

Long-term survival and clinical implications of allogeneic stem cell transplantation in relapse/refractory lymphoma: A 20-year Singapore experience

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ABSTRACT

Introduction: Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is a curative option for relapse/refractory (R/R) lymphomas that have failed autologous transplantation or for high-risk lymphomas in the upfront setting. We conducted a retrospective analysis on consecutive lymphoma patients who underwent allo-HSCT over a 20-year period (2003–2022) at Singapore General Hospital and National University Hospital Singapore.

Method: A total of 121 patients were included in the study. Median age was 41 years. Diagnoses include Hodgkin lymphoma (HL, 15%), B-cell non-Hodgkin lymphoma (B-NHL, 34%), T-cell non-Hodgkin lymphoma (T-NHL, 31%) and natural killer T-cell lymphoma (NKTL, 20%). Moreover, 27% of patients had prior auto-haematopoietic stem cell transplantation (auto-HSCT), and 84% received reduced intensity conditioning (RIC). Donor types were matched sibling donor (45%), matched unrelated donor (29%), haploidentical donor (19%) and cord blood (CB, 7%).

Results: After median follow-up of 56 months, estimated 4-year progression-free survival (PFS) and overall survival (OS) for all patients were 38% and 45%, respectively. Non-relapse mortality (NRM) was 15% at day 100 and 24% at 1 year. On univariate analysis, complete remission status at transplant and RIC confers superior OS. On multivariate analysis, HL was associated with superior OS compared to NHL, whereas matched unrelated donor transplant was associated with significantly inferior OS compared to matched sibling donor.

Conclusion: Long-term curative durability was observed with allo-HSCT for patients with relapsed/refractory lymphomas. This real-world data serves as

a valuable historical benchmark for future studies on lymphomas in Singapore and the Asia Pacific region.

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Keywords: allogeneic, haematology, lymphoma, refractory, transplant

CLINICAL IMPACT

What is New

- This nationwide retrospective study evaluated a 20-year dataset of patients with R/R lymphoma undergoing allogeneic transplantation.
- To authors' knowledge, this collaborative study that involves 2 national cancer centres in Singapore is the first to evaluate the efficacy and safety of allogeneic haematopoietic stem cell transplantation for R/R lymphomas in Singapore.
- It also serves as a potential benchmark for policymakers for cost and efficacy comparison analysis with more novel treatment options.
- Disease status at transplant, conditioning regimen, subtype of lymphoma and donor selection influence outcomes.

Clinical Implication

- This real-world data form a basis for future studies on R/R lymphomas in Singapore and the region.

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INTRODUCTION

Over the past few decades, a wide array of novel therapies has become available for the treatment of relapsed/refractory (R/R) lymphoma. Despite these advancements, outcomes and the durability of disease control remain poor for many patients. While autologous hematopoietic stem cell transplantation (auto-HSCT) may be appropriate for some lymphoma patients as consolidation therapy, a significant proportion of high-risk patients experience relapse after auto-HSCT. Anti-Cluster of Differentiation 19 (CD19) chimeric antigen receptor T-cell (CAR-T) therapy and bispecific T-cell engager (BiTE) therapy have revolutionised the treatment landscape for B-cell non-Hodgkin lymphoma (B-NHL). However, their utilisation is limited by factors such as resource availability, accessibility and high costs. There also remains a high relapse rate post-CAR-T, and allogeneic stem cell transplantation (allo-HSCT) remains a potential treatment option in this context. Additionally, CAR-T cell therapy and bispecific antibodies are not yet available for Hodgkin lymphoma (HL), T-cell NHL (T-NHL), and some of the less common but aggressive B-NHL subtypes.

Mamez¹, Corradini² and Schmitz et al.³ (for T-cell lymphoma), Sureda⁴ (for HL) and Bento⁵ (for DLBCL) have explored the potential of allo-HSCT in patients who had high-risk, R/R or progressive disease after auto-HSCT. The preparative conditioning regimen, along with the potential for graft-versus-lymphoma effect, offers the possibility of disease-free survival and significant overall survival (OS) in this population. Furthermore, the use of non-myeloablative/reduced intensity conditioning (RIC) and haploidentical donors in stem cell transplantation has sparked renewed interest in allo-HSCT, as fitness and donor availability become less of a barrier. This makes it feasible for patients with high-risk lymphoma to access safer stem cell transplantation. Moreover, the graft-versus-lymphoma effect is potentially applicable to all subtypes of lymphomas. Studies have shown favourable outcomes with allo-HSCT in patients with advanced HL,⁶ and there is increasing application of allo-HSCT in non-HL patients.⁷

Historically, Singapore performed its first adult allo-HSCT in 1985. Forty years later, we evaluate real-world efficacy and safety of allo-HSCT in patients with R/R lymphoma. Our primary objective was OS post-allo-HSCT. Secondary objectives included progression-free survival (PFS), non-relapse mortality (NRM) and rate of acute graft-versus-host disease (GVHD).

