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

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Secondary central nervous system lymphoma (SCNSL) is a rare, aggressive disorder with historically dismal prognosis of <6 months [1]. Patients may present *de novo* with systemic disease or at relapse, either with isolated CNS disease or synchronous systemic involvement. These differing presentations present a therapeutic challenge of control of both 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 heterogenous histological subtypes. Transplant specific outcomes are not well characterised [2-4]. Performing large trials is challenging, with the largest prospective series reporting only 37 patients proceeding to ASCT [12]. The largest retrospective series (n=151) reported no patients with thiotepa-based conditioning, with the majority receiving BEAM (carmustine, etoposide, cytarabine, melphalan)-conditioned ASCT [5]. Thiotepa-based conditioning with carmustine or busulfan has superior CNS bioavailability [6] compared with BEAM and has superior outcomes in primary CNS lymphoma (PCNSL) [7]. We analysed the survival outcomes of the largest SCNSL cohort focused exclusively on patients with DLBCL or transformed lymphoma treated with chemoimmunotherapy and consolidated with thiotepa-conditioned ASCT.

Consecutive adult patients treated from 31/Jan/2013 - 24/Feb/20 with thiotepa-based ASCT consolidation were retrospectively reviewed across 17 centres and 3 countries (UK, Italy and Germany). Patients were followed up to 1/Dec/21. 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 with secondary end points of incidence 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 (STATAcorp, Texas).

134 patients (85 male, 49 female) with SCNSL underwent thiotepa-conditioned ASCT. Baseline characteristics are outlined (Table 1). Forty-four patients did not have a CNS biopsy and were diagnosed with a biopsy from a systemic site or neuroimaging alone. At the time of SCNSL diagnosis, 52 (39%) patients had *de novo* presentation of SCNSL (synchronous systemic and CNS disease and treatment naïve), 82 (62%) patients had relapsed DLBCL: 62 (46%) isolated CNS relapse and 20 (15%) with 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 R-CHOP~~-like~~ chemotherapy (including 2 patients with additional etoposide). Among all patients, methotrexate-cytarabine-based induction was most frequently used (123; 92%). Complete response (CR) or partial

response (PR) to induction as assessed pre-ASCT on PET-CT/CT was achieved in 77/94 (82%) / 13/94 (14%) and on MRI head in 83/127(65%) / 37/127(29%), respectively. Conditioning regimens employed were most commonly carmustine-thiotepa (112; 84%), busulfan-thiotepa (18; 13%), busulfan-lomustine-thiotepa (2; 1%), thiotepa-etoposide-cytarabine-melphalan (1; 1%) and thiotepa alone (1; 1%). Median CD34+ cells infused was 4.4 x 10^6/kg (range 1.4-37.1). Median days to neutrophil and platelet engraftment were 11 (IQR 10-12) and 13 (IQR 11-17) days. Neutrophil and platelet engraftment were defined as the first of 2 consecutive days with an absolute neutrophil count >0.5 x 10^9/l and platelet count >20 x 10^9/l, unsupported.

At ASCT, the median duration of hospitalisation was 22 (range 14-298) days 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 (IQR 29-60) months, the 3-year OS and PFS rates were 71.6% (95% CI 61.9-NR%) and 61.1% (95% CI 52.2-68.9%), respectively (Figure 1). Ninety patients with histologically confirmed CNS disease 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 relapse documented. One hundred-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 AML (1/14) and unknown (5/14: all post 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 supports that patients in PR pre-ASCT (either CNS, systemic or both) have good outcomes. Those in PR after induction chemotherapy in the systemic compartment (by PET-CT/CT) or in the CNS (by MRI) did not differ significantly in PFS/OS/time to relapse when compared with CR (Table 2 and Supplemental Table 1). Combining response data showed a better OS for patients who were in CR by both PET and MRI vs PR in either (p=0.032, p=0.076, p=0.055). Two of six patients transplanted with progressive disease (PD) responded, and are in CR, nevertheless outcomes were worse when compared to all other patients, with 4/6 progressing.

