognostic index (NK-PI) (low/low intermediate-risk vs high intermediate/high-risk NK-PI) was not significantly associated with the risk of disease relapse (HR=0.81, 95%CI: 0.28-2.35, *p*=0.70), PFS (HR=0.89, 95%CI: 0.37-2.12, *p*=0.80) or OS (HR=1.11, 95%CI: 0.44-2.80, *p*=0.83). Among patients receiving late (after >1 line of prior therapy) vs. upfront allo-HCT (after first-line therapy), the risk of relapse (HR=0.86, 95%CI: 0.42-1.77, *p*=0.69), PFS (HR=1.10, 95%CI: 0.60-1.98, *p*=0.77) and OS (HR=1.20, 95%CI: 0.61-2.28, *p*=0.58) were not significantly different. Remission status at the time of allo-HCT (CR vs. PR vs. chemoresistant disease) did not impact the relapse risk (*p*=0.93), PFS (*p*=0.59) or OS (*p*=0.51). There was no statistically significant difference between the outcomes of patients receiving RIC vs. MAC regimens in terms of relapse (HR=0.56, 95%CI: 0.26-1.21, *p*=0.14), NRM (HR=1.72, 95%CI: 0.75-3.92, *p*=0.20), PFS (HR=0.92, 95%CI: 0.54-1.58, *p*=0.77) and OS (HR=0.95, 95%CI: 0.54-1.68, *p*=0.85).

Literature evaluating the role of allo-HCT in ENKL is limited to small retrospective studies, exclusively in Asian populations(Table 1S) . The largest previously reported study included 22 patients with ENKL, noting a 2-year PFS and OS of 34% and 40%, respectively(Murashige *et al*, 2005). In this study, no disease relapse was reported beyond 10 months, hinting at durable remissions with allo-HCT. In our analysis, allo-HCT in ENKL was associated with durable remission and survival in approximately one-third of the patients, with a 3-year PFS and OS of 28% and 34%, respectively and, notably, no relapses were reported beyond 2 years post-transplantation, suggesting potent graft-versus-lymphoma effects. However, disease relapse remained the main reason for treatment failure and death. This observation provides the unique opportunity for implementing better surveillance modalities in the first two years after transplantation or investigating novel maintenance strategies to mitigate risk of relapse(Kim *et al*, 2015, Iqbal *et al*, 2011, Koo *et al*, 2012, Tse & Kwong, 2013, Hari *et al*, 2016).

Post-transplant relapse risk, NRM and survival were not affected by patient race, remission status, NK-PI, prior L-asparaginase use, timing of HCT (late vs. upfront) or conditioning intensity. The current study is the only report to evaluate allo-HCT for ENKL in a predominantly Caucasian patient cohort. The similar 3-year OS, of 35% in Caucasian and 33% in Asian patients, is noteworthy and implies the broader applicability of allo-HCT in non-Asian

cohorts**.** In our analysis, the 3-year PFS and OS by pre-HCT remission status were similar, suggesting that even a subset of patients with chemorefractory disease can benefit from allo-HCT. The risk of disease relapse was numerically lower with MAC regimens compared to RIC (50% vs. 30%, *p*=0.07), albeit not statistically significant and was offset by higher NRM associated with MAC regimens (40% vs. 23%, *p*=0.12) resulting in no difference in PFS and OS by conditioning intensity. Murashige *et al* (2005), previously reported a 2-year NRM of 30% and 20% with MAC and RIC regimens, comparable to our findings .

Being a retrospective study utilizing registry data is an inherent limitation of this analysis. The sample size limits the power to detect small differences in outcomes in our population. Notwithstanding these limitations, this CIBMTR study evaluating the role of allo-HCT in ENKL is the largest study to date and included patients only after a careful central review of biopsy reports. In conclusion, our data suggests that allo-HCT is a viable curative option in a subset of ENKL and should be considered in advanced or relapsed/refractory disease irrespective of patient race. Relapse remains a major cause of treatment-failure, highlighting the need for active surveillance and use of pre-emptive or maintenance strategies to mitigate relapse risk.