METHOD

This retrospective analysis included all patients who underwent allo-HSCT for lymphoma over a

20-year period (2003–2022) at 2 of the largest national transplant centres in Singapore. They were identified from medical databases after approval from the institution review board. All patients provided written informed consent for transplantation according to each local institution. The lymphoma diagnoses were based on World Health Organization 2002, 2008 and 2016 classification histologic subtype, depending on when the diagnosis was made. Staging and assessment of disease response were based on CT and PET CT referring to Cheson (2007) and Lugano (2014) criteria.^{8,9} Transplants were based on physician discretion, following international bone marrow stem cell transplant society guidelines. Patient demographics, OS, PFS, NRM and factors associated with survival were examined. PFS was defined as time from date of allo-HSCT till date of disease progression or death from any cause. OS was defined as the duration of survival from the date of allo-HSCT until death. NRM is defined by the absence of progressive disease at the time of death.

Statistical methods

Using GraphPad Prism version 10.0 software (GraphPad Inc, La Jolla, US), chi-squared and Fisher's Exact two-sided tests were used to compare categorical variables, and t-test was used for continuous variables. Two-sided *P* values of <0.05 were statistically significant. The survival probabilities, PFS and OS, were calculated using the Kaplan-Meier estimator. Log-rank analysis was used to compare the different groups. Cox regression analysis was used for multivariate variable analysis.

RESULTS

Baseline demographics

A total of 121 patients were included in the study with median age of 41 years. Of these, 76 (63%) were male. Lymphoma subtypes included B-NHL (n=41, 34%), followed by T-NHL (n=38, 31%), natural killer T-cell lymphoma (NKTL) (n=24, 20%) and HL (n=18, 15%) (Table 1). Moreover, 27% of the patients had prior auto-HSCT; 60%, 22% and 16% were in complete remission (CR), partial remission (PR) or stable disease/progressive disease (SD/PD) at transplant.

Conditioning regimen

Myeloablative conditioning (MAC) was used in 14% of the patients, while the rest received RIC regimens. GVHD prophylaxis consisted of calcineurin inhibitor with 1 of the 2 from methotrexate or mycophenolate. Anti-thymocyte globulin (ATG) was administered to all patients

Table 1. Patients’ characteristics.

Characteristics	Details	n (%) Total 121 (100%)
Sex	Male	76 (63)
	Female	45 (37)
Median age at transplant		41 years
Diagnosis/histological subtype	DLBCL/PMBCL	26 (21)
	PTCL	32 (26)
	NKTL	24 (20)
	Other T-NHL	6 (5)
	Other B-NHL	8 (7)
	HL	18 (15)
	CLL (Richter transformation)	7 (6)
Donor type	MSD	54 (45)
	MUD	35 (29)
	Haploidentical	23 (19)
	CB	9 (7)
Conditioning	MAC	17 (14)
	RIC	104 (86)
	Missing data	2 (2)
Previous auto-HSCT		33 (27)
Disease status at transplant	CR	73 (60)
	PR	26 (22)
	SD/PD	19 (16)
	Missing data	3 (2)
Period of transplant	Before 2010	29 (24)
	2010–2015	39 (32)
	After 2015	53 (44)

Auto-HSCT: autologous hematopoietic stem cell transplantation; B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CLL: chronic lymphocytic leukaemia; CR: complete remission; DLBCL: diffuse large B-cell lymphoma; HL: Hodgkin lymphoma; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; PR: partial remission; PTCL: peripheral T-cell lymphoma; RIC: RIC: reduced intensity conditioning; SD/PD: stable disease/progressive disease; T-NHL: T-cell non-Hodgkin lymphoma

receiving matched unrelated grafts. Post-transplant cyclophosphamide (PTCy) or ex-vivo stem cell manipulation (alpha-beta T-cell depletion) was used in haploidentical donor transplant based on physician discretion.