Adverse predictors of PFS and OS on univariable analysis were older age, ECOG 2-3, number of prior lines of therapy for SCNSL and PD on MRI pre-ASCT. 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 ≥2 prior lines of therapy. For OS, only age and ≥2 lines of SCNSL treatment remained significant. This is consistent with data in PCNSL and systemic DLBCL [8].

Patients presenting with synchronous relapse of SCNSL remain a challenge, with the poorest outcomes. 3-year PFS in this group when compared with *de novo* and isolated relapse presentation was 40.0% (19.3-60.1) vs 62.7% (47.9-74.4) vs 67.7% (53.1-77.1) (Table 2). This is comparable to the CORAL data of 3-year PFS of 39% in 68 patients with relapsed/refractory DLBCL undergoing BEAM-conditioned ASCT [9]. This appears to be driven by a higher rate of systemic relapse post-ASCT in our cohort (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 synchronous relapse presentation than those with *de novo*/isolated presentations (HR (vs *de novo*) 14.36 (95% CI 4.03-51.1%), HR vs isolated: 54.64 (95% CI 7.1-421.8), log rank p<0.0001).

Relapse post-ASCT resulted in very poor outcomes. As in the CORAL study, a shorter time to relapse post-ASCT was associated with inferior survival [9]. In our study, 43 patients relapsed post-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 post-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 that relapsed 3-6 months post-ASCT and 21.6 months (95% CI 9.6-NR) for those that 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 suggests superior OS/PFS in patients with SCNSL undergoing this strategy compared to cohorts receiving BEAM-conditioning. However, the proportion of SCNSL presentation is not characterised in these studies [4,5]. No patients underwent thiotepa-busulfan-cyclophosphamide conditioning which has been used in primary CNS lymphoma with higher rates of NRM and similar risk of all-cause mortality after six 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]. Haemopoietic 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 those ≤70 years, with restrictive criteria for organ function and exclusion of those with HIV or hepatitis [12,13]. There are no prospective data for those >70 years. 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, 17; 13%) at SCNSL diagnosis, prior high-dose methotrexate use (13; 10%), well-controlled HIV (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 had inherent limitations. We were unable to accurately identify all patients presenting with SCNSL and only included those that proceeded to. 44% of those with relapsed SCNSL presentation presented within a year of DLBCL diagnosis, whereas typically 90% of CNS relapses occur during the first year of follow-up [12], demonstrating a possible selection bias as we postulate a cohort of patients who relapse early may not proceed to ASCT. Data was incomplete or not uniformly performed on baseline risk factors (including cell of origin/gene rearrangements) and therefore may have limited analysis of potential confounders. Despite this being the largest cohort SCNSL 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.

Thiotepa-conditioned ASCT is an effective consolidative 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 with synchronous SCNSL presentation at relapse have poor outcomes mainly due to post-ASCT systemic relapse, and may benefit from a different treatment approach. Patients achieving either PR or CR post-induction therapy achieve durable remissions with thiotepa-based ASCT. The lack of requirement of CR prior to ASCT may help to minimise treatment-related toxicity by abbreviating courses of induction chemotherapy.

