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Management of Advanced and Relapsed/Refractory Extra-Nodal Natural Killer T-Cell Lymphoma (ENKL): An Analysis of Stem Cell Transplant and Chemotherapy Outcomes

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Introduction

Extra-nodal natural killer/T-cell lymphoma (ENKL) is a rare lymphoma representing approximately 5–10% of T-cell non-Hodgkin lymphomas diagnosed in the United States each year.[1, 2] ENKL is universally associated with Epstein-Barr virus (EBV) infection, and is more frequent in Asian, Central American and South American populations, where it constitutes 5–15% of all lymphomas.[3–5] Patients with advanced stage ENKL (stage III-IV) and relapsed/refractory early stage disease are treated with systemic chemotherapy with or without radiotherapy.[6] Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) based therapy was historically used in these patients, but resulted in significant rates of relapse, due to the activity of the MDR (multi-drug resistance p-glycoprotein) in ENKL cells and subsequent diminished activity of anthracyclines.[7, 8] Over the past ten years, it has become increasingly recognized that ENKL is particularly sensitive to L-asparaginase whose

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activity is independent from the activity of MDR. The novel SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) regimen was developed in Asia, and resulted in overall response (ORR) and complete response (CR) rates of 79% and 45% respectively, with 1-year overall survival (OS) rate of 55%.[9] Similar results of SMILE were obtained from the Asia Lymphoma group with ORR of 81%, CR rate of 66%, and 5-year OS and disease-free survival (DFS) of 50% and 64% respectively.[10] These results have led to 2–4 cycles of SMILE-based chemotherapy as the preferred regimen for advanced (stage III-IV) ENKL at diagnosis, or relapsed/refractory disease for patients able to tolerate intensive therapy.

The role of stem cell transplantation (SCT) for the treatment of ENKL is controversial, and the majority of publications are small, retrospective cohorts. Autologous SCT (auto-SCT) is typically used either for consolidation of first complete remission (CR1), in stage III/IV disease with a high NK-IPI score, or upon achievement of CR after relapse.[11, 12] Allogeneic stem cell transplantation (allo-SCT) is sometimes utilized for patients who are unable to obtain a remission, with reports of OS at 40–50%, though this approach may be limited by non-relapse mortality (NRM).[12–14] The role of SCT in advanced staged and relapsed/refractory ENKL remains undefined.

Given the rarity of ENKL, and limited data on outcomes for these patients outside of Asian populations, we conducted an analysis of chemotherapy outcomes of patients with advanced ENKL at the University of Texas MD Anderson Cancer Center (UTMDACC). Additionally, we conducted a separate analysis of SCT outcomes of patients treated at multiple transplant centers. The aim of this study is to describe outcomes of patients receiving therapy for advanced stage and relapsed/refractory ENKL in an effort to provide insights into both the chemotherapy and SCT management of patients with this aggressive disease.

Methods

Chemotherapy Treated Patients

First, we evaluated all patients with advanced stage or relapsed/refractory ENKL treated at UTMDACC between 2000–2014. All patients with newly diagnosed stage III/IV ENKL and relapsed/refractory disease after an initial treatment for stage I/II ENKL were included. The primary endpoint was to determine the overall survival (OS) and progression-free survival (PFS) of patients with advanced/relapsed/refractory ENKL treated with systemic chemotherapy. Patients with a diagnosis of blastic NK/T lymphoma, now classified as plasmacytoid dendritic cell leukemia were excluded. This study was approved by the Institutional Review Board (IRB) at UTMDACC. Univariate probabilities of OS and PFS were estimated utilizing the Kaplan-Meier method. OS was estimated from the time of diagnosis until death. Progression-free survival was estimated from the time of diagnosis until progression or death of any cause, whichever comes first. The log-rank test was utilized for all comparisons of OS and PFS on univariate analysis. Cox Proportional Hazards regression was used on multivariate analysis to assess predictors of OS and PFS.

Stem Cell Transplantation Patients

For the stem cell transplantation analysis, data were collected from four institutions including: UTMDACC, Oregon Health and Science University (OHSU), National University Cancer Institute of Singapore (NUH), and University Hospitals Case Medical Center (UH). All patients with a diagnosis of ENKL who received either an auto-SCT or allo-SCT between January 1, 2000 and March 1, 2014 were included in the analysis. Patients with blastic NK/T lymphoma were excluded. Patients referred to SCT were considered to be high-risk, since intensive consolidation with transplantation was recommended by the treating physician. Therefore, patients with all stages of ENKL who received SCT were evaluated. This study was approved by the institutional review board at participating institutions. SCT patients were evaluated independently of the chemotherapy-treated patients given the population of patients in the SCT group were a pooled collection of several institutions. Univariate probabilities of OS and PFS were estimated utilizing the Kaplan-Meier method.[15] Probabilities of NRM, RM, and graft-versus-host disease (GVHD) were calculated utilizing the cumulative incidence procedure to accommodate for competing risks. For RM, NRM was considered a competing risk. The log-rank test was utilized for all comparisons of OS and PFS on univariate analysis. Fine-Gray proportional sub-distribution hazards regression was performed to compare outcomes with competing risks.

All statistics and Kaplan-Meier estimates were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY). Cumulative incidences were determined utilizing EZR software, available at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html.[16]

Results

Up-Front Management of Advanced ENKL

First, we evaluated thirty-seven patients from the UTMDACC lymphoma database who received treatment for advanced stage and relapsed/refractory ENKL from 2000–2014. This included stage III-IV patients at diagnosis (22/37), or patients who were stage I-II who subsequently had refractory or relapsed disease (15/37). Baseline characteristics can be seen in Table 1. The majority of patients were male (60%), between the ages of 30–65 years of age (median 55 years, range 17–93 years), and with stage III-IV disease (59%). Eighty-five percent of patients were non-Asian, including 46% white and 35% Hispanic.

