Evaluation of the site of central nervous system (CNS) relapse in patients with Diffuse Large B-cell lymphoma (DLBCL) by the CNS risk model

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OBJECTIVES

Background

We recently validated the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) CNS prognostic model which incorporates the 5 IPI factors and kidney/adrenal involvement to stratify diffuse large B-cell lymphoma (DLBCL) patients into 3 risk groups: 0-1 factors– low risk (LR); 2-3 factors– intermediate risk (IR); and 4-6 factors– high risk (HR), with a 2 y risk of CNS relapse of ≤ 1%, ~5% and > 10%, respectively (Savage ASH 2014, 394a). However, the site of CNS relapse in these risk groups has not been reported which would help to guide the optimal strategy for CNS prophylaxis in HR patients.

We aim to evaluate the site of central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) in the CNS risk model

METHODS

Patient selection

The British Columbia Cancer Agency (BCCA) Centre for Lymphoid Cancer Database was used to identify all patients ≥ 16 yrs and diagnosed with *de novo* DLBCL, between December 2000 and August 2014, and received at least one cycle of curative intent R-CHOP.

Patients with primary mediastinal B-cell lymphoma (PMBCL), composite lymphoma, transformed lymphoma and Burkitt's lymphoma were excluded. Patients with Human Immunodeficiency Virus infection and those with central nervous system (CNS) lymphoma at the time of diagnosis were also excluded.

Baseline patient characteristics at diagnosis and at CNS relapse, including site of CNS relapse and whether it occurred in isolation or with systemic disease were recorded.

Statistics

The time to CNS relapse was calculated from the date of diagnosis to the date of CNS relapse using the Kaplan-Meier (KM) method (1 - KM) and groups compared using the log-rank test. Patient characteristics were compared using the Chi-square test

RESULTS

A total of 1852 patients were identified, including 1597 patients from the original validation cohort (Savage ASH 2014, 394a). 120 patients were excluded due to missing information. The remaining 1732 patients were analysed

Table 1. Baseline patient characteristics

	All N= 1732	Low-risk N= 519	Intermediate N= 797	High-risk N= 416	P
	n (%)	n (%)	n (%)	n (%)	
Age >60 years	1128 (65)	226 (43.5)	558 (70)	344 (82.7)	<0.01
Elevated LDH	859 (49.6)	39 (7.5)	437 (54.8)	383 (92.1)	<0.01
ECOG PS ≥2	651 (37.6)	18 (3.5)	276 (34.6)	357 (85.8)	<0.01
Stage III/IV	1009 (58.3)	62 (11.9)	543 (68.1)	404 (97.1)	<0.01
EN site ≥2	457 (26.4)	14 (2.7)	166 (20.8)	277 (66.7)	<0.01
IPI ≥3	803 (46.4%)	0 (0%)	387 (48.6%)	416 (100%)	<0.01
Kidney/adrenal involvement	71 (4.1)	0 (0)	5 (0.6)	66 (15.9)	<0.01
Testicular involvement	52 (3)	24 (4.6)	17 (2.1)	11 (2.6)	<0.03
Bone marrow involvement	146 (8.4)	2 (0.4)	67 (8.4)	77 (18.5)	<0.01

LDH = Lactate dehydrogenase, ECOG PS= Eastern cooperative oncology group performance status, EN = Extra-nodal, IPI = International prognostic index