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Table I. Baseline characteristics of patients with extranodal NK/T-cell Lymphoma, nasal type

Variable	N=82 (%)
Median age at HCT (range), years	44 (20-70)
Male sex	54 (66)
Karnofsky performance score before HCT	
80-100%	64 (78)
< 80%	12 (15)
Unknown	6 (7)
HCT-CI	
0	35 (43)
1-2	16 (20)
≥ 3	13 (16)
Not collected (prior to 2007)	18 (22)

Variable	N=82 (%)
Race	
Caucasian	54 (66)
Asian	16 (19)
Others[1] or Unknown	12 (15)
History of prior autologous HCT	11 (13)
Median interval from diagnosis to HCT, months (range)	11 (3-137)
<1 year	47 (57)
≥1 year	33 (40)
Disease stage at diagnosis	
Stage I/II	35 (43)
Stage III/IV	22 (27)
Unknown	25 (30)
NK/T-cell Lymphoma Prognostic Index[2]	
Low or low-intermediate	7 (8)
High or high-intermediate	26 (32)
Unknown	49 (60)
First line of therapy	
Chemotherapy alone (n=41)	
CHOP- or HyperCVAD-like	20 (24)
DeVIC or VIPD	4 (5)
SMILE	11 (13)
AspaMetDex	2 (2)
Gemcitabine-based	2 (2)
Others	2 (2)

Variable	N=82 (%)
Chemotherapy + radiation (n=27)	
CHOP- or HyperCVAD-like + Radiation	14 (17)
De-VIC or VIPD + Radiation	8 (10)
SMILE + Radiation	2 (2)
AspaMetDex + Radiation	2 (2)
Other + Radiation	1 (1)
Radiation alone (n=5)	5 (6)
Unknown 1st line therapy	9 (11)
Response to first line of therapy	
Complete remission	25 (30)
Partial remission	23 (28)
Refractory disease	18 (22)
Unknown	16 (20)
Median (range) lines of therapy before HCT	2 (1-7)
Received L/peg-asparaginase containing therapy (any time before HCT)	31 (38)
Timing of transplantation	
Upfront (after first line therapy)	25 (30)
Late (>1 line of therapy prior to HCT)	49 (60)
Unknown	8 (10)
Remission status prior to HCT	
Complete remission	37 (45)
Partial remission	25 (30)
Chemorefractory	10 (12)
Untreated /unknown	10 (12)
Donor type	
Matched related donor	50 (61)
Unrelated donor	23 (28)
Umbilical cord blood	5 (6)

Variable	N=82 (%)
Haploidentical related donor	3 (4)
Missing	1 (1)
Conditioning regimen intensity	
Reduced-intensity conditioning	48 (59)
Myeloablative conditioning	31 (38)
Missing	3 (4)
Graft Source	
Bone marrow	4 (5)
Peripheral blood	73(89)
Cord blood	5 (6)
GVHD prophylaxis	
Calcineurin inhibitor + mycophenolate mofetil	23 (28)
Calcineurin inhibitor + methotrexate ± others[3]	35 (43)
Calcineurin inhibitor ± others[4]	16 (20)
Others[5]	6 (6)
Missing	2 (2)
Donor or recipient CMV positive	57 (69)
Number of centers	43
Median follow-up of survivors (range), months	3 (1-121)

Abbreviations: AspaMetDex = pegaspargase, methotrexate, dexamethasone; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CMV = cytomegalovirus; DeVIC = dexamethasone, etoposide, ifosfamide and carboplatin; GVHD = graft-versus-host disease; HCT = haematopoietic cell transplantation; HCT-CI = haematopoietic cell transplantation-comorbidity index; Hyper-CVAD = hyperfractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone; SMILE = steroid, methotrexate, ifosfamide, L-asparaginase, etoposide; VIPD = etoposide, ifosfamide, cisplatin, dexamethasone.

[1]Others = African-American (n=1), Native American (n=3) and Other, not otherwise specified (n=2)

[2]NK/T-cell Lymphoma Prognostic score - 1 point for each of the following: serum lactate dehydrogenase > normal, B symptoms at diagnosis, lymph node involvement at diagnosis, Ann Arbor stage IV at diagnosis. Low: 0, Low-intermediate: 1, High-Intermediate: 2, High: 3-4

[3]Calcineurin inhibitor+methotrexate alone (n=31) or with sirolimus (n=4)

[4]Calceneurin inhibitors alone (n=8), or with steroid (n=2), or with sirolimus (n=6)

[5]Mycophenolate/sirolimus (n=1), sirolimus (n=1), post-transplant cyclophosphamide-based (n=3), CD34 selection (n=1)

Figure Legends:

Figure 1.

Cumulative incidence of non-relapse mortality (1A) and lymphoma relapse (1B) and Kaplan-Meir estimates of progression-free survival (1C) and overall survival (1D).