Most patients received CHOP-based chemotherapy prior to 2012, as the SMILE regimen entered clinical practice around 2011. The median number of chemotherapy cycles was 3 (range 1–6). For patients who received SMILE, the median number of cycles was 4 (range 1–6); whereas for CHOP, the median number of cycles was six. Nineteen (51%) patients had a CR and one patient obtained a partial remission (PR) (3%), whereas fourteen (38%) patients had progressive disease. Six patients received an up-front auto-SCT in this UTMDACC cohort, all in CR.

Of patients receiving SMILE, 6/9 (66%) attained a CR while three had progressive disease. Patients receiving CHOP attained identical rates of CR (6/9, 66%), with three who had progressive disease, though it took more cycles to attain a CR. While there was no difference in OS/PFS across chemotherapy regimens, of the patients who entered CR1 after SMILE,

only 1/6 relapsed, as compared to 6/6 patients who relapsed with CHOP. However, patients who initially received CHOP were able to be salvaged with further chemotherapy and auto-SCT, so there was no overall difference in OS.

The OS for all advanced stage and relapsed/refractory NK-T cell patients (n=37) was 73% at one year, and 30% at 3 years. PFS was 45% at 1-year and 19% at 3 years (Figure 1). The median time to progression (TTP) was 7.8 months (range 0.4–36.5 months). Of the patients receiving auto-SCT in CR1, 2/6 died, one of relapsed ENKL, and one from secondary AML for a total OS of 66%. Amongst only stage III/IV patients treated up-front for ENKL (excluding early stage relapsed/refractory patients, n=19), patients treated with the SMILE regimen had improved PFS compared to those treated with other regimens (PFS 50% vs 0%, p=0.08), though there was no difference in OS (18% vs 48%), p=0.268.

Prognostic Factors for Upfront Management of Advanced ENKL

On univariate analysis for PFS, only the presence of CR and consolidative auto-SCT in CR1 were predictive for improved PFS. One-year PFS for patients in CR was 83% versus 36% in patients without a CR (p<0.00001). PFS for the 34 patients eligible (</= age 75) for auto-SCT was improved for the patients who received a consolidative auto-SCT versus no consolidative auto-SCT at 1-year (83% vs 57%) and 3-years (83% vs 14%), p=0.013. There was no difference in outcomes for age <55 vs >55, sex, stage at diagnosis (I-II vs III-IV), NK-IPI score 1–2 vs 3–4, race, concomitant chemo-radiotherapy versus chemotherapy alone, or use of SMILE regimen versus other regimens. On multivariate analysis, when disease stage, presence of CR, NK-IPI score, and consolidative auto-SCT were included in the model, only CR was predictive for improved PFS (HR 0.072 95% confidence interval (CI) 0.024–0.217, p<0.0001).

On univariate analysis for OS, there was improvement in OS for patients with CR versus no CR at 1 year (94% versus 55%) and this difference was maintained at 5-years at 55% vs 8%, p<0.0001. Additionally, there was improved OS for patients with lower-risk NK-IPI risk group of 1–2 versus 3–4 with 1 year OS of 83% vs 57% and 3-year OS of 46% vs 22%, (p=0.038). There was a trend toward improved OS for patients with early stage disease at diagnosis (stage 1–2), up-front auto-SCT, and concomitant chemo-radiotherapy versus chemotherapy alone. OS for the concomitant chemo-radiotherapy group versus chemotherapy alone trended toward improvement at 1-year (75% vs 65%) and 3-years (34% vs 14% at 3-years) p=0.189. OS for up-front consolidative auto-SCT versus no auto-SCT was 83% vs 71% at 1-year, and 85% vs 24% at 3-years p=0.158. OS for stage I-II vs stage III-IV disease at diagnosis was 78% vs 58% at 1 year and 39% vs 25% at 3-years, p=0.119. There was no effect of age, sex, race, or the use of SMILE versus other chemotherapy on OS. On multivariate analysis for OS using CR status, NK-IPI score, up-front auto-SCT, and concomitant chemo-radiotherapy, only the presence of CR after initial chemotherapy resulted in improved OS (HR 0.245 95% CI 0.067–0.896, p=0.002).

Outcomes of Progressive Advanced ENKL

Of the initial 37 patients, 27 had progressive disease despite upfront therapy and had sufficient data to analyze outcomes, demonstrating the aggressive nature of this rare disease.

Table 2 presents data for these patients including chemotherapy regimens, response, and use of auto-SCT. OS for the patients with progressive advanced ENKL (n=27) was 62% at 1-year, 33% at 2-years, and 25% at 5-years. PFS was 30% at 1-year and 11% at 3-years. Interestingly, there was a difference between outcomes of relapsed versus refractory patients. The OS for relapsed patients at 1 and 3-years was 91% and 55% versus 47% and 0% for refractory patients, $p<0.00001$. The median TTP for refractory patients was 3.5 months versus 13.5 months for relapsed patients. No additional risk factor analysis was done for the progressive disease cohort as only 14 patients received therapy, and numbers are too small to make any statistically valid conclusions.

Salvage therapy for Progressive Advanced ENKL

Only fourteen patients (7 refractory/7 relapsed) received salvage chemotherapy and had sufficient data for analysis. Table 3 provides a detailed description of the management of the patients with progressive advanced ENKL who received salvage treatment. The majority of patients treated with salvage therapy (36%) received SMILE at relapse. Forty-three percent of relapsed/refractory patients achieved a CR and two patients (14%) had a partial response (PR), for an overall response rate (ORR) of 57%. Thirty-six percent had progressive disease. PFS at one year for the treated relapse/refractory group was 29%, and 19% at 2 years (Figure 2). Five of six patients achieved a CR with salvage therapy. One of these patients was lost to follow-up, leaving five patients of which 2/5 (40%) achieved long-term cure. The other three patients died of disease relapse post-transplant. One patient received allo-SCT during relapse but had progressive disease after a brief PR.

