International multicenter retrospective analysis of thiotepa-based autologous stem cell transplantation for secondary central nervous system lymphoma

Secondary central nervous system lymphoma (SCNSL) is a rare, aggressive disorder with a historically dismal prognosis of <6 months.[1] Patients may present *de novo* with systemic disease or at relapse, either with isolated central nervous system (CNS) disease or synchronous systemic involvement. These differing presentations create the therapeutic challenge of controlling both the systemic and CNS disease. Thiotepa-based autologous stem cell transplant (ASCT) in first remission has been explored in SCNSL as a means of overcoming the poor outlook. Retrospective studies including consolidative ASCT in SCNSL generally include small series of patients with heterogeneous histological subtypes. Transplant-specific outcomes are not well characterized.[2-4] Performing large trials is challenging, with the largest prospective series reporting only 37 patients proceeding to ASCT.[5] The largest retrospective series (n=151) reported no patients who had received thiotepa-based conditioning, with the majority having undergone BEAM (carmustine, etoposide, cytarabine, melphalan)-conditioned ASCT.[6] Thiotepa-based conditioning with carmustine or busulfan has greater CNS bioavailability[7] compared with BEAM and produces superior outcomes in primary CNS lymphoma.[8] We analyzed the survival outcomes of the largest cohort of patients with SCNSL, focused exclusively on patients with diffuse large B-cell lymphoma (DLBCL) or transformed lymphoma, who were treated with chemoimmunotherapy and consolidated with thiotepa-conditioned ASCT.

Consecutive adult patients treated from January 31, 2013 to February 24, 2020 across 17 centers and three countries (UK, Italy and Germany) with thiotepa-based ASCT consolidation were retrospectively reviewed. Patients were followed up to December 1, 2021. CNS involvement was confirmed by brain biopsy and/or cerebrospinal fluid studies and/or neuroimaging. Baseline characteristics, details of therapy and response were collected. The primary endpoints were 3-year progression-free survival (PFS) and overall survival (OS) from time of stem cell infusion; secondary endpoints were the incidences of CNS and systemic relapse and of non-relapse mortality (NRM). OS and PFS estimates were generated using the Kaplan-Meier method and groups were compared using Cox regression and the log-rank test. Backwards selection with P=0.05 for inclusion was used for multivariable analyses. All statistical analyses were conducted using STATA v16.1 software (STATAcorp, College Station, TX, USA).

One hundred thirty-four patients (85 male, 49 female) with SCNSL underwent thiotepa-conditioned ASCT. These patients' baseline characteristics are outlined in Table 1. Forty-four patients did not have a CNS biopsy and were diagnosed based on a biopsy from a systemic site or neuroimaging alone. At the time of SCNSL diagnosis, 52 (39%) patients had a *de novo* presentation of SCNSL (synchronous systemic and CNS disease and were treatment-naïve) and 82 (62%) patients had relapsed diffuse large B-cell lymphoma, of whom 62 (46%) had isolated CNS relapse and 20 (15%) had a synchronous relapse presentation (systemic and CNS disease with prior therapy). For those with CNS involvement at relapse, the majority (77/82; 94%) had received prior chemotherapy with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone), including two patients who were given etoposide in addition to R-CHOP. Among all patients, methotrexate-cytarabine-based induction was most frequently used (n=123; 92%). Complete responses or partial responses to induction, as assessed before ASCT by positron emission tomography (PET) with computed tomography (CT) or CT alone, were achieved in 77/94 (82%) and 13/94 (14%) patients, respectively, and by 83/127 (65%) and 37/127 (29%), respectively, according to magnetic resonance imaging (MRI) of the head. The conditioning regimens employed were carmustine-thiotepa (n=112; 84%), busulfan-thiotepa (n=18; 13%), busulfan-lomustine-thiotepa (n=2; 1%), thiotepa-etoposide-cytarabine-melphalan (n=1; 1%) and thiotepa alone (n=1; 1%). The median number of $CD34^+$ cells infused was $4.4x10^6$/kg (range, $1.4x10^6$/kg - $37.1x10^6$/kg). The median days to neutrophil and platelet engraftment were 11 (interquartile range, 10-12) and 13 (interquartile range, 11-17). Neutrophil and platelet engraftment were defined as the first of 2 consecutive days with an absolute neutrophil count >$0.5x10^9$/L and a platelet count >$20x10^9$/L, without transfusion support.

