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Central nervous system prophylaxis in aggressive B-cell non-Hodgkin lymphomas

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Central nervous system prophylaxis in aggressive B-cell non-Hodgkin lymphomas

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An abstract of a thesis submitted to the

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Abstract

Central nervous system prophylaxis in aggressive B-cell non-Hodgkin lymphomas

By Victor Orellana-Noia, MD

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=0.4), 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. Development of follow-up studies and anticipated future directions for the prevention and management of CNS relapse are described.

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Table of Contents

I. Preface – The Patient

Late in my intern year, I was completing a rotation on the inpatient neurology service at Rhode Island Hospital when I admitted a patient with new-onset confusion. This was not unusual for the service – many paths lead to confusion when the brain is sick – except that he was young, within a year or two of my age, and his decline had been as rapid as it was ruthless.

Right up until a few weeks before I met him, my patient had been working full-time as an electrical engineer at a nanotechnology start-up company outside of Boston. Now he struggled even to chew his food, and would often be dribbling the pureed mush he was spoon-fed for breakfast when I came in to see him before rounds. He experienced seizures multiple times daily, losing bladder and bowel continence with most episodes. Worst of all, he barely recognized his own family sitting across from him. His wife and parents watched helplessly as their loved one gazed blankly at the walls, offering incoherent garbles on the rare occasion he could respond to their questions.

A few months earlier, this otherwise-healthy young man began a standard frontline treatment regimen for diffuse large B cell lymphoma (DLBCL), an aggressive type of non-Hodgkin lymphoma (NHL) and the most common hematologic malignancy in the United States[1]. While approximately 60% of patients with this form of cancer are considered to be cured with frontline therapy[2], my patient's experience was one of the rare individuals whose cancer recurs in the central nervous system (CNS). Like so many who find themselves in this situation, he began having signs of neurologic impairment shortly after completing his frontline chemotherapy regimen, with a subsequent MRI showing multiple areas of parenchymal brain involvement and surrounding edema. His symptoms progressed rapidly over the ensuing weeks despite salvage chemotherapy, and by the time I met him there were few remaining options.

In large part because it is so rare – affecting roughly 5% of patients with his type of lymphoma[3] – modern regimens for DLBCL do not standardly include CNS-penetrant therapies. Instead, these are generally designed to treat the systemic sites of nodal and/or extranodal (i.e., non-lymph node) disease south of the blood-brain barrier, though additional chemotherapy agents may be added depending on the patient and

regimen to help penetrate the CNS. Who receives such additions and what approach(es) may be used are not standardized, and there are many debates in the lymphoma field in this area.

This paper will focus specifically on how we administer CNS prophylaxis and its impact on CNS relapse in DLBCL and similar NHL histologies. This question is something I became interested in while taking care of my patient the engineer, whose brain and ultimately his life were stolen from him despite so many efforts to save him. Looking back, his disease started initially with testicular involvement – a well-described if uncommon risk factor for CNS relapse. He received several doses of prophylactic intrathecal chemotherapy (i.e., directly admitted into the cerebrospinal fluid via lumbar puncture) during his frontline treatment with a regimen known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Both his chemotherapy regimen and CNS prophylaxis approach were fully consistent with the standards of care for his disease, and many other lymphoma specialists would have prescribed the very same therapy. And yet that treatment still failed him, as did all the treatments that followed.

Why did they fail?

Which part of his treatment was not enough? Where could we have done something sooner to prevent such an early and devastating end to this young man's life?

In the years that followed, I learned more of the growing controversy surrounding CNS prophylaxis in DLBCL. It was disconcerting at first to learn how few data truly guided our preventive strategies in this setting, which are largely extrapolated from established practices in other blood cancers such as Burkitt lymphoma and acute lymphoblastic leukemia where CNS relapses are far more common. As I started prescribing chemotherapy during my hematology/oncology fellowship , many of my supervising attending physicians would debate whether this or that prophylactic strategy was indicated. So often it would come down to what a given attending "believed in" – some felt strongly about using intrathecal prophylaxis, others that only systemic administration would be effective. At first this was hard to rectify. I had seen these same attendings debate endlessly on the clinical trial data justifying a given therapeutic approach, yet when

it came to prophylactic chemotherapy to prevent a CNS relapse, somehow this came down to intuition more than any other factor. As I learned more, it became clear how this discrepancy was far from unique to my institution. This was how prophylaxis was applied, where the limited data we had were easily bent to fit a given provider's approach, rather than used to guide more consistent and effective practice across the field.

John Wennberg, whose public health research founded the Dartmouth Atlas, once wrote that "unwarranted variation is a ubiquitous feature in US healthcare." While much of his own work centered around economic incentives and patient decision-making, he and countless others have argued that strong practice-informing data are always the first foundational step in seeking to improve healthcare delivery. Coming into this project, CNS prophylaxis in DLBCL was a clear example of unwarranted variation, borne largely out of incomplete data to guide our approach to these high-risk patients. The work described below is my own attempt to rectify that need, and with it to determine how best to treat the next patient in front of me.

II. Introduction

As noted above, CNS relapse in DLBCL occurs in approximately 5% of patients overall and carries a median overall survival (OS) of only 3-7 months[3,4]. This dreaded complication historically occurs within months of initial DLBCL diagnosis, prompting the use of CNS-directed prophylaxis with frontline therapy in select patients[5,6]. Compared to Burkitt lymphoma, where CNS risk is higher and prophylaxis is considered standard practice[7,8], allocation of CNS prophylaxis in DLBCL is generally reserved for patients with high-risk features[9]. These may include involvement of specific extranodal (EN) sites, such as kidneys, adrenal glands, or testes; molecular features, such as double-hit (DH) status; or a combination thereof. Which factor(s) may be used to justify CNS prophylaxis commonly varies across providers and institutions[10], and there is no clear standard of care in terms of which patients should or should not receive prophylaxis or by which route(s) this should be administered.