Donor demographics

Matched sibling donors (MSD; n=54, 45%) were the majority followed by matched unrelated donors

(MUD; n=35, 29%) in which 6 of them had 1 allele mismatched. The rest were from haploidentical (n=23, 19%) and CB (n=9, 7%) (Table 1).

Post-transplant outcome

With a median follow-up duration of 56 months, the estimated 4-year PFS and OS were 38% and 45%, respectively (Figs. 1A and 1B). Sixty-eight patients died post-transplant with the most

common cause due to lymphoma in 32 patients. NRM at 100 days and 1 year were 15% and 24%, respectively. Among all NRM, pneumonia (n=16, 44%) was the most common, followed by other infections (n=11, 31%), cerebral haemorrhage (n=4, 11%), GVHD (n=3, 8%), myocarditis (n=1, 3%) and thrombotic microangiopathy (n=1, 3%). The cumulative incidence of acute GVHD was 36% with 5 patients (4%) having grade IV GVHD.

Patients who were in CR at transplant exhibited 4-year PFS and OS of 45% and 55%, respectively, compared to PR and SD/PD; 4-year PFS 27% and 21%, 4-year OS 29% and 27%, respectively (Figs. 1E and 1F).

RIC confers significant superior PFS and OS compared to MAC with 4-year PFS and OS of 44% and 51%; 0% and 10%, respectively (Table 2) (Figs. 1G and 1H).

Regarding donor type, transplants with MSD resulted in 4-year PFS and OS 41% and 49%, respectively, while MUD transplant had 4-year PFS and OS of 29% and 44%, respectively. For haploidentical and CB donor transplants, the 4-year PFS and OS rates were 52% and 56%; 38% and 45%, respectively (Table 2; Figs. 1I and 1J).

Post-transplant outcome for HL subtype appeared the best with 4-year PFS and OS of 61% and 62%, respectively, while patients transplanted for NK-T cell lymphoma had lowest 4-year PFS and OS of 19% and 30%, respectively (Table 3; Figs. 1C and 1D).

There was a numerical trend towards improved PFS and OS in the transplants performed after 2015 (n=53) compared to those transplanted in 2010–2015 (n=39) and before 2010 (n=29) (Table 2).

Univariate analysis showed that CR status at transplant improved OS compared to PR and SD/PD (log-rank $P=0.023$). Meanwhile, RIC resulted in superior OS than MAC (log-rank $P=0.011$).

Multivariable analysis showed that MUD was associated with poorer OS compared to MSD with HR 3.56 $P=0.004$, 95% confidence interval (CI) 1.49–8.31. (Table 5). Similarly, HL had superior OS when compared to B-NHL with HR 0.33 ($P=0.025$), 95% CI 0.12–0.85 (Table 5). These differences were not seen on multivariable analysis of factors affecting PFS (Table 4).