Only four patients received therapy after second relapse. One was treated with radiotherapy alone, one with gemcitabine and pentostatin, one underwent multiple lines of therapy including gemcitabine/oxaliplatin (GemOx), radiotherapy, ICE, and AUY-122, and one received CHOP. The patient who received CHOP entered a CR and is alive 87 months after initial diagnosis.

Stem Cell Transplantation Outcomes for ENKL

Nineteen patients received SCT for ENKL at the UTMDACC. Of these patients, eight were referred by the UTMDACC lymphoma service to the SCT service at UTMDACC; a rate of referral of 22%. The remaining twelve patients treated in the UTMDACC SCT department were referred from outside locations. In order to enhance the numbers of patients receiving SCT for ENKL, we added patients from three additional centers. This resulted in 27 patients from four different centers that were utilized to evaluate SCT outcomes for patients with ENKL.

Twenty-seven patients, with a median age of 48 years (range 22–68), and a median of 2 prior chemotherapy lines (range 1–5) received SCT for ENKL; 14 auto-SCT and 13 allo-SCT. Seventy percent were performed at the UTMDACC. Sixty-seven percent were male, 30% were not in CR at transplant, and 40% had an NK-IPI risk group of 3–4. Seventy-four percent of patients received myeloablative (MAC) conditioning, with the most common regimen being BEAM (BCNU, etoposide, cytarabine, melphalan) in 55% of allo-SCT and 65% of auto-SCT patients. All patients received peripheral blood as the stem cell source

except one who received cord blood. Details of transplantation and disease characteristics can be found in Table 4.

Survival Outcomes for Stem Cell Transplantation in ENKL

With a median follow-up time of 11 years, OS and PFS for the entire group were 51% and 50%. The cumulative incidence (CI) NRM was 19% at 1 and 2 years and the CI relapse mortality (RM) was 16% at 1 year, 26% at 2 years, and 40% at 11 years (Figure 3). Amongst allo-SCT recipients, there were 2 cases of grade II-IV acute GVHD (14% of ALLO) and 5 cases of chronic GVHD (1 limited, 4 extensive, 36% of ALLO). PFS was significantly better for patients in CR versus those not in remission at transplant (67% vs 13%, p=0.002). There was no impact of MAC vs non-MAC conditioning, disease stage at diagnosis (I-II vs III-IV), prior number of chemotherapy lines, hematopoietic cell transplantation comorbidity index, NK-IPI risk group 1–2 vs 3–4, age >50, sex, or race on PFS or OS. Due to low patient numbers, multivariate analysis was not conducted.

Autologous and Allogeneic SCT for Advanced ENKL

We did an exploratory analysis of transplant outcomes between the auto-SCT and allo-SCT groups. Characteristics of patients in the auto-SCT and allo-SCT groups were similar, with the exception that more patients in the allo-SCT group (46% vs 17%, p=0.082) were not in CR at the time of transplant. PFS for auto-SCT and allo-SCT recipients were 67% and 31% at 1 and 3 years (Figure 4). OS for auto-SCT and allo-SCT recipients was 75% and 54% at 1 year, and 64% and 39% at 3 years, respectively. One patient received an allo-SCT with progressive disease and survived. Additionally, 3 of 4 patients who received allo-SCT after prior auto-SCT survived, though one died of a second malignancy eleven years post-transplant. One of these patients received a prior auto-SCT but developed graft failure and subsequently received an allo-SCT and was counted in the allo-SCT group. CI NRM was higher in allo-SCT patients compared to auto-SCT patients at 1 year (39% vs 0%). CI of RM was higher in the first year in the auto-SCT vs allo-SCT patients at 1 year (26% vs 8%), though by 3-years this difference was diminished (36% vs 23%).

Discussion

Here we present a large, detailed analysis of patients with advanced stage and relapsed/refractory ENKL. Furthermore, we analyzed a multi-center cohort of patients who received SCT and describe SCT outcomes for both auto-SCT and allo-SCT. Together, we present a comprehensive review of the management of advanced stage and relapsed/refractory ENKL in a predominantly non-Asian population.

Remission status remained the most clinically significant prognostic factor for patients with ENKL. Whether associated with up-front therapy, therapy for progressive disease, or SCT, remission status was prognostic for improved outcomes. Among patients who received up-front therapy, CR was highly predictive for both PFS (HR 0.024, p<0.00001) and OS (HR 0.245, p=0.002), likely due to the high-risk nature of this cohort. For patients receiving up-front chemotherapy, both CHOP and SMILE produced CR at identical rates (66%), though patients receiving CHOP received a median of 6 cycles of chemotherapy versus 4 cycles for