At ASCT, the median duration of hospitalization was 22 days (range, 14-298) and the Intensive Care Unit admission rate was 8% (11/130). Grade 3-4 renal impairment was observed in 6% (8/130) and hepatic impairment in 4% (5/130). With a median follow-up of 47 months (interquartile range, 29-60), the 3-year OS and PFS rates were 71.6% (95% confidence interval [95% CI]: 61.9% – not reached) and 61.1% (95% CI: 52.2-68.9%), respectively (Figure 1). Ninety patients with histologically confirmed CNS disease

Table 1. Patients' baseline characteristics prior to autologous stem cell transplantation.

	Presentation			All presentations			
	De novo **N=52**	**Relapsed N=82**	***P*** **value[a]**	***De novo*** **N=52**	**Isolated relapse N=62**	**Synchronous relapse N=20**	***P*** **value[b]**
Age at ASCT in years, median (IQR)	53 (46-66)	60.5 (52-66)	0.99	53 (46-66)	61 (51- 68)	59.5 (55.5- 63.5)	0.23
Histology, N (%)							
DLBCL	48 (92.3)	71 (86.6)	0.31	48 (92.3)	56 (90.3)	15 (75.0)	0.099
Transformed indolent lymphoma	4 (7.7)	11 (13.4)		4 (7.7)	6 (9.7)	5 (25.0)	
CNS site, N (%)							
Parenchymal only	29 (55.8)	56 (68.3)	0.28	29 (55.8)	49 (79.0)	7 (35.0)	0.002
Leptomeningeal only	15 (28.9)	13 (15.9)		15 (28.9)	7 (11.3)	6 (30.0)	
Parenchymal + leptomeningeal	6 (11.5)	8 (9.8)		6 (11.5)	5 (8.1)	3 (15.0)	
Direct CNS invasion**	2 (3.9)	5 (6.1)		2 (3.9)	1(1.6)	4 (20.0)	
CNS biopsy, N (%)							
No	18 (34.6)	26 (31.7)	0.85	18 (34.6)	18 (29.0)	8 (40.0)	0.60
Yes	34 (65.4)	56 (68.3)		34 (65.4)	44 (71.0)	12 (60.0)	
Prior CNS prophylaxis (relapsed only), N (%)							
None	-	49 (61.3)	-	-	36 (59.0)	13 (68.4)	0.19
IT MTX only	-	18 (22.0)		-	14 (23.0)	4 (21.1)	
IV MTX only	-	9 (11.3)		-	9 (14.8)	0	
Both	-	4 (5.0)		-	2 (3.3)	2 (10.5)	
Unknown	-	2		-	1	1	
Time to SCNSL, N (%)							
>1 year	-	35 (42.7)	-	-	27 (42.6)	8 (40.0)	0.92