DISCUSSION

Survival outcomes and non-relapse mortality

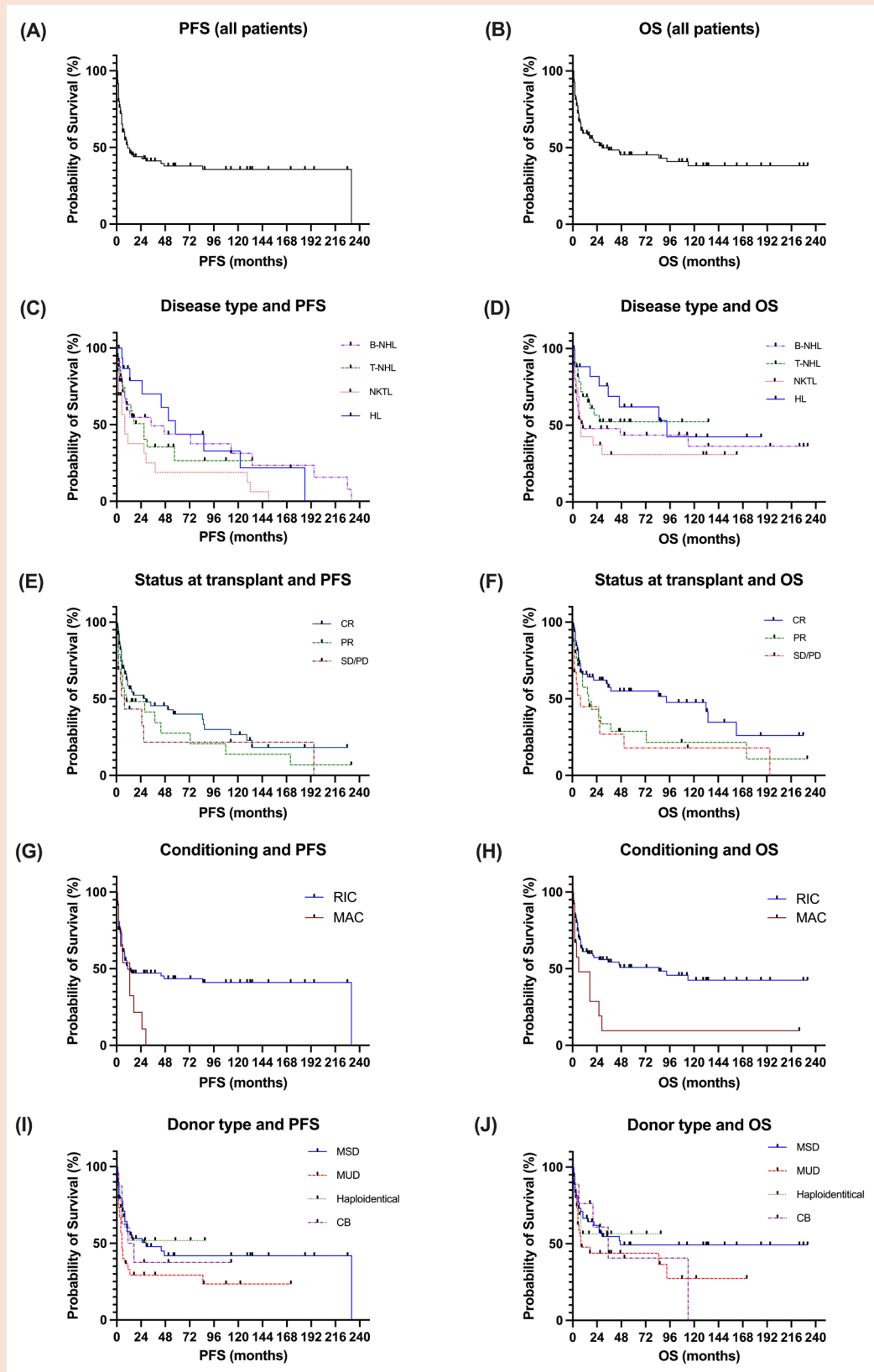
Our study confirmed that allo-HSCT is associated with durable response and long-term survival. This was seen in 38% of patients who remained alive and disease-free while 45% remained alive at 4 years. However, allo-HSCT has significant

toxicity evidenced by NRM of 24% at 1 year. This is comparable to the historical cohort reported by the European Society for Blood and Bone Marrow Transplant (EBMT) and Centre for International Blood and Marrow Transplant Research (CIBMTR) registry. Berning et al. evaluated the outcomes of allo-HSCT in patients in the EBMT cohort with R/R DLBCL and showed NRM rates of 18.8% at 1 year (patient cohort from 2010 to 2015).¹⁰ Real-world data from the Korean Society of Blood and Marrow Transplantation registry also reported NRM rates at 1 year post-transplant of 23.4% at 1 year for patients with T-cell lymphoma.¹¹ In our cohort, 27 patients demised from infective complications, with pneumonia being the most common cause. Of which, 1 died of COVID-19 pneumonia during the pandemic. It is known that conditioning regimens eliminate host innate and humoral immunity. Additionally, the delayed recapitulating immune ontogeny post-transplant and the effects of GvHD contribute to this vulnerability to endogenous and exogenous pathogens.¹² It has also been shown that the outcome of COVID-19 infection in allo-HSCT recipients is uniformly poor compared to the general population.^{13,14} Fortunately, the COVID-19 pandemic was deemed well-controlled in Singapore, and an early vaccination programme mitigated its impact on this highly vulnerable group. While infection has been the primary cause of NRM, the institution-specific protocols follow strict guidelines for infection prevention and monitoring. Since 2017, Singapore stem cell transplant centres have kept with the updated international recommendations for cytomegalovirus (CMV) prophylaxis; letermovir being approved and adopted for patients deemed high risk for CMV reactivation. For patients who are low-risk, pre-emptive monitoring is performed routinely and treatment instituted at the onset of significant viremia. Fungal prophylaxis is likewise incorporated in the standard protocols of each institution, and risk assessment for individual patients are assessed regularly relative to the degree and duration of neutropenia and immunosuppression. Recently, ruxolitinib has been approved for its use in steroid refractory acute GVHD, which has been effective compared to other second-line GVHD treatment. As our data span from 2003 to 2022, the benefit of effective therapies mentioned above might not reflect well in our study.^{15,16}