the SMILE group. Only one of the six patients who attained a CR with SMILE relapsed, compared to all six patients who received CHOP and attained a CR. However, due to the effect of salvage therapy, there was no OS/PFS difference in the SMILE treated patients versus CHOP-treated patients. Although with limited numbers, these findings are in agreement with a recent report which found higher CR rates with SMILE versus CHOP, but no statistically significant difference in survival outcomes.[17] At the time of progressive disease in this cohort, CR was attained in six patients (43%). Of the remaining seven patients who did not achieve a CR, only one patient attained a long-term remission, further demonstrating the importance of obtaining a second CR (CR2) at relapse or progression. For patients attaining CR2, auto-SCT was universally used, resulting in a long-term cure rate of 40%, which was superior to the 2-year PFS rate of 19% for patients who did not receive an auto-SCT or CR2. Additionally, amongst the SCT cohort, PFS was improved for those in CR versus no CR (67% vs 13%, p=0.002), suggesting only those in CR received benefit. Taken together, these results suggest that CR status both up-front, and after treatment for relapsed/refractory disease is the primary driver of treatment outcomes, independent of NK-IPI score or other disease-related factors. While the numbers of patients receiving SMILE in this cohort are relatively small, the improved PFS and CR rates seen in this study, coupled by analyses both by Qi et al. and Kim et al, suggest that SMILE is the preferred therapy for advanced stage and relapsed/refractory disease front-line for ENKL.[6, 17] Attainment of a CR and durable remission is particularly important in ENKL, as only 14 of the 27 patients who relapsed (52%) were able to receive salvage therapy.

Given the limited number of patients receiving SCT in the primary cohort, we evaluated a cohort of 27 patients who received SCT across four institutions, of which approximately half were allografts in order to gain insight into the use of SCT in ENKL. Of particular interest is the role of up-front consolidative auto-SCT, as it is often used in peripheral T-cell lymphomas to reduce relapse. In our cohort, there are too few patients to make any definitive conclusions. However, on univariate analysis (in the primary cohort), for the patients who underwent a consolidative auto-SCT in CR1, PFS was improved at 1-year (83% vs 57%) and 3-years (83% vs 14%). A large retrospective matched analysis by Lee et al suggested that patients with high NK-IPI score should proceed with a consolidative auto-SCT where they noted a 2.1-fold reduction in risk of death (p=0.006) in patients proceeding with a consolidative auto-SCT.[11] Taken together, these data suggest that auto-SCT should be strongly considered as consolidation therapy for patients with advanced ENKL who are fit for transplantation. Additionally, given the high NRM noted in our series of allo-SCT patients, we would not recommend allo-SCT in CR1. Amongst patients with relapsed/refractory disease beyond CR1, the choice of auto-SCT versus allo-SCT is more difficult. Patients who relapsed after auto-SCT or who fail to achieve CR2 are by definition chemo-refractory, and should be referred for allo-SCT. Indeed, our data suggest that there is a significant graft-versus-lymphoma affect, as long-term cure was noted in 31% of allo-SCT recipients, despite the fact that 46% were not in CR at the time of transplantation. However, for patients with chemo-sensitive relapse who enter CR2, our data suggests that auto-SCT should be utilized given improved PFS (67% vs 31%) and decreased NRM 39% vs 0%) over allo-SCT. Prospective clinical trials will be needed to definitively answer these important questions.

Our results compare reasonably to published results. Tse et al. published a multi-center analysis from the Asia Lymphoma Study group with a promising 5-year EFS of 51% using allo-SCT in ENKL, though it is important to note that 9/18 patients (50%) were in CR1 and only 2 patients were not in CR.[18] While the NRM in our cohort was high (39%), many of these patients entered transplant not in CR, and after CR1, and were heavily pre-treated making it a much more high-risk group. Amongst auto-SCT patients in CR1, the 3-year PFS of 83% in our cohort compares favorably to those published by Lee et al of 87%, though at 5-years.

Given many different conditioning regimens for utilized in this study, it is difficult to determine the optimal conditioning regimen. Amongst allo-SCT recipients, there was no difference in myeloablative versus non-myelablative transplant in this cohort, though the differential effects of individual treatment regimens cannot be elucidated due to low patient numbers. For patients proceeding with allo-SCT, standard myeloablative regimens such as BuFlu or BuCy can be utilized, while FluMel140 or RIC BuFlu (particularly with AUC targeting) can be considered per institutional protocols for less fit patients or those with a high co-morbidity index. For auto-SCT, the standard BEAM conditioning therapy can be utilized, though novel combinations are needed. Finally, only 22% of patients at UTMDACC with ENKL were referred for SCT. It is difficult to conclude retrospectively which patients were fit for transplantation. However, given the promising results of SCT, particularly in CR, referral for SCT is indicated for all ENKL patients with advanced disease up-front and relapsed/refractory disease. Further study in a collaborative, multi-institutional setting is needed to definitively identify the role of SCT in ENKL.

This study has multiple limitations. This is a retrospective study, including patients treated over a long period of time. The types of therapy utilized varied during the course of the study period, and it is difficult to make firm conclusions given the heterogeneity of patients, disease states, and stage of disease. Furthermore, due to the retrospective nature of this study, data on EBV titers, which has been correlated with treatment outcomes, particularly in early-stage patients was unavailable.[19–21] Due to the recent publication of the PINK score, sufficient information was not available to evaluate whether the PINK score correlated with outcomes in this cohort.[6] Finally, the SCT cohort was heterogeneous, with auto-SCT and allo-SCT patients, transplanted at multiple centers with differing standards of care and different approaches to management. Comparison of auto-SCT and allo-SCT outcomes is inherently biased, so no firm conclusions can be made regarding the superiority of one SCT modality over the other. Despite these limitations, given the rarity of ENKL, large prospective trials are unlikely to be performed, making large retrospective series of patients important in understanding the management of this disease-particularly in non-Asian populations.

In conclusion, we present a large, primarily non-Asian cohort of patients with advanced stage and relapsed/refractory ENKL with a discussion of disease management both up-front and at the time of relapse or progression. Our results suggest that achievement of a CR is imperative in ENKL at all stages of disease, and is desirable for any patient for whom auto-SCT is utilized. SMILE-based chemotherapy appeared effective in attaining a CR, and was also an effective salvage regimen. For patients attaining a first CR, auto-SCT should be

strongly considered, but should be utilized in patients attaining CR2. For patients with refractory disease, allo-SCT can be considered in a selected group of patients. Future clinical trials should be directed towards attaining an early CR and developing novel predictive markers to direct post-remission therapy.