3 months – 1 year	-	20 (24.4)		-	14 (22.6)	6 (20.0)	
<3 months	-	16 (19.5)		-	13 (21.0)	3 (15.0)	
On therapy	-	11 (13.4)		-	8 (12.0)	3 (15.0)	
Time from SCNSL to ASCT in months, median (IQR)	6.6 (5.0-8.8)	5.2 (3.8-6.8)	0.0004	6.6 (5.0-8.8)	4.8 (3.5-6.5)	6.5 (4.9-8.1)	0.0001
Number of lines of therapy from SCNSL to ASCT, N (%)							
1	48 (92.3)	73 (89.0)	0.55[c]	48 (92.3)	54 (87.1)	19 (95.0)	0.89
2	2 (3.9)	6 (7.3)		2 (3.9)	5 (8.1)	1 (5.0)	
3	2 (3.9)	3 (3.7)		2 (3.9)	3 (4.8)	0	
ECOG score before ASCT, N (%)							
0	18 (35.3)	30 (38.0)	0.80[c]	18 (35.3)	22 (38.3)	8 (40.0)	0.85
1	26 (51.0)	32 (40.5)		26 (51.0)	24 (40.7)	8 (40.0)	
2	4 (7.8)	11 (13.9)		4 (7.8)	9 (15.3)	2 (20.3)	
3	3 (5.9)	6 (7.6)		3 (5.9)	4 (6.8)	2 (20.0)	
Missing	1	3		1	3	0	
Systemic (PET-CT/CT) response before ASCT, N (%)							
Complete response	37 (80.4)	40 (83.3)	0.74[c]	37 (80.4)	28 (87.5)	12 (75.0)	0.80
Partial response	7 (15.2)	6 (12.5)		7 (15.2)	3 (9.4)	3 (18.8)	
Stable disease	1 (2.2)	0		1 (2.2)	0	0	
Progressive disease	1 (2.2)	2 (4.1)		1 (2.2)	1 (3.1)	1 (6.3)	
Unknown/not performed	6	34		6	30	4	
CNS (MRI) response before ASCT, N (%)							
Complete response	28 (56.0)	55 (71.4)	0.071[c]	28 (56.0)	45 (73.8)	10 (62.5)	0.33
Partial response	18 (36.0)	19 (24.7)		18 (36.0)	14 (23.0)	5 (31.3)	
Stable disease	2 (4.0)	0		2 (4.0)	0	0	
Progressive disease	2 (4.0)	3 (3.9)		2 (4.0)	2 (3.3)	1 (6.3)	
Unknown/not performed	2	5		2	1	4	
Induction therapy regimen							
MATRix alone	6 (11.5)	18 (22.0)	<0.001	6 (12.0)	16 (26.2)	2 (10.0)	<0.001
MATRix + RICE/DeVIC combination	22 (42.3)	16 (19.5)		22 (44.0)	11 (18.0)	5 (25.0)	
MTX+ Ara-c combination	14 (26.9)	39 (47.6)		14 (28.0)	31 (50.8)	8 (40.0)	
RCODOXM/RIVAC	8 (15.4)	0		8 (16.0)	0	0	
Ifosfamide-containing, other*	2 (3.8)	6 (7.3)		2	3	3 (30.0)	
Other	0	3 (3.7)		0	1 (1.6)	2 (10.0)	