Conditioning regime and donor selection

Patients who received RIC had improved OS compared to those who underwent MAC, regardless of age, with the median age being 41 years. This trend is consistent with findings from

Fig. 1. Kaplan-Meier curves of all patients.



(A) PFS (B) OS; various disease subtypes (C) PFS (D) OS; status at transplant (E) PFS (F) OS; type of conditioning (G) PFS (H) OS; donor type (I) PFS (J) OS

B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CR: complete remission; HL: Hodgkin lymphoma; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; OS: overall survival; PFS: progression-free survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable disease/progressive disease; T-NHL: T-cell non-Hodgkin lymphoma

Table 2. Univariate analysis of allografted patients.

Classification	n (%)	PFS		OS	
		% Patients (4-year survival)	P log-rank	% Patients (4-year survival)	P log-rank
All	121 (100)				
Status at allo-HSCTT			0.297		0.023
CR	73 (60)	45		55	
PR	29 (24)	27		29	
SD/PD	19 (16)	21		27	
Conditioning			0.050		0.011
MAC	17 (14)	0		10	
RIC	104 (86)	44		51	
Donor type			0.182		0.500
MSD	54 (44.6)	41		49	
MUD	35 (28.9)	29		44	
Haploidentical	23 (19)	52		56	
CB	9 (7.4)	38		41	
Period of transplant			0.30		0.23
Before 2010	29 (24)	30		40	
2010 to 2015	39 (32)	35		42	
After 2015	53 (44)	49		57	

Allo-HSCT: allogeneic-haematopoietic stem cell transplantation; CB: cord blood; CR: complete remission; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; OS: overall survival; PFS: progress-free survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable diseases/progressive-free disease
Values in bold are statistically significant.

Table 3. Median PFS and OS of each lymphoma subtype.

Diagnosis/histological subtype	n (%)	% Patients (4-year survival, months)	Median PFS, months	% Patients (4-year survival, months)	Median OS, months
B-NHL	41 (34)	43	34	43	47
T-NHL	38 (32)	35	27	52	not reached
NKTL	24 (20)	19	8	30	8
HL	18 (15)	61	58	62	93

B-NHL: B-cell non-Hodgkin lymphoma; HL: Hodgkin lymphoma; NKTL: natural killer T-cell lymphoma; OS: overall survival; PFS: progress-free survival; T-NHL: T-cell non-Hodgkin lymphoma

Hamadani et al.,¹⁷ who evaluated data from the observational CIBMTR database. They reported better OS among patients with R/R DLBCL who underwent RIC conditioning compared to MAC, attributable to higher rates of NRM in the MAC cohort. Similar to above studies, Kharfan

et al. examined the outcome of mantle cell lymphoma and showed that RIC was superior than MAC.¹⁸ Likewise, the use of RIC among the R/R lymphoma population was supported by a CIBMTR study in 2012 where NRM was higher after MAC, although the relapse risk was lower.¹⁹ RIC is

Table 4. Multivariate analysis of factors influencing PFS in lymphoma patients receiving allo-HSCT.

Variable	n	HR	95% CI	P
Diagnosis				
B-NHL	41	1		Reference
T-NHL	38	0.84	0.31–2.23	0.72
NKTL	24	1.89	0.71–5.07	0.20
HL	18	1.28	0.43–3.70	0.64
Disease status at transplantation				
CR	73	1		Reference
PR	29	1.12	0.32–4.09	0.86
SD/PD	19	1.71	0.32–4.09	0.54
Donor type				
MSD	54	1		Reference
MUD	35	1.10	0.38–2.88	0.85
Haploidentical	23	0.63	0.13–2.75	0.55
CB	9	4.09	0.42–32.3	0.20
Conditioning				
RIC	102	1		Reference
MAC	17	0.64	0.19–1.83	0.43

Allo-HSCT: allogeneic-haematopoietic stem cell transplantation; B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CI: confidence interval; CR: complete remission; HL: Hodgkin lymphoma; HR: hazard ratio; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; PFS: progress-free survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable disease/progress-free disease; T-NHL: T-cell non-Hodgkin lymphoma

currently the standard conditioning regime used in allo-HCT for lymphoma.