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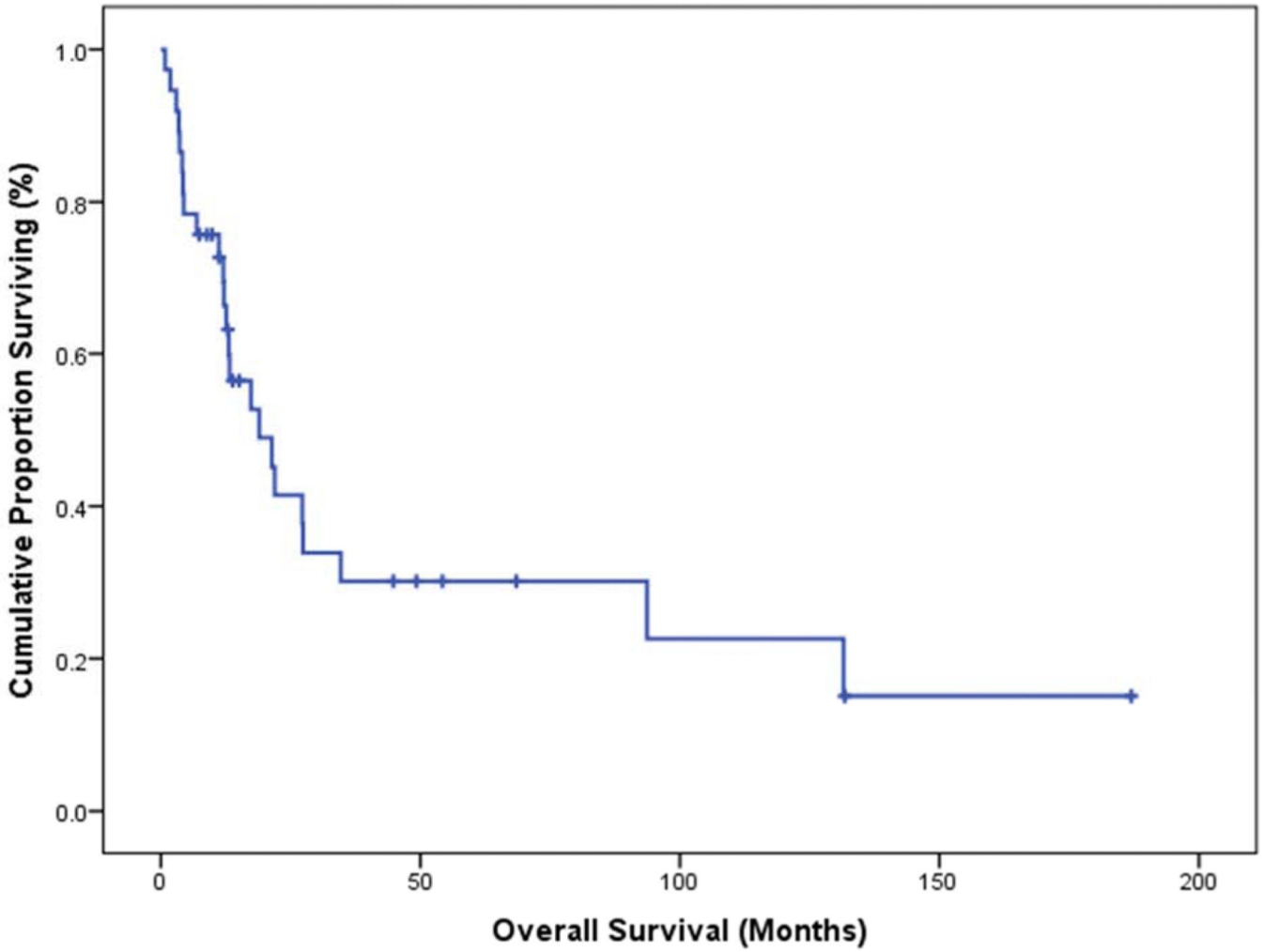