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[a]*P* value comparing all relapsed *vs. de novo* cases. [b]*P* value comparing all three groups. *P* values are for the χ^2 or Fisher exact test except for [c]the χ^2 test for trend. *Ifosfamide-containing regimens included ifosfamide-etoposide-epirubicin, ifosfamide-etoposide ± carboplatin, and ifosfamide-etoposide-cytarabine. **Direct central nervous system invasion refers to infiltration from craniofacial or epidural masses into the central nervous system. ASCT: autologous stem cell transplantation; IQR: interquartile range; DLBCL: diffuse large B-cell lymphoma; CNS: central nervous system; IT: intrathecal; IV: intravenous; MTX: methotrexate; SCNSL: secondary central nervous system lymphoma; ECOG: Eastern Cooperative Oncology Group; PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging; MATRix: methotrexate, cytarabine, thiotepa, and rituximab; RICE/DeVIC: rituximab, ifosfamide, carboplatin and etoposide/dexamethasone, VP16, ifosfamide, and carboplatin; Ara-C: cytarabine; RCODOXM/RIVAC: rituximab, cyclophosphamide, doxorubicin, vincristine, and methotrexate/rituximab, ifosfamide, etoposide, and high-dose cytarabine.

and 44 patients assessed with neuroimaging alone had similar OS (3-year rates: 70.2% [95% CI: 59.3-78.7] *vs.* 67.2% [95% CI: 50.9-79.1], log rank *P*=0.92) and PFS (3-year rates: 59.0% [95% CI: 47.9-68.5] *vs.* 65.5% [95% CI: 49.4-77.6], *P*=0.44). During the study period, 48 patients died, 43 relapsed and 14 died without documented relapse. The 100-day NRM was 3% and the cumulative incidence at 1 and 3 years was 8.4% (4.7-14.6). Causes of NRM were infection (6/14), respiratory failure (2/14), secondary acute myeloid leukemia (1/14) and unknown (5/14: all beyond day 100). Most relapses occurred within 2 years of ASCT (34/43; 79%).

The optimal depth of disease response that must be achieved prior to ASCT has previously been uncertain. Our data indicate that patients with a partial response (CNS, systemic or both) prior to ASCT have good outcomes. Those with a partial response after induction chemotherapy in the systemic compartment (by PET-CT/CT) or in the CNS (by MRI) did not differ significantly for PFS, OS or time to relapse when compared with those who had a complete response (Table 2, *Online Supplementary Table S1*). Combining response data showed a better OS for patients who were in complete remission according to both PET and MRI than for those in partial remission according to either technique (*P*=0.032, *P*=0.076, and *P*=0.055). Two of six patients transplanted with progressive disease responded, and are in complete remission; nevertheless outcomes were worse than those in all other patients, with four of the six progressing.

Adverse predictors of PFS and OS on univariable analysis were older age, Eastern Cooperative Oncology Group score 2-3, number of prior lines of therapy for SCNSL and progressive disease on pre-ASCT MRI. Presentation (relapsed DLBCL with synchronous presentation *vs. de novo*/isolated relapse) was significantly associated with inferior PFS. The only factors that were associated with poorer PFS in multivariable analysis were synchronous presentation, age and two or more prior lines of therapy. For OS, only age and two or more lines of SCNSL treatment remained significant. This is consistent with data in primary CNS lymphoma and systemic DLBCL.[9]

Patients presenting with synchronous relapse of SCNSL remain a challenge and have the poorest outcomes. The 3-year PFS in this group was 40.0% (19.3-60.1), compared to 62.7% (47.9-74.4) and 67.7% (53.1-77.1) in the groups with *de novo* and isolated relapse presentations (Table 2). This is comparable to the CORAL data of a 3-year PFS of 39% in 68 patients with relapsed/refractory DLBCL undergoing BEAM-conditioned ASCT.[10] In our cohort this appears to be driven by a higher rate of systemic relapse after ASCT (55.0% *vs.* 6.0% *de novo vs.* 2.1% isolated) and may therefore reflect the difficulty in achieving control of systemic disease at relapse. The risk of systemic failure was greater for those with a synchronous relapse presentation than those with *de novo*/isolated presentations (hazard ratio synchronous *vs. de novo* = 14.36 [95% CI: 4.03-51.1%], hazard ratio synchronous *vs.* isolated = 54.64 [95% CI: 7.1-421.8], log rank *P*<0.0001).

Relapse after ASCT resulted in very poor outcomes. As in the CORAL study, a shorter time to relapse after ASCT was associated with inferior survival.[10] In our study, 43 patients relapsed after ASCT (27 CNS only, 13 systemic only, 3 both), at a median of 4.9 months (range, 1-49.3); 34 died with a median survival of 3.7 months (range, 2.1-7.2). Those relapsing <3 months after ASCT had a median survival of 1.5 months (95% CI: 0.72-2.04) compared with 3.7 months (95% CI: 3.01-4.37) for those who relapsed 3-6 months after ASCT and 21.6 months (95% CI: 9.6-not reached) for those who relapsed at ≥6 months (log rank *P*<0.0001). Of 21 patients receiving salvage chemotherapy, 15 (71%) have died, all due to progressive disease.