Consensus guidelines commonly recommend using the CNS-International Prognostic Index (CNS-IPI) to help guide prophylaxis use[6,11]. This scoring system is validated for CNS relapse risk estimation and allocates one point each for conventional IPI risk factors as well as renal/adrenal EN involvement, where a

score of ≥4 points is associated with a CNS relapse risk of 12% or greater[12]. Prophylaxis was utilized in only a small subset of included patients for both initial and subsequent validation studies of the CNS-IPI and was not standardized across the respective cohorts. Additionally, disease features not included in the CNS-IPI such as double-hit status or testicular involvement may affect the ability of this model to accurately discriminate "low-risk" patients. Thus, it remains unknown whether prophylaxis modifies CNS relapse risk across settings where it is commonly prescribed, and substantial differences exist between routes of administration which may further impact this.

Most modern regimens utilize methotrexate (MTX) by either intrathecal (IT) or via high-dose (HD) systemic administration, the latter typically defined as doses of ≥3g/m^2 for adequate CNS penetration[13]. Differences between routes of administration include greater parenchymal penetration with HD-MTX at the cost of greater hematologic, renal, and other toxicities, versus more restricted distribution with IT administration but generally fewer toxicities or related delays in backbone therapy. Additionally, HD-MTX administration requires specialized monitoring and expertise which are not commonly available in community centers. While these distinctions may result in different patient subgroups receiving a given administration route, the relative efficacies of single-route IT versus HD-MTX have not been compared head-to-head in the context of modern regimens beyond single-center analyses. Finally, CNS relapses in DLBCL more frequently present with parenchymal CNS involvement[4], often centering around blood vessels as reflects the intrinsic hematologic spread of lymphomas, though it is unclear whether this finding due to selection bias from greater use of IT prophylaxis or to biologic mechanisms inherent to the underlying disease process.

Given these uncertainties, we developed a multi-center retrospective cohort study of patients with aggressive B-cell non-Hodgkin lymphomas (NHL) across 21 US cancer centers who received single-route CNS prophylaxis. This study design was selected based on the low event rates commonly seen with CNS relapse, the heterogeneous variations in clinical practice regarding CNS prophylaxis route (requiring broad geographic sampling), and the prohibitive costs in terms of funding, personnel, and time that would be

required with prospective evaluation. We collected detailed clinical and outcomes data with the principal aim of comparing CNS relapse rate across prophylaxis routes, hypothesizing that HD-MTX would result in fewer CNS relapses (based on its enhanced parenchymal penetration) at the expense of added toxicity.

III. Methods

Eligible patients were adults (age ≥18) with DLBCL, high-grade B cell lymphoma (HGBL), or transformation to either histology from an indolent B-NHL who received frontline chemoimmunotherapy plus single-route CNS prophylaxis between 2013-2019. This interval was chosen based on more widespread adoption of HD-MTX for primary prophylaxis following retrospective data published by Abramson et al[13] and to allow sufficient time for maturity of survival data. Of note, standard frontline chemoimmunotherapy regimens were relatively stable over this time period, with NCCN guidelines generally recommending either RCHOP (majority of patients) or REPOCH regimens (primarily for double hit, primary mediastinal, and HIV-associated large B cell lymphomas)[11].

Burkitt lymphoma and transformations from underlying chronic lymphocytic leukemia were excluded; the former because of its high CNS relapse rate and more standardized considerations of CNS prophylaxis and the latter because current standard of care is to consider consolidative allogeneic stem cell transplantation once CR is achieved (this is not the case of transformations from other indolent NHL histologies).

This study was approved by the institutional review board at each of the 21 participating centers. Of the 1277 cases originally identified, 115 were excluded, due to: planned receipt of dual-route prophylaxis (n=35), CNS involvement prior to frontline therapy (n=15), ineligible NHL histology (n=8), or incomplete clinical information (n=59). Patients who underwent initial diagnostic lumbar puncture (LP) with IT prophylaxis followed exclusively by prophylactic HD-MTX (n=15) were included and analyzed as HD-MTX recipients. Those who switched prophylaxis route due to intolerance (n=32) were assessed for toxicity but excluded from the primary analysis.

Variables and Endpoints

Lactate dehydrogenase (LDH) was reported according to institutional reference ranges. Performance status (PS) was standardized according to the Eastern Cooperative Oncology Group (ECOG) scale. CNS-IPI and National Comprehensive Cancer Network (NCCN)-IPI[14] scores were extrapolated for each patient based on available clinical data; those with missing data who still met criteria for high risk (e.g., missing LDH value but with a CNS-IPI already scoring 4 or greater) were included in the respective analyses, whereas those with incomplete data that may affect their classification were excluded.

Double-hit (DH) lymphoma was defined according to fluorescence in-situ hybridization (FISH) as genetic rearrangements involving *Myc* as well as *BCL2* and/or *BCL6*. DH evaluability included patients with confirmed DH or those with known testing of *Myc, BCL2,* and *BCL6* irrespective of results (i.e., not all patients underwent requisite FISH testing to evaluate for DH). Cell-of-origin (COO) was assessed locally by immunohistochemistry (IHC) using