Figure 1:
OS for all Patients

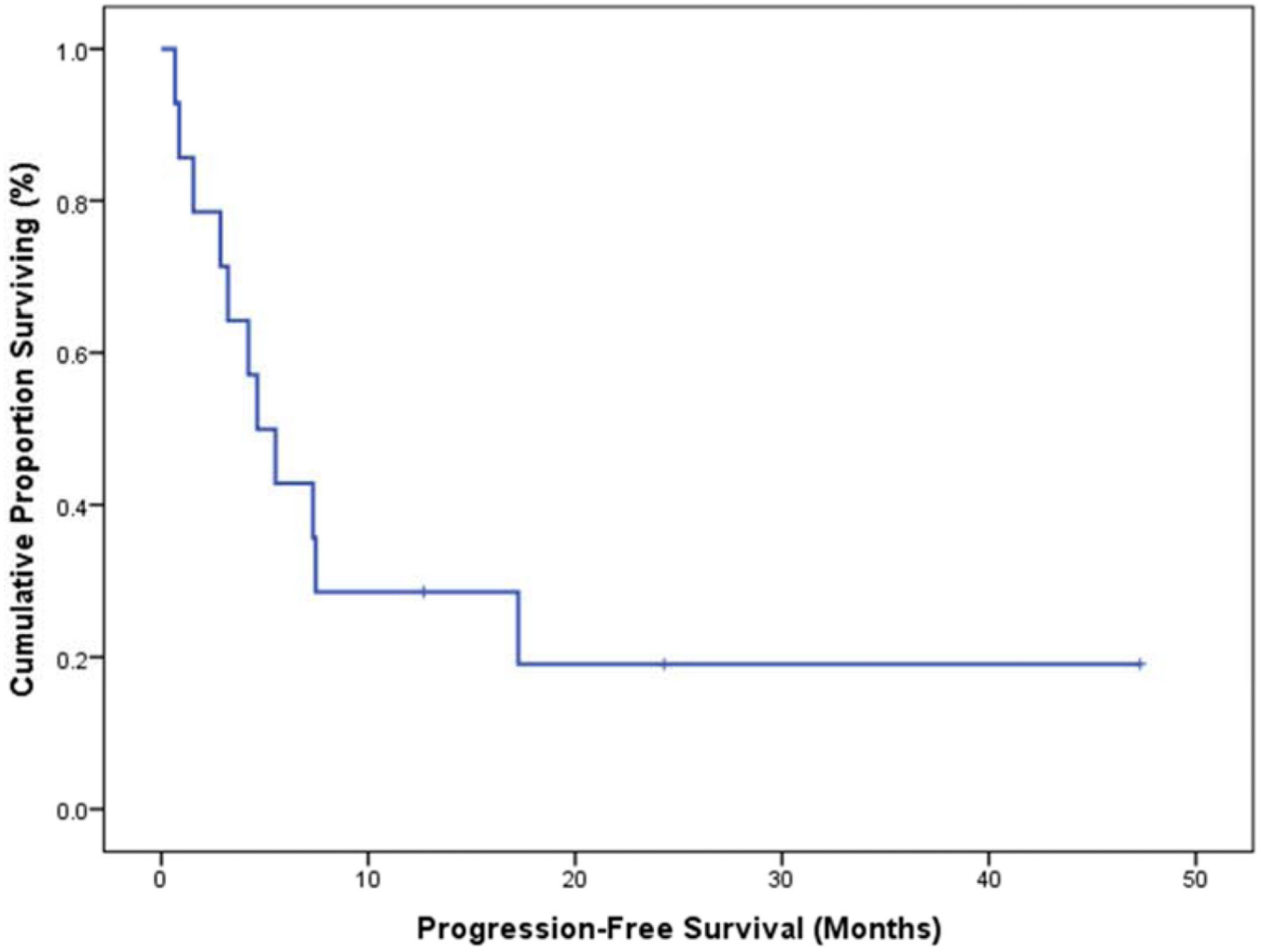

Figure 2:
PFS of Relapsed/Refractory Advanced ENKL Receiving Therapy (n=14)

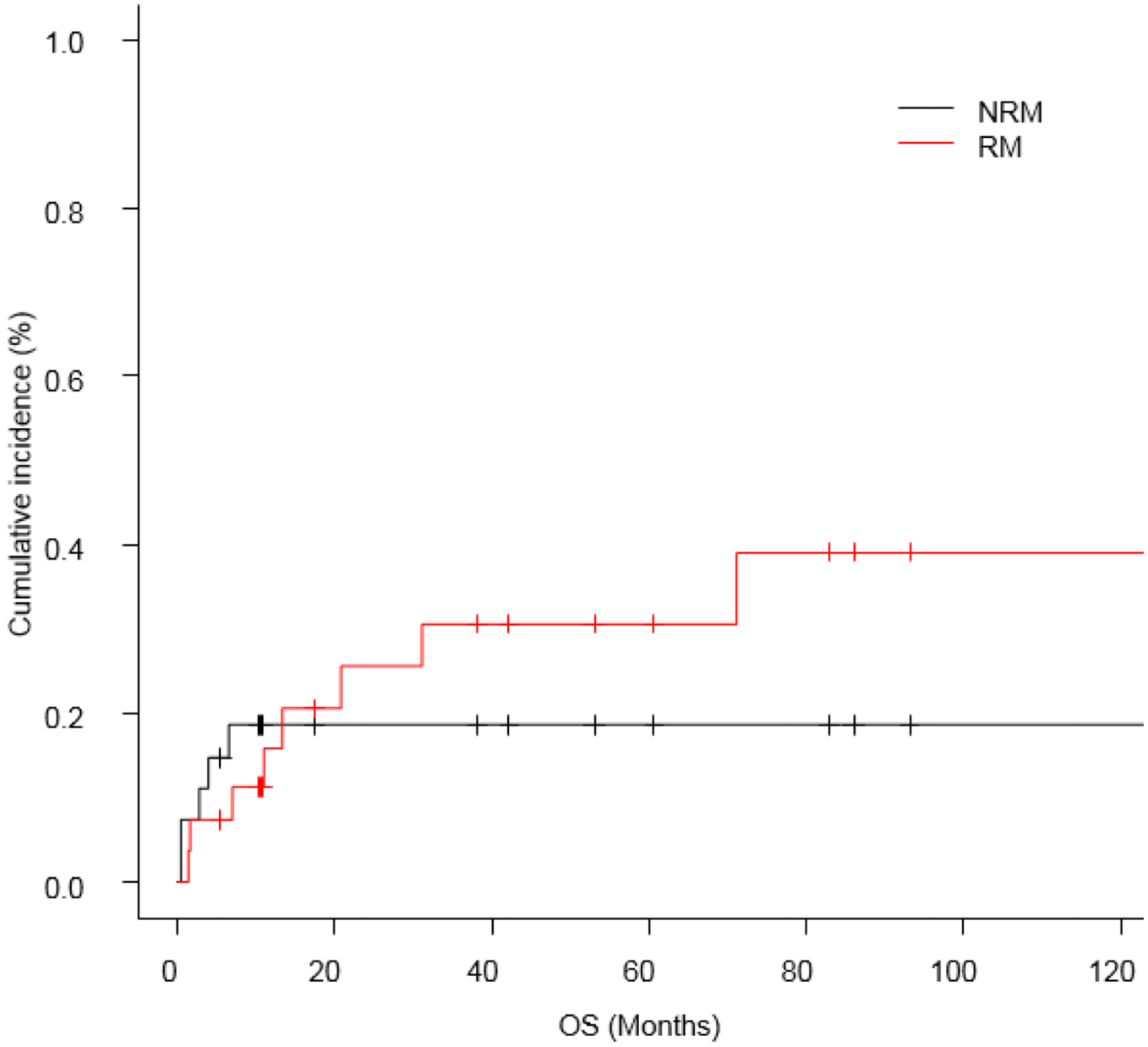

Figure 3:
Cumulative Incidence of Non-Relapse Mortality & Relapse Mortality for the Entire Cohort