Overall, our data support thiotepa-based ASCT as a standard of care of conditioning in SCNSL. Our data suggest that patients with SCNSL undergoing this strategy have superior OS and PFS compared to cohorts receiving BEAM conditioning, although the proportion of SCNSL presentation was not characterized in these studies.[4,6] No patients underwent thiotepa-busulfan-cyclophosphamide conditioning which has been used in primary CNS lymphoma with higher rates of NRM and a similar risk of all-cause mortality after 6 months. In our study, the 100-day NRM was 3% and 8.4% at 3 years, with others reporting 100-day NRM of approximately 10% in SCNSL.[2,3] Hematopoietic recovery times and intensive care admission rates were comparable to those previously published.

Factors significantly associated with inferior PFS and OS in our series included number of prior lines of therapy for SCNSL and older age. Despite this, carefully selected patients >70 years still have good outcomes and should not be excluded. Two prospective trials included patients ≤70 years old, with restrictive criteria for organ function and exclusion of those with human immunodeficiency virus in-

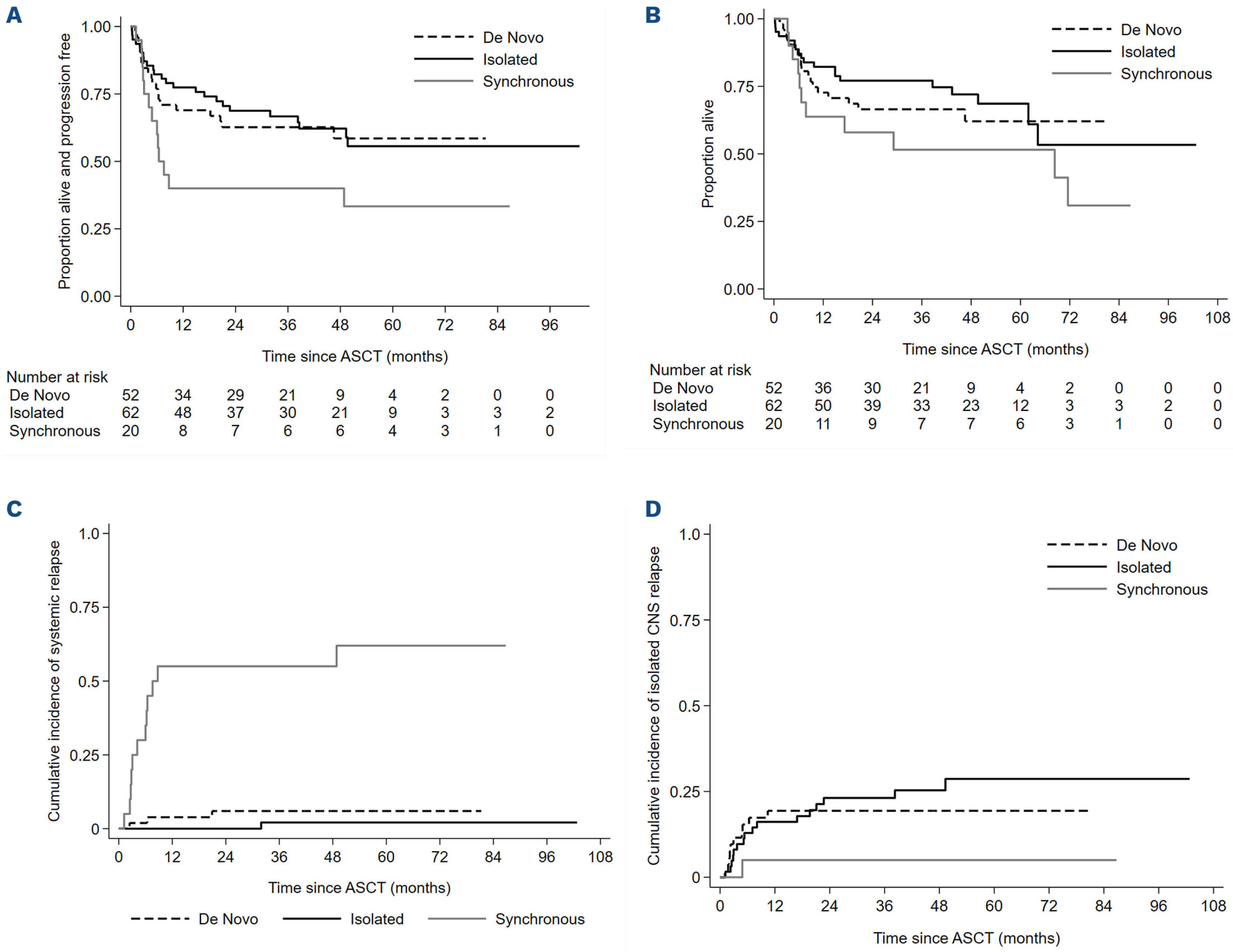

Figure 1. Outcomes after autologous stem cell transplantation for secondary central nervous system lymphoma. (A) Progression-free survival. (B) Overall survival. (C) Incidence of systemic relapse after autologous stem cell transplantation (ASCT). (D) Incidence of isolated central nervous system relapse after ASCT.