References

1. Hollender A, Kvaloy S, Lote K, Nome O, Holte H. Prognostic factors in 140 adult patients with non-Hodgkin's lymphoma with systemic central nervous system (CNS) involvement. A single centre analysis. Eur J Cancer. 2000;36(14):1762-1768.
2. Alvarnas JC, Negrin RS, Horning SJ, et al. High-dose therapy with hematopoietic cell transplantation for patients with central nervous system involvement by non-Hodgkin's lymphoma. Biol Blood Marrow Transplant. 2000;6(3A):352-358.
3. Kasamon YL, Jones RJ, Piantadosi S, et al. High-dose therapy and blood or marrow transplantation for non-Hodgkin lymphoma with central nervous system involvement. Biol Blood Marrow Transplant. 2005;11(2):93-100.
4. Akin S, Hosing C, Khouri IF, et al. Autologous Stem Cell Transplantation for Large B-cell Lymphoma with Secondary Central Nervous System Involvement. Blood Adv. 2022;6(7):2267-2274.
5. Maziarz RT, Wang Z, Zhang MJ, et al. Autologous haematopoietic cell transplantation for non-Hodgkin lymphoma with secondary CNS involvement. Br J Haematol. 2013;162(5):648-656.
6. Wiebe VJ, Smith BR, DeGregorio MW, Rappeport JM. Pharmacology of agents used in bone marrow transplant conditioning regimens. Crit Rev Oncol Hematol. 1992;13(3):241-270.
7. Scordo M, Wang TP, Ahn KW, et al. Outcomes Associated With Thiotepa-Based Conditioning in Patients With Primary Central Nervous System Lymphoma After Autologous Hematopoietic Cell Transplant. JAMA Oncol. 2021;7(7):993-1003.
8. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3(5):e217-227.
9. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-4190.
10. Korfel A, Elter T, Thiel E, et al. Phase II study of central nervous system (CNS)-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation for CNS relapse of aggressive lymphomas. Haematologica. 2013;98(3):364-370.
11. Doorduijn JK, van Imhoff GW, van der Holt B, et al. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study. Hematol Oncol. 2017;35(4):497-503.
12. Ferreri AJM, Doorduijn JK, Re A, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. Lancet Haematol. 2021;8(2):e110-e121.
13. Ferreri AJ, Donadoni G, Cabras MG, et al. High Doses of Antimetabolites Followed by High-Dose Sequential Chemoimmunotherapy and Autologous Stem-Cell Transplantation in Patients With Systemic B-Cell Lymphoma and Secondary CNS Involvement: Final Results of a Multicenter Phase II Trial. J Clin Oncol. 2015;33(33):3903-3910.
14. El-Galaly TC, Cheah CY, Bendtsen MD, et al. Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma. Eur J Cancer. 2018;93:57-68.
15. Bromberg JE, Doorduijn JK, Illerhaus G, et al. Central nervous system recurrence of systemic lymphoma in the era of stem cell transplantation--an International Primary Central Nervous System Lymphoma Study Group project. Haematologica. 2013;98(5):808-813.

Table 1. Baseline characteristics pre-ASCT

	Presentation			All presentations			
	De novo	Relapsed	p-value[1]	*De novo*	Isolated relapse	Synchronous relapse	p-value[2]
	n=52	n=82		n=52	n=62	n=20	
Age at ASCT (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							
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							
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							
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.£)		34 (65.4)	44 (71.0)	12 (60.0)	
Prior CNS prophylaxis (relapsed only)							
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							
>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 (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 SCNSL to ASCT							
1	48 (92.3)	73 (89.0)	0.55[3]	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)	

	Presentation			All presentations			
	De novo	Relapsed	p-value[1]	*De novo*	Isolated relapse	Synchronous relapse	p-value[2]
	n=52	n=82		n=52	n=62	n=20	
3	2 (3.9)	3 (3.7)		2 (3.9)	3 (4.8)	0	
ECOG pre-ASCT							
0	18 (35.3)	30 (38.0)	0.80[3]	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 pre ASCT							
CR	37 (80.4)	40 (83.3)	0.74[3]	37 (80.4)	28 (87.5)	12 (75.0)	0.80
PR	7 (15.2)	6 (12.5)		7 (15.2)	3 (9.4)	3 (18.8)	
SD	1 (2.2)	0		1 (2.2)	0	0	
PD	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 pre ASCT							
CR	28 (56.0)	55 (71.4)	0.071[3]	28 (56.0)	45 (73.8)	10 (62.5)	0.33
PR	18 (36.0)	19 (24.7)		18 (36.0)	14 (23.0)	5 (31.3)	
SD	2 (4.0)	0		2 (4.0)	0	0	
PD	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)	

