Anatomical Pattern of CNS Relapse in Aggressive B-Cell Lymphomas

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INTRODUCTION

- Aggressive B-cell lymphomas are heterogeneous in pathological characteristics, cell of origin, cytogenetic abnormalities and mutation profile.[1]
- The risk of CNS relapse is variable among different subtypes and is a major factor driving prognosis and survival.[2]
- There are algorithms to estimate CNS relapse risk, but the predilection and tropism for anatomical compartments in the CNS is not well understood.[3]
- The understanding of biological and molecular mechanisms for preferential homing to the anatomical compartments in the CNS can potentially help determining the best CNS prophylaxis strategy.

AIM

- The objective of this study is to evaluate the impact of cell of origin, *MYC* and *BCL2/BCL6* double/triple hit lymphoma (DHL/THL) status, BCL6 expression, and *MYD88* L265P mutation status on the anatomical pattern of CNS relapse in patients with aggressive B cell lymphomas.

METHODS

- Patients with CNS relapse of aggressive B-cell lymphoma treated at Mayo Clinic (2002-2023) were identified using Mayo Clinic Lymphoma Database and medical records.
- BCL6 expression cutoff (via IHC): ≥30% positivity in lymphoma cells.
- Cell of origin determination: Hans algorithm.
- DHL/THL status determination: FISH analysis on *MYC*, *BCL2*, and *BCL6.*
- Differential involvement of brain parenchyma vs leptomeningeal related to various biological factors was evaluated by Chi square or Fisher's exact test as appropriate.

RESULTS

- 193 patients with CNS relapse of aggressive large B-cell lymphomas were identified, with 52.3% experiencing CNS-only relapse and 47.7% experiencing concomitant CNS/systemic relapse.
- Localization of CNS relapse: 58.5% in brain parenchyma, 33.2% in leptomeningeal compartment, and 8.3% in both.
- 51 patients received CNS prophylaxis: high-dose methotrexate (n=26), intrathecal methotrexate (n=23), or both (n=2).
- BCL6 expression by IHC was significantly associated with brain parenchymal involvement (p = 0.008).
- *MYD88* L265P mutation was significantly associated with brain parenchymal involvement (p = 0.049).
- Cell of origin (Non-GCB vs GCB) was not associated with CNS relapse localization (p = 0.328).
- DHL/THL status was not associated with CNS relapse localization (p = 0.232).

Table 1. Association of biological factors with CNS relapse sites

Biological Factors		CNS Relapse Sites			P-value
		Parenchymal	Leptomeningeal	Both	
Cell of origin	Non-GCB (n=86)	53	26	7	0.328[1]
	GCB (n=82)	44	30	8	
MYC and BCL2 and/or BCL6 rearrangement	Yes (n=27)	12	13	2	0.232[1]
	No (n=99)	54	34	11	
MYD88 mutation	Yes (n=12)	11	1	0	0.049[2]
	No (n=19)	10	8	1	
BCL6 expression by IHC	Yes (n=113)	72	30	11	0.008[1]
	No (n=37)	16	19	2	

[1]Chi-Square test and [2]Fisher's Exact test

P-values calculated based on either parenchymal or leptomeningeal relapse only.

CONCLUSIONS

- Our study findings suggest that **BCL6 expression and *MYD88* L265P mutation are associated with preferential brain parenchymal relapse** while cell of origin and DHL/THL status are not associated with any preferential anatomical relapse pattern.
- Further research is necessary to identify other biological factors responsible for preferential homing of lymphoma to specific anatomical CNS compartments.
- Validated biomarkers could be important in choosing the ideal CNS prophylaxis strategy.

REFERENCES

1. Alizadeh, A. A., et al. (2000). "Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling." Nature **403**(6769): 503-511.
2. Hill, Q. A. and R. G. Owen (2006). "CNS prophylaxis in lymphoma: who to target and what therapy to use." Blood Rev **20**(6): 319-332.
3. Schmitz, N., et al. (2016). "CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP." J Clin Oncol **34**(26): 3150-3156.

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This abstract has been accepted and presented at the EHA Annual Congress 2024.