fection or hepatitis.[5,11] There are no prospective data for patients >70 years old.[12,13] Our unselected retrospective series reflects real-world practice: 30% (38/127) would not have met MARIETTA trial eligibility criteria at SCNSL diagnosis (n=30) or prior to ASCT (n=8) (age up to 77 years [>70 years, n=17; 13%] at SCNSL diagnosis, prior high-dose methotrexate use [n=13; 10%], well-controlled human immunodeficiency virus infection [n=2; 1%], impaired renal function prior to ASCT [glomerular filtration rate <60 mL/min, 6/129; 5%] and left ventricular ejection fraction <50% [3/112; 3%]).

Our data are retrospective and have inherent limitations. We were unable to accurately identify all patients presenting with SCNSL and only included those who proceeded to ASCT. Forty-four percent of those with a relapsed SCNSL presentation presented within a year of a diagnosis of DLBCL, whereas typically 90% of CNS relapses occur during the first year of follow-up,[5] demonstrating a possible selection bias as we postulate a cohort of patients who relapse early may not proceed to ASCT. Data were incomplete or not uniformly performed on baseline risk factors (including cell of origin/gene rearrangements) and therefore analysis of potential confounders may be limited. Despite this being the largest cohort of SCNSL patients treated with thiotepa-conditioned ASCT to date, good outcomes (therefore small numbers of events) limited our ability to run full multivariable models or multivariable analysis by relapse type, and treatment choice bias will limit any comparison of treatment regimens.

In conclusion, thiotepa-conditioned ASCT is an effective consolidation therapy with low NRM and leads to durable responses particularly in those with *de novo* or isolated relapse presentation. Advanced age (>70 years) does not preclude consideration for this consolidation strategy. Patients presenting with synchronous SCNSL at relapse have

Table 2. Risk factors for progression-free survival and overall survival.