[1]*p-value compared all relapsed vs de novo.* [2]*p-value comparing all three groups. p-values are Chi-squared or Fisher's exact except* [3]Chi-squared test for trend

*Ifosfamide containing regimens included ifosfamide-etoposide-epirubicin, ifosfamide-etoposide +/-carboplatin, ifosfamide-etoposide-cytarabine

**Direct CNS invasion refers to infiltration from craniofacial or epidural masses into the CNS

Table 2. Risk factors for PFS and OS

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 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 – 1.098)	0.7779
Number of lines of SCNSL therapy pre 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 pre ASCT						
Systemic (PET-CT/CT) response						
CR	32/77	1.00	0.40	26/77	1.00	0.13
PR	7/13	1.42 (0.63 – 3.22)		7/13	1.87 (0.81 – 4.34)	
CNS (MRI) response						
CR	31/56	1.00	0.31	26/83	1.00	0.18
PR	13/23	1.34 (0.75 – 2.40)		16/37	1.53 (0.82 – 2.86)	
Combined response						
Both CR	23/67	1.00		18/67	1.00	

Risk factor	Progression Free Survival			Overall Survival		
	Events/N	HR (95% CI)	p-value	Events/N	HR (95% CI)	p-value
Either PR	21/41	1.71 (0.95 – 3.09)	0.076	19/41	2.03 (1.06 – 3.90)	0.032
Non-CR (PR/SD/PD in 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		-	-	-
Synchronous relapse	13/20	2.18 (1.16 - 4.12)	0.016	-	-	
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 pre ASCT						
1	48/117	1.00		48/117	1.00	0.039
≥2	8/13	2.53 (1.18 - 5.46)	0.018	8/13	2.36 (1.04 – 5.33)	

[§] *Systemic vs de novo/isolated: HR (PFS) 2.04 (1.10 – 3.80) p=0.022, HR (OS): 1.64 (0.83 – 3.28), p=0.15*

**Log-rank test for trend.*

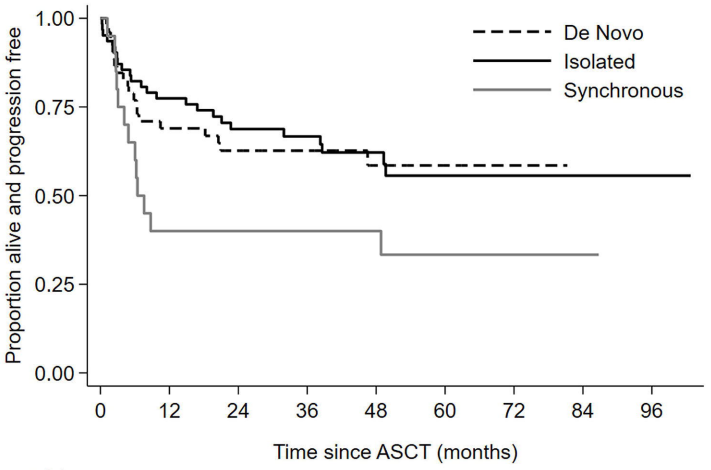
*** All non-conditioning parameters (presentation, age, ECOG, number of prior lines of SCNSL therapy) and backwards selection (p=0.05 for inclusion) was used to select the final model presented above. Including pre-ASCT response within the same model reduced complete cases from N=130 to N=113; for PFS synchronous disease and ≥2 lines remain significant but age does not. For OS, no factors reach significance at p=0.05. As response did not reach significance in either PFS or OS, the model without has been included.*

[¤] *Patients with PD at ASCT N=6 (N=2 systemic PD, CR in CNS, n=1 CNS PD (PET not performed; isolated presentation), n=1 systemic PD CNS PR and n=2 PD in both systemic and CNS compartment.*

