Multicenter Retrospective Analysis of Single-Route CNS prophylaxis in Aggressive B-cell Lymphomas

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Abstract

Relapses involving the central nervous system (CNS) are uncommon among patients with diffuse large B cell lymphoma (DLBCL) but carry very poor prognosis. Prophylaxis is heterogeneously prescribed around the time of frontline therapy to prevent this outcome, with no clear standard of care in terms of recipient selection or route of administration. We retrospectively evaluated 1162 adult patients across 21 US academic centers with DLBCL or similar histologies who received single-route CNS prophylaxis as part of frontline chemoimmunotherapy between 2013-2019.

Prophylaxis was administered intrathecally (IT) in 894 (77%) and using systemic high-dose methotrexate (HD-MTX) in 236 (20%); 32 patients (3%) switched route due to toxicity and were assessed separately. By CNS-International Prognostic Index (IPI), 18% were considered low-risk, 51% moderate, and 30% high. Double-hit lymphoma (DHL) was confirmed in 243 of 866 evaluable patients (21%).

Sixty-four patients (5.7 %) had CNS relapse, after median 7.1 months from diagnosis, including 15 of 64 (23%) within the first 6 months. There was no significant difference in CNS relapse between IT and HD-MTX recipients (5.4 vs 6.8%, p=0.40), including after propensity score matching to account for differences between respective recipient groups. Weighting by CNS-IPI, expected versus observed CNS relapse rates were nearly identical (5.8 vs 5.7%). Testicular involvement was associated with high risk of CNS relapse (11.3%) despite most having lower CNS-IPI scores. DHL did not significantly predict for CNS relapse after single-route prophylaxis, including with adjustment for treatment regimen and other factors.

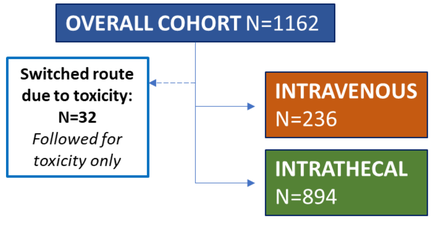
This large study of CNS prophylaxis recipients with DLBCL found no significant difference in CNS relapse rates between routes of administration. Relapse rates among high-risk subgroups remain elevated, and reconsideration of prophylaxis strategies in DLBCL is of critical need. Treatments following CNS relapse were heterogeneous, with poor outcomes for the vast majority of patients.

Background

- CNS prophylaxis is used variably in aggressive B-cell lymphomas, mostly among high-risk populations
- Whether prophylaxis modifies baseline CNS risk is unknown - no randomized study has been performed in this context
- **Major differences exist between routes of prophylaxis administration**, as well as the patient populations who receive each respective approach

Primary Objective

To compare CNS relapse rates between recipients of single-route intrathecal versus systemic prophylaxis administration



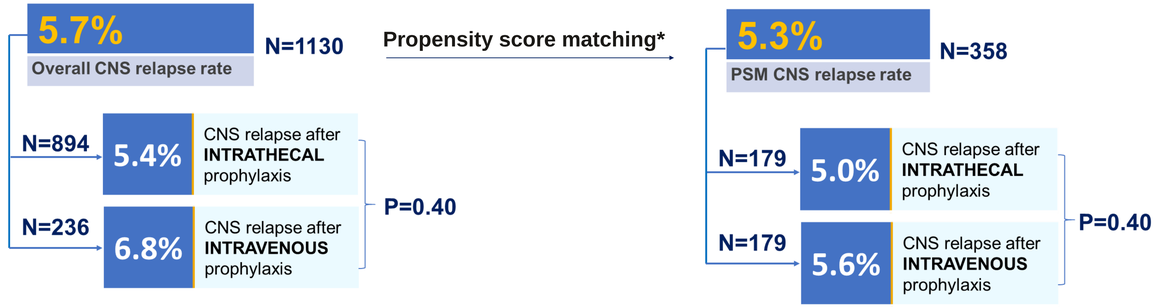
Materials & Methods

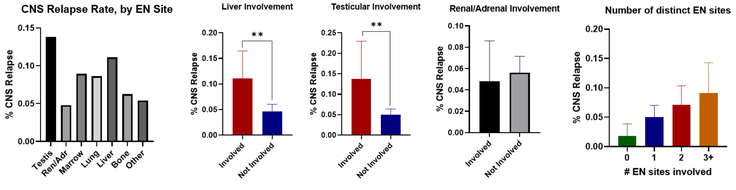
Multicenter retrospective study; IRB approved at each site
N=1162 patients, across 21 US academic institutions

Key eligibility criteria:
- DLBCL, HGBL, or transformation from non-CLL histology
- No known CNS involvement at start of therapy
- Received single-route prophylaxis as part of frontline anthracycline-based therapy

Study N, by CNS-IPI score:	Low	Moderate	High
	196	546	321
Predicted CNS relapse risk:	*0.8%*	*3.9%*	*12%*

Predicted baseline CNS relapse risk, weighted by CNS-IPI score: **5.8%**





Propensity Score Matching Covariates*:

Sex	Testis involvement
Number EN sites	DH positive
Renal/adrenal involvement	DH evaluable
B symptoms	Frontline chemo regimen
NCCN-IPI category	Age (continuous)
CNS-IPI category	

Summary

- Route of prophylaxis administration did not affect subsequent CNS relapse rates
- Outcomes were not substantially different from baseline predictions via CNS-IPI
  - ➢ These raise concern that prophylaxis by either route does not prevent CNS relapse

Discussion

- Each patient reported here received **single-route** prophylaxis. We do not have comparisons against dual-route or non-prophylaxis arms.
- Prophylaxis indications were at physician discretion and varied considerably.
- Each patient received methotrexate as primary prophylaxis (some also received IT cytarabine).
  - ➢ The role of other CNS-penetrant agents as prophylaxis remains incompletely studied.
- Other contemporary studies have highlighted similar findings for each respective route vs no prophylaxis

References

1. Single-route CNS prophylaxis for aggressive non-Hodgkin lymphomas: real-world outcomes from 21 US academic institutions. Orellana-Noia VM, et al. *Blood*. 2022 Jan 20; 139(3)413-423
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3. High-dose methotrexate is not associated with reduction in CNS relapse in patients with aggressive B-cell lymphoma. Lewis KL et al, ASH 2021. *Blood* (2021) 138 (Suppl 1): 181.

These results were first presented at the ASH 2020 Annual Meeting and published in *Blood* (PMID 34570876)