Risk factor	Progression-Free Survival			Overall Survival		
	Events/N	HR (95% CI)	*P* value	Events/N	HR (95% CI)	*P* value
Presentation[§]						
De novo	20/52	1.00	0.069	18/52	1.00	0.29
Isolated relapse	24/62	0.91 (0.50-1.65)		19/62	0.80 (0.42-1.63)	
Synchronous relapse	13/20	1.94 (0.96-3.91)		11/20	1.46 (0.68-3.14)	
Timing of relapse (relapsed only)						
>1 year	14/35	1.00	0.20*	9/35	1.00	0.073*
3 months-1 year	8/20	0.90 (0.38-2.16)		7/20	0.87 (0.36-2.08)	
<3 months	8/16	1.33 (0.56-3.18)		7/16	1.48 (0.61-3.58)	
On therapy	7/11	2.02 (0.81-5.03)		7/11	2.40 (0.95-6.08)	
Age at ASCT, for an increase of 10 years	57/134	1.39 (1.09-1.75)	0.007	48/134	1.35 (1.04-1.75)	0.022
ECOG score at ASCT						
0-1	43/106	1.00	0.073	34/106	1.00	0.014
2-3	13/24	1.76 (0.94-3.27)		13/24	2.19 (1.15-4.16)	
Time to ASCT, for an increase of 1 month	57/134	1.01 (0.94-1.08)	0.85	48/134	1.01 (0.94-1.09)	0.77
Number of lines of SCNSL therapy before ASCT						
1	49/121	1.00	0.025	41/121	1.00	0.023
2-3	8/13	2.36 (1.11-5.02)		7/13	2.48 (1.10-5.60)	
Response before ASCT						
Systemic (PET-CT/CT) response						
Complete response	32/77	1.00	0.40	26/77	1.00	0.13
Partial response	7/13	1.42 (0.63-3.22)		7/13	1.87 (0.81-4.34)	
CNS (MRI) response						
Complete response	31/56	1.00	0.31	26/83	1.00	0.18
Partial response	13/23	1.34 (0.75-2.40)		16/37	1.53 (0.82-2.86)	
Combined response						
Both complete response	23/67	1.00	0.076	18/67	1.00	0.032
Either partial response	21/41	1.71 (0.95-3.09)		19/41	2.03 (1.06-3.90)	
Non-CR (PR/SD/PD by either MRI or PET)[‡]	25/50	1.74 (0.98-3.06)	0.057	23/50	2.15 (1.15-4.00)	0.016

Risk factor (multivariable analysis)**	Progression-Free Survival			Overall Survival		
	Events/N	HR (95% CI)	*P* value	Events/N	HR (95% CI)	*P* value
Presentation						
De novo or isolated CNS relapse	43/110	1.00	0.016	-	-	-
Synchronous relapse	13/20	2.18 (1.16-4.12)		-	-	
Age at ASCT, for an increase of 10 years	56/130	1.38 (1.07-1.1.76)	0.012	47/130	1.33 (1.02-1.73)	0.033
Number of lines of SCNSL therapy before ASCT						
1	48/117	1.00	0.018	48/117	1.00	0.039
≥2	8/13	2.53 (1.18-5.46)		8/13	2.36 (1.04-5.33)	

[§]Synchronous relapse *versus de novo*/isolated presentation hazard ratio for progression-free survival = 2.04 (1.10-3.80) P=0.022; hazard ratio for overall survival = 1.64 (0.83-3.28) *P*=0.15. *Log-rank test for trend. **All non-conditioning parameters (presentation, age, Eastern Cooperative Oncology Group score, number of prior lines of therapy for secondary central nervous system lymphoma) and backwards selection (*P*=0.05 for inclusion) were used to select the final model presented above. Including pre-transplant response within the same model reduced the number of complete cases from 130 to 113; for progression-free survival, synchronous disease and ≥2 lines remain significant but age does not. For overall survival, no factors reach statistical significance at *P*=0.05. As response did not reach significance for either progression-free or overall survival, the model without has been used. [‡]Six patients had progressive disease (PD) at transplantation: two with systemic PD, complete remission in central nervous system; one with central nervous system PD (positron emission tomography not performed; isolated presentation); one with systemic PD, partial response in central nervous system; and two with PD in both systemic and central nervous system compartments. HR: hazard ratio; 95% CI: 95% confidence interval; ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; SCNSL: secondary central nervous system lymphoma; PET: positron emission tomography; CT: computed tomography; CNS: central nervous system; MRI: magnetic resonance imaging; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

poor outcomes, mainly due to post-ASCT systemic relapse, and may benefit from a different treatment approach. Patients having a partial or complete response after induction therapy can achieve durable remissions with thiotepa-based ASCT. The lack of requirement of a complete response prior to ASCT may help to minimize treatment-related toxicity by shortening courses of induction chemotherapy.