Figure 1. Outcomes post-ASCT

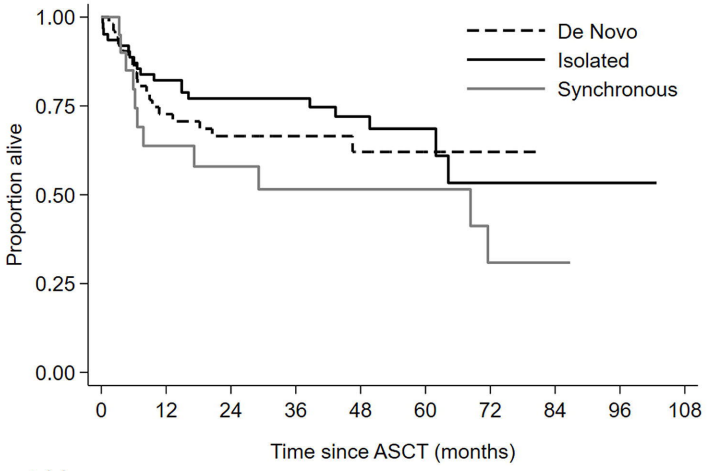
a) **Progression free survival**
b) **Overall survival**
c) **Incidence of systemic relapse post-ASCT**
d) **Incidence of isolated CNS relapse post-ASCT**

a)



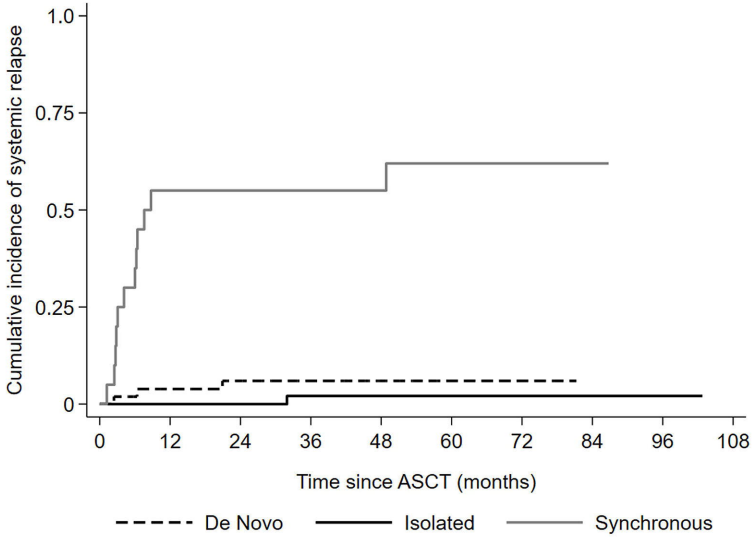
Number at risk									
De Novo	52	34	29	21	9	4	2	0	0
Isolated	62	48	37	30	21	9	3	3	2
Synchronous	20	8	7	6	6	4	3	1	0

b)