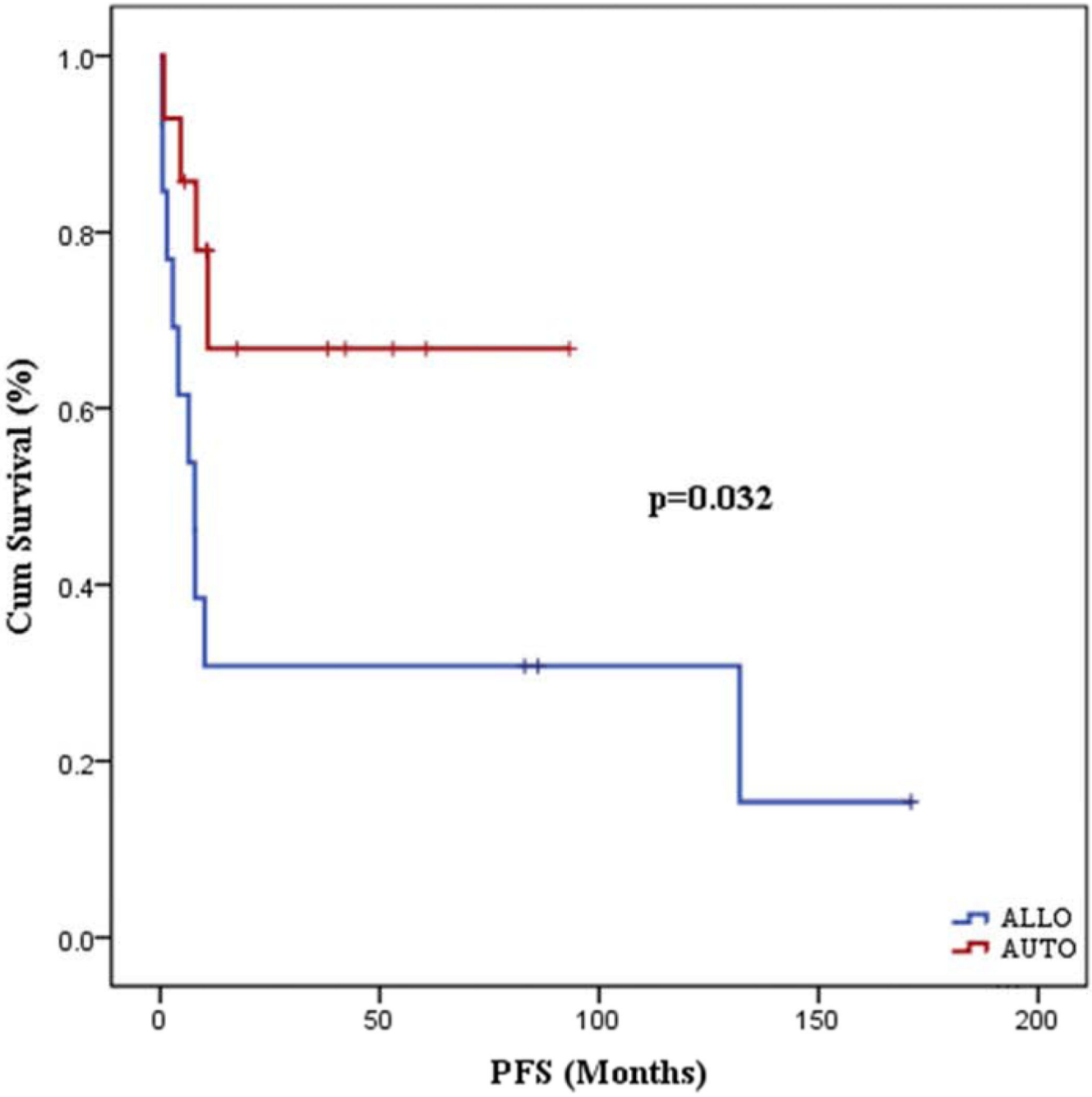

Figure 4:
Progression-Free Survival Between Autologous and Allogeneic Transplant

Table 1:

Upfront Treatment of Advanced ENKL

Characteristic	N=37 (%)
Age at Diagnosis	
17–30	4 (11%)
30–65	25 (67%)
65+	8 (22%)
Sex	
Male	22 (60%)
Female	15 (40%)
Race	
Asian	5* (15%)
Black	2 (5%)
White	17 (46%)
Hispanic	13 (35%)
Ann Arbor Disease Stage at Diagnosis	
I	8 (22)
II	7 (19)
III	3 (8)
IV	19 (51)
NK-IPI Group	
1–2	24 (65%)
3–4	13 (35%)
Frontline Chemotherapy Regimen	
CHOP	9 (24%)
SMILE	9 (24%)
HCVIDD	3 (8%)
Hyper-CVAD	2 (5%)
Cytoxan	1 (3%)
CMED	1 (3%)
ICE	1 (3%)
CEOP	1 (3%)
DeVIC	2 (6%)
VIPD	2 (6%)
Gemcitabine	1 (3%)
GemOx+Asparaginase	1 (3%)
XRT Alone	4 (11%)
Concurrent Chemo-Radiotherapy	
Yes	13 (35%)