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Disclosures

JK, AAK, LKI, SS, HG, LP, TF, KF, NE, LE, SC, NT, AK, NMC, and GI have no conflicts of interest to disclose. EN has received grant funding, speaker fees, and travel fees from KITE/Gilead; sat on advisory boards and received conference fees from Novartis: and sat on advisory boards for BMS/Celgene. KML has received research funding from Blood Cancer UK, Roy Castle Lung Cancer Foundation, Beigene, Genmab, Roche, and Celgene; has provided consultancy services for Genmab and Roche; has received honoraria and speakers bureau fees from Roche, Aptitude Health and Hartley Taylor; has been or is a member of the Board of Directors or advisory committees of Celgene, Kite and Karyopharm; and has received travel support from Celgene and Janssen. KEP has received sponsorship for educational meetings from AbbVie. TAE has received educational and advisory board honoraria, and travel support to attend scientific conferences from Roche; honoraria, research support, and travel support to attend scientific conferences from Gilead; educational and advisory board honoraria from KITE; honoraria from Janssen; honoraria and travel support to attend scientific conferences from AbbVie; honoraria, research funding, and travel support to attend scientific conferences from AstraZeneca; advisory board honoraria, and trial steering committee fees from Loxo Oncology; advisory board honoraria and research funding from Beigene; and advisory board honorarium from Incyte and Secura Bio. JS has received honoraria and sponsorship for meetings from AbbVie, Janssen and AstraZeneca. TC has provided consultancy for Janssen-Cilag; and collaborated with Sandoz, Hema for a future project. DES has received honoraria from Abbvie, AstraZeneca, Janssen, Roche and Takeda; has received conference or travel support from Abbvie and Novartis; and has served on advisory boards for Abbvie, ASTEX, AstraZeneca, Beigene, Janssen, and Kyowa Kiirin. WO has served on advisory boards for Roche, Takeda, Servier, Kite Gilead, MSD, Novartis, Beigene, Autolus, Kyowa Kirin, and Incyte; and has received honoraria from Roche, Takeda, Kite Gilead, Novartis, Kyowa Kirin, Incyte, Astra Zeneca, Pfizer, Syneos, Abbvie, and BMS/Celgene. CPF is an advisory board member for Celgene/BMS, Abbvie , GenMab, Gilead/Kite, Morphosys, Incyte, Janssen, Roche, Takeda, and Atarabio; provides remunerated speaker/educational activities for Gilead/Kite, Janssen, Roche, and Takeda; has received research funding from BeiGene; and has received travel support to attend scientific conferences from Roche. AJMF has received speaker fees from Gilead and Roche; is a member of advisory boards for Gilead, Juno, Novartis, PletixaPharm, and Roche; currently receives research grants from ADC Therapeutics, Bayer HealthCare Pharmaceuticals, Beigene, Bristol Myers Squibb, Genmab, Gilead, Hutchison Medipharma, Incyte, Janssen Research & Development, MEI Pharma, Novartis, PletixaPharm, Pharmacyclics, Protherics, Roche, and Takeda; and holds patents on NGR-hTNF-α in brain tumors and NGR-hTNF/R-CHOP in relapsed or refractory primary CNS lymphoma and SNGR-hTNF in brain tumors. ES has received research funding and speakers' honoraria from Riemser. KC has played a consulting/advisory role for Roche, Takeda, Celgene, Atara, Gilead, KITE, Janssen, and Incyte; served on speakers bureau for Roche, Takeda, KITE, Gilead, and Incyte, and received conference/travel support from Roche, Takeda, KITE, Janssen, and BMS.

Contributions

JK and KC designed the study, analyzed data and wrote the

manuscript. ES, AJMF, CF, GI, and NMC analyzed data and reviewed the manuscript. AAK performed the statistical analysis and reviewed the manuscript. JK, SS, HG, LP, LKI, TF, EN, KF, KML, KEP, NE, LE, TAE, SC, NT, AK, TC, JS, DES, and WO collected data and reviewed the manuscript.

Data-sharing statement

The data supporting the findings of this study are available within the article and its supplementary materials. Additional data are available on request from the corresponding author.

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