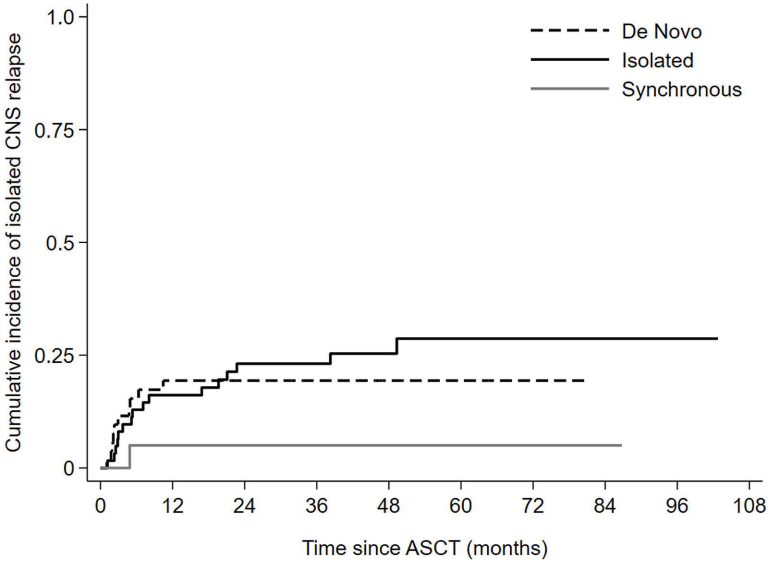


Number at risk										
De Novo	52	36	30	21	9	4	2	0	0	0
Isolated	62	50	39	33	23	12	3	3	2	0
Synchronous	20	11	9	7	7	6	3	1	0	0

c)



d)



Supplemental table 1. Risk factors for time to CNS and systemic relapse post-ASCT

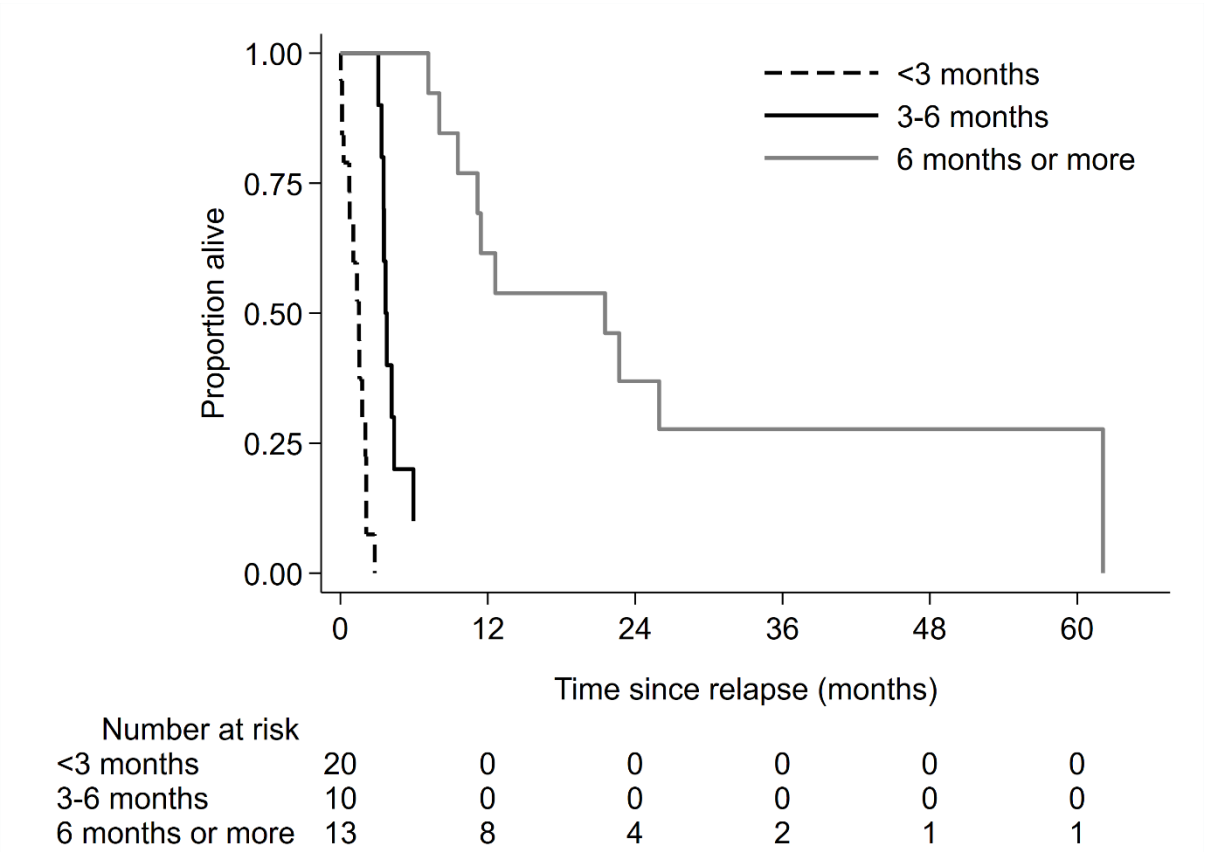
Risk factor	Time to CNS relapse			Time to systemic relapse		
	Events/N	HR (95% CI)	p-value	Events/N	HR (95% CI)	p-value
Presentation[§]						
De novo	11/52	1.00	0.64	3/52	1.00	<0.0001
Relapsed: isolated	16/62	1.14 (0.53 – 2.45)		1/62	0.26 (0.03 – 2.53)	
Relapsed: synchronous	3/20	0.63 (0.18 – 2.28)		12/20	14.36 (4.03 – 51.15)	
Timing of relapse (relapsed only)						
>1 year	7/35	1.00	0.10*	4/35	1.00	0.19*
3 months-1 year	4/20	0.92 (0.27 – 3.15)		3/20	1.34 (0.30 – 6.00)	
< 3 months	4/16	1.24 (0.36 – 4.24)		3/16	1.70 (0.38 – 7.61)	
On therapy	4/11	2.13 (0.62 – 7.29)		3/11	2.71 (0.60 – 12.15)	
Age at ASCT (for an increase of 10 years)	30/134	1.11 (0.84 – 1.48)	0.45	16/118	1.24 (0.81 – 1.89)	0.32
ECOG at ASCT						
0-1	23/106	1.00	0.57	12/106	1.00	0.85
2-3	6/24	1.30 (0.53 – 3.19)		3/24	1.13 (0.32 – 4.00)	
Time to ASCT, for an increase of 1 month	30/134	1.02 (0.94 – 1.11)	0.67			
Number of lines of SCNSL therapy pre ASCT						
1	24/121	1.00	0.016	15/121	1.00	0.66
2	6/9	3.03 (1.23 – 7.43)		1/13	0.64 (0.08 – 4.84)	
Response pre ASCT						
Systemic (PET-CT/CT) response						
CR	21/77	1.00	0.41	8/77	1.00	0.15
PR	2/13	0.55 (0.13 – 2.33)		3/13	2.54 (0.67 – 9.58)	
CNS (MRI) response						