In our cohort, MUD transplantation was associated with poorer OS on multivariable analysis. This was attributed to higher NRM in this group (34%) when compared to the rest. Castagna et al. showed that MUD was associated with poorer OS, although due to small sample size, it was underpowered to detect the difference statistically. This was in contrast to Hamadani et al.²⁰ who studied CIBMTR registry on mature T-cell lymphoma and showed that donor type did not significantly affect post-allo-HCT survival. Although our registry data does not contain information on the lines of treatment prior to allo-HSCT, we postulate that these patients required longer waiting time for a suitable donor. This delay might have potentially resulted in more lines of bridging therapies and therefore affected fitness level pre-transplant. The duration of donor search varies greatly depending on the ethnicity of recipient. Given the multi-ethnic population in Singapore, we noticed difficulty in looking for MUD

if one is of Malay race. This was similar to the US where unrelated donor search needs to be initiated early in non-white populations.²¹

Another factor of higher NRM in MUD transplant may be related to the ATG, which is associated with delayed immune reconstitution and an increased risk of infection.²² Our lymphoma patients were more likely to be lymphodepleted after lines of lymphoid-targeted therapies. Higher ATG dosage together with low absolute lymphocyte count (ALC) at time of ATG infusion is associated with increase fungal infection rate in recent studies.^{23,24} We routinely practised weight-based ATG dosing regardless of ALC. Further local study is required to confirm this, as our registry dataset lacks information on the relationship between dosage of ATG and ALC.

Efforts to replace ATG with PTCy in MUD transplantation have not consistently shown clear survival benefits but have been associated with decreased incidences of chronic GVHD, potentially allowing for a reduction in immunosuppressant

Table 5. Multivariate analysis of factors influencing OS in lymphoma patients receiving allo-HSCT.

Variable	n	HR	95% CI	P
Diagnosis				
B-NHL	41	1		Reference
T-NHL	38	0.56	0.25–1.21	0.12
NKTL	24	1.08	0.51–2.27	0.83
HL	18	0.33	0.12–0.85	0.025
Disease status at transplantation				
CR	73	1		Reference
PR	29	1.02	0.41–2.61	0.98
SD/PD	19	1.680	0.41–7.82	0.49
Donor type				
MSD	54	1		Reference
MUD	35	3.56	1.49–8.31	0.004
Haploidentical	23	1.82	0.42–6.68	0.40
CB	9	2.93	0.43–17.2	0.25
Conditioning				
RIC	102	1		Reference
MAC	17	1.65	0.49–4.61	0.38

Allo-HSCT: allogeneic-haematopoietic stem cell transplantation; B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CI: confidence interval; CR: complete remission; HL: Hodgkin lymphoma; HR: hazard ratio; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; OS: overall survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable disease/progress-free disease; T-NHL: T-cell non-Hodgkin lymphoma

use and a consequent decrease in infective complications.^{25,26} In myelodysplastic syndrome (MDS), Chalandon et al. showed that in the setting of MUD transplants, GVHD prophylaxis using PTCy, compared to ATG, resulted in better OS and PFS.²⁷ Among patients with R/R HL, evidence suggests the utility of PTCy specifically in the MUD and mismatch-related transplant, allowing one to postulate that PTCy can target the lymphoma itself.²⁸ PTCy could be an attractive GVHD prophylaxis option in MUD other than ATG, especially in lymphoma.

Interestingly, the outcome of transplants using haploidentical donors appeared comparable, if not superior, to those using MSD. This might be because haploidentical donor transplant was performed in more recent years and utilised either PTCy (n=15) or ex-vivo T-cell alpha-beta depletion (n=7) with the availability of novel GVHD prophylaxis and improvements in supportive care measures. Haploidentical donor transplantation presents an attractive option due to favourable availability.