Figure 1. Risk of CNS relapse by CNS risk groups

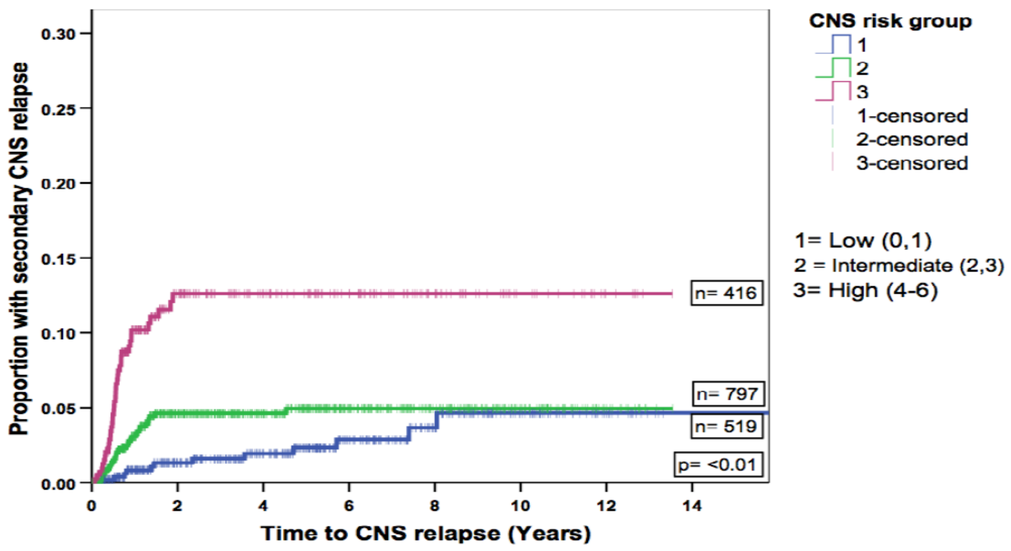


Table 2. CNS relapse characteristics

Factors	All N= 1732	Low-risk N= 519	Intermediate N= 797	High-risk N= 416	P
	n (%)	n (%)	n (%)	n (%)	
2-yr risk of CNS relapse	77 (5.3)	6 (1.3)	31 (4.6)	40 (12.6)	<0.01
Median time to CNS relapse (mos)	7.2	17.5	7.3	6.3	<0.01
Early relapse (< 1 yr from diagnosis)*	61 (72.6)	4 (33.3)	22(68.8)	35 (87.5)	<0.01
CNS prophylaxis					
All	48 (2.8)	13 (2.5)	20 (2.5)	15 (3.6)	0.07
IT chemotherapy	36 (75)	11 (84.6)	17 (85)	7 (46.7)	
HDMTx	12 (25)	2 (15.4)	3 (15)	8 (53.3%)	
Type of CNS relapse*					
Isolated	45 (53.6)	8 (66.7)	16 (50)	21 (52.5)	0.60
Concurrent systemic	39 (46.4)	4 (33.3)	16 (50)	19 (48.7)	
Site of CNS relapse*					
Parenchymal	51 (60.7)	7 (58.3)	23 (71.9)	21 (52.5)	0.06
Leptomeningeal	32 (38.1)	4 (33.3)	9 (28.1)	19 (47.5)	
Isolated leptomeningeal	22 (26.2)	3 (25)	7 (21.9)	12 (30)	
Concurrent parenchymal	10 (11.9)	1 (8.3)	2 (6.3)	7 (17.5)	
Intraocular	1 (1.2)	1 (8.3)	0 (0)	0 (0)	

*denominator = Patients with CNS relapse (n= 84), IT= Intrathecal, HDMTx= High dose methotrexate 3.5 g/m^2

Figure 2. Any parenchymal relapse according to CNS risk group

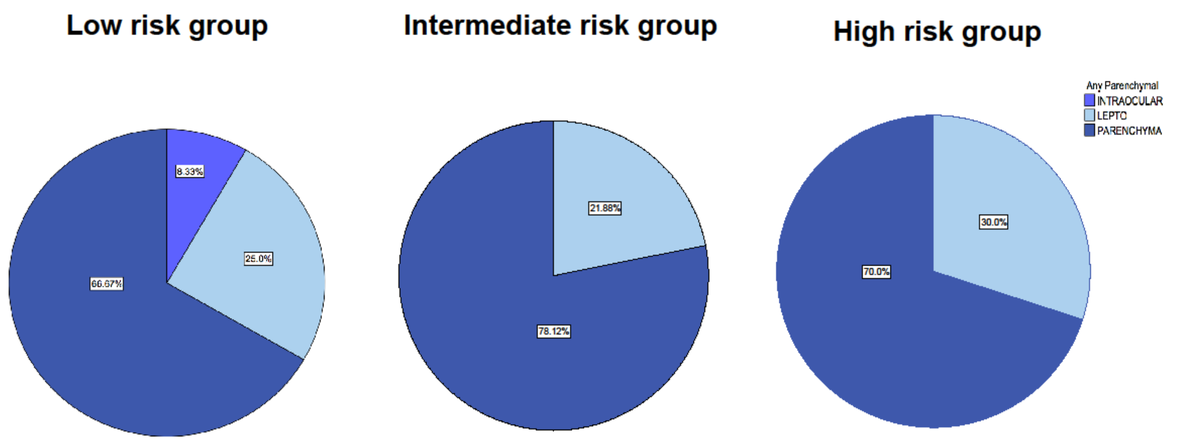
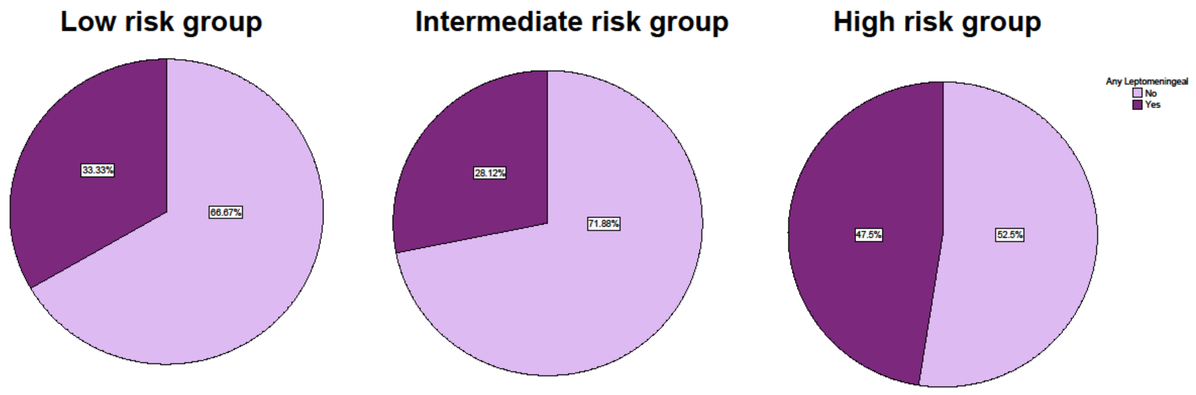


Figure 3. Any leptomeningeal relapse according to CNS risk group



CNS prophylaxis was not protective, against LM or parenchymal involvement, even in high risk groups but use was low

CONCLUSIONS

- Approximately 2/3 of CNS relapses involve the brain parenchyma, reflecting the poor CNS penetration of the R-CHOP components, including rituximab
- In the high risk group, leptomeningeal disease also frequently occurs and relapses occur early (< 6 mos), thus cerebrospinal fluid (CSF) analysis at diagnosis is warranted
- This data supports further investigation of CNS prophylaxis, particularly in high-risk groups using high dose methotrexate and other novel agents that can penetrate all CNS compartments

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TOPIC: AGGRESSIVE B-CELL LYMPHOMA

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