Risk factor	Time to CNS relapse			Time to systemic relapse		
	Events/N	HR (95% CI)	p-value	Events/N	HR (95% CI)	p-value
CR	19/83	1.00	0.41	8/83	1.00	0.82
PR	6/37	0.68 (0.27 – 1.71)		4/37	1.15 (0.34 – 3.80)	
Combined response						
Both CR	15/67	1.00		3/67	1.00	
PR	8/41	0.88 (0.37 – 2.08)	0.77	6/41	3.56 (0.89 – 14.22)	0.055
Non-CR (PR/SD/PD in either MRI or PET)	12/50	1.15 (0.54 – 2.45)	0.72	7/50	3.46 (0.89 – 13.38)	0.056

*[§]Systemic vs de novo/isolated: HR (CNS) 0.59 (0.18 – 1.94) p=0.38, HR (systemic): 18.2 (11.3 – 29.3), p<0.001 *Log-rank test for trend. Time to CNS relapse is calculated from the date of ASCT until CNS relapse, patients who have systemic only relapse or die in remission are counted as competing risks. Time to systemic relapse includes only systemic relapse as an event with CNS alone relapse treated as a competing risk.*

Supplemental figure 1. Overall survival in those that relapsed post-ASCT

There is a significant difference by time to relapse p <0.0001



Number at risk						
<3 months	20	0	0	0	0	0
3-6 months	10	0	0	0	0	0
6 months or more	13	8	4	2	1	1