Disease status at transplant

Our series showed that there was superior OS with better disease status at transplant. This finding is echoed by Hamadani et al. who evaluated patients with mature T-cell lymphoma from accredited EBMT and CIBMTR centres and showed improved PFS and OS in those in CR prior to allo-HSCT.²⁰ However, it is challenging to achieve CR pre-transplant in a significant proportion of patients with R/R high-risk lymphoma. Frontline treatment of lymphoma in Singapore was similar to National Comprehensive Cancer Network guidelines but not in the R/R setting. Although in certain parts of Asia, such as Japan and China where trials for novel therapies like valemetostat, linperlisib and golidocitinib have been made available for patients with refractory T-cell lymphomas,^{29,30} access to clinical trials for our patients remains limited. This adds to the challenge of achieving CR in refractory lymphoma patients. Notably, SD/PD patients still benefitted from allo-HSCT with the effect of graft-versus-lymphoma effect evidenced by 4-year PFS

and OS of 21% and 27%, respectively. Hamadani et al. showed that certain subtypes of T-cell lymphoma are especially sensitive to graft-versus-lymphoma effect, making it possible to proceed with allo-HSCT at less than CR in those specific subtypes (e.g. angioimmunoblastic lymphoma). Balancing the benefit of CR pre-transplant against the potential risk of jeopardising fitness after multiple lines of bridging therapies has to be individualised based on disease tempo and health.²⁰

Lymphoma subtype analysis

Comparing outcomes across different subtypes of lymphoma comes with caveats due to varying risks, patient demographics and disease biology. However, we observed that allo-HSCT exhibited the most promising curative potential among patients with R/R HL, with a 4-year PFS and OS of 61% and 62%, respectively. Our findings align with those of prospective phase 2 studies and retrospective reviews (GELTAMO and EBMT), where the 1-year and 4-year OS were 71% and 43%, respectively.³¹

HL patients tend to be younger, potentially resulting in better performance status, which could lead to improved tolerance of salvage regimens and, consequently, better disease control prior to allo-HSCT. Additionally, the availability of Brentuximab vedotin and PD1 inhibitors in the later era of analysis significantly contributed to achieving better responses among the relapsed subset.³² While PD-1 blockade has helped bridge patients to allo-HSCT, it is associated with treatment-refractory GVHD.³³ Given its long half-life, it is advised to implement a wash-out period of at least 6 weeks before allo-HSCT.^{34,35}

The significant proportion of the patients in our study had T-NHL, achieving 4-year PFS and OS of 35% and 52%, respectively. Our results were consistent with those reported by Schmitz et al. whose study, coordinated by the French Lymphoma Study Association and the German Lymphoma Alliance, revealed a 5-year PFS of 40% and a 3-year OS of 57% in patients with T-NHL who underwent allo-HSCT following upfront chemotherapy.³⁶ These comparable findings suggest to defer allo-HSCT to second-line setting as most T-NHL patients in our study received allo-HSCT at relapse.

In our study, NKTL ranks third in terms of the number of cases. In Asia, there is a higher prevalence of NKTLs compared to the West.³⁷ CIBMTR data on allo-HSCT in extranodal NKTLs reported 3-year PFS and OS of 28% and 34%, respectively. A Japanese registry study by Murashige et al. (2005),³⁸ which included 28 patients, reported 2-year OS 40%. A

multicentre study by the Asia Lymphoma Study Group reported by Tse et al.³⁹ revealed a 5-year OS of 57%. Compared to the above, our patients exhibited inferior outcome, with a 4-year PFS and OS of 19% and 30%, respectively. This discrepancy could be attributed to a larger proportion of patients in our subgroup undergoing transplantation while not in CR (46%). There remains a significant unmet need for salvage options in R/R NKTL. PD-1 inhibitors have shown early promising activity in this subtype of lymphoma and could potentially optimise pre-transplant disease control.⁴⁰ However, the issue of hyperacute GVHD in PD-1 inhibitor post-transplantation settings necessitates careful consideration.

Among patients with B-NHL, DLBCL emerges as the most common subtype. In our study, these patients exhibited a 4-year PFS of 43% and an OS of 43.5%. These results closely align with findings from the Spanish multicentre GETH/GELTAMO study reviewed by Bento et al.,⁵ where the 3-year event-free survival and OS were reported as 38% and 44%, respectively. However, other studies have demonstrated a wide range of outcomes for PFS (12–80%) and OS (28–80%), which can be attributed to the heterogeneity of the study populations, differences in conditioning regimens and variations in donor selection.^{2,41,42}

Considering the prohibitive issues associated with allo-HSCT, including toxicities and donor availability, CAR-T cell therapy has emerged as a promising alternative. In patients with R/R B-cell lymphoma and high-risk cytogenetics, CAR-T cell therapy has demonstrated a 58% CR rate⁴³ and exhibited a 5-year PFS and OS of 31.8% and 42.6%, respectively (ZUMA-1).⁴⁴ However, the unique adverse risk of CAR-T cell therapy includes cytopenias, neurological complications and cytokine release syndrome.