Characteristic	N=37 (%)
No	24 (65%)
Response to Therapy	
Complete Remission	19 (51%)
Partial Remission	1 (3%)
Progressive Disease	14 (38%)
Not Assessed*	3 (8%)
Up-Front Autologous Stem Cell	
*Transplantation**	
Yes	6 (16%)
No	31 (84%)
Overall Survival	
1-year	73%
3-year	30%
Progression-Free Survival	
1-year	45%
3-year	19%

* one patient of middle eastern descent

* all patients receiving up-front auto had a CR

* Patients for whom no assessment were done were removed from the analysis for relapsed/refractory disease

Table 2:

Treatment of Progressive Advanced ENKL

Characteristic	N=27 (%)
Primary Refractory	15 (56%)
Relapsed	12 (44%)
Salvage Chemotherapy Regimen	
No Therapy/Missing Data	13 (48%)
SMILE*	1 (3.7%)
ICE+RT	1 (3.7%)
IE	1 (3.7%)
ESHAP	1 (3.7%)
Hyper-CVAD	1 (3.7%)
Denileukin diftitox	1 (3.7%)
Brentuximab	2 (8%)
IPI-145	1 (3.7%)
Upfront Allo-SCT	1 (3.7%)
Response to Second Line Therapy	N=14
Complete Remission	6[#] (43%)
Partial Response	2 (14%)
Not Assessed	1 (7%)
Progressive Disease	5 (36%)
Salvage Autologous Stem Cell Transplantation	N=14
Yes	5 (36%)
No	8 (57%)
Unknown	1 (7%)

[#]5/6 patients who received a CR at salvage proceeded to ASCT. One of the patients had planned to get an ASCT but was lost to follow-up. 2/5 patients survived, the remainder died of relapse. One patient who received an allo-SCT was not included in the response assessment

Table 3:

Salvage Therapy for Progressive Advanced ENKL

Patient	Diagnosis (year)	Age/Sex	Stage (Dx)	Relapsed/ Refractory	Salvage Chemo (Year)	Response	SCT	PFS[#]	Alive[+]
1	1999	46 M	1	Relapsed	ESHAP (2001)	CR	AUTO	20	Yes
2[*]	1999	59 M	1	Relapsed	Brentuximab (2014)	PD	None	174	Yes
3	2000	44 M	1	Refractory	Allo-SCT (2001)	PR	ALLO	14	No
4	2003	26 M	4	Refractory	Denileukin Diftitox (2004)	PD	None	6	No
5	2003	65 M	4	Refractory	IE (2004)	PD	None	2.5	No
6	2005	55 F	1	Relapsed	SMILE (2013)	NA	None	93	No
7	2010	61 F	4	Relapsed	SMILE (2011)	CR	AUTO	7	Yes
8	2010	52 M	2	Relapsed	Hyper-CVAD (2011)	CR	AUTO	10	No
9	2010	42 F	3	Relapsed	ICE+RT (2013)	CR	AUTO	36.5	Yes
10	2011	72 M	1	Relapsed	IPI-145 (2012)	PD	None	16	No
11	2012	66 M	4	Refractory	SMILE+IT (2012)	CR	AUTO	3.4	No
12	2012	45 F	2	Relapsed	SMILE (2013)	CR	AUTO	13.5	No
13	2013	46 F	4	Refractory	Brentuximab (2013)	PD	None	3	No
14	2013	43 M	2	Relapsed	SMILE (2014)	PD	None	10	No

[*] Patient #2 attained a long-term remission after CHOP-based salvage therapy

[#] Progression-Free Survival (Months)

[+] Alive at last follow-up

Table 4:

Baseline Characteristics for Patients Receiving Stem Cell Transplantation

Characteristic	N=27 (%)
Institution	
MD Anderson	19 (70%)
Oregon Health & Science	2 (7.5%)
University Hospital Cleveland	2 (7.5%)
National University Singapore	4 (15%)
Sex	
Male	18 (67%)
Female	9 (33%)
Ann Arbor Disease Stage at Diagnosis	
I-II	13 (48%)
III-IV	14 (52%)
NK-IPI Score	
0–1	12 (60%)
2–4	8 (40%)
HCT-CI Score	
0–2	13 (65%)
3+	7 (35%)
Response Prior to Transplant	
Complete Remission	19 (70%)
No Complete Remission	8 (30%)
Prior Chemotherapy Lines	
1–2	15 (56%)
3+	12 (44%)
Transplant Type	
ALLO	13 (48%)
AUTO	14 (52%)
Donor Type (ALLO)	
Matched Sibling	9 (69%)
Unrelated Donor (1 UCBT)	4 (31%)
Transplant Intensity	
Myeloablative	20 (74%)
Not Myeloablative	7 (26%)
Conditioning Regimens (ALLO)	
BEAM	7 (55%)

Characteristic	N=27 (%)
Flu/Mel	2 (15%)
Other	4 (30%)
Conditioning Regimens (AUTO)	
BEAM	9 (65%)
BEP	2 (14%)
Gem/Bu/Mel	2 (14%)
BCNU/Thiotepa	1 (7)

Abbreviations: ALLO: allogeneic stem cell transplant; AUTO: autologous stem cell transplant; UCBT: Umbilical cord blood transplant; BEAM: BCNU, etoposide, ARA-C, Melphalan; Flu/Mel: fludarabine/melphalan; BEP:BCNU, etoposide, cisplatin; Gem/Bu/Mel: gemcitabine/busulfan/melphalan