Despite its effectiveness and safety, accessibility to CAR-T cell therapy remains limited in many Asian countries. Therefore, in settings where CAR-T cell therapy is unavailable or prohibited due to factors such as incipient MDS, or in patients with disease relapse post-CAR-T,^{45,46} allo-HSCT may continue to offer PFS and OS benefits and serve as a reasonable alternative. There is paucity of evidence comparing the economic burden of allo-HSCT relative to CAR-T cell therapy. Each has different indications and subsequent complications which add to the cost. Traditionally, the cost of allo-HSCT has been supported by local government and private insurance policy. There were recent changes in financial policy support for CAR-T cell therapy. Unfortunately, this has not been generalised to all patients.⁴⁷ Despite the

CAR-T cell therapy advancement in B-NHL, allo-HSCT remained standard for HL, T-NHL and NKTL.

Period of transplantation

Our study showed an improved trend in terms of outcomes—both PFS and OS over the last decade. This is likely due to improvement in patient selection, deeper remission status, improved conditioning regime and supportive care peri-transplant. Over the last decades, we have seen the new supportive care in this field, including newer generation of antimicrobial, ruxolitinib for steroid refractory GVHD, letemovir for CMV prophylaxis in high-risk patients, as well as novel agents used in salvage treatment prior to allo-HSCT. Improvement in hospital and community care are other contributory factors.

Relevance of our data

Epidemiologically, there are significant geographical differences for lymphomas, especially Peripheral T Cell Lymphomas, compared to Europe and North America. In addition, the model of healthcare reimbursement and accessibility to clinical trials is different in Asia compared to western countries. As one of the largest real-world datasets looking at allo-HSCT in lymphoma in Asia, our data provides more relevant clinical outcome data for local and regional government organisations to which novel therapies can be benchmarked against for cost-effectiveness analysis for reimbursement considerations. For example, in B-NHL, the improved toxicity profile of CD19 CAR-T cell therapy and the NRM of <10% from large cohorts^{43,48} compared favourably with the NRM of allo-HSCT of 24%, as demonstrated in our allo-HSCT cohort. Together with the efficacy data of CAR-T cell therapy, this has supported the use of CAR-T over allo-HSCT, and contributed to the approval for CAR-T cell therapy in Singapore. In contrast, the favourable outcomes of allo-HSCT for HL (4-year PFS and OS of 61% and 62%, respectively), comparable to outcome results worldwide, supports its use as a consolidation option for younger patients relapsing post-autologous transplant. Importantly, compared to other datasets from Japan, Korea and China,^{37,38,40} results from our dataset may be more relevant and applicable to Southeast Asian countries, especially in subpopulations such as HL and T-NHL, where there is paucity of clinical trials for patients relapsing after standard of care treatment. Thus, results for our dataset will also provide an important benchmark and unique perspective for Asian-specific lymphoma treatment guidelines.

Limitation

This is a retrospective analysis that inevitably consists of physician and patient selection bias. Patients with better performance status were chosen for allo-HSCT and may not reflect the actual demographic of patients with R/R lymphoma who may have poorer fitness and difficulty in disease control. Additionally, there were some patients with missing data that could have affected the accuracy of the final analysis. Last, despite the collaboration between 2 centres, sample size remained small when performing subgroup analyses. Further evaluation in a larger cohort through collaborations with other transplant centres in the Asia-Pacific region (Singapore is part of the Asia Pacific Blood and Bone Marrow Transplant group) may help improve statistical power and provide systematic directions to standardise the role of allo-HSCT in the R/R lymphoma treatment algorithms.

CONCLUSION

Allo-HSCT is an effective treatment modality that leads to durable disease control for patients with R/R lymphoma. These real-world results form a historical benchmark for future studies of high-risk and R/R lymphomas in Singapore and in the Asia Pacific.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2015/2419) and National University Hospital Domain Specific Review Board (2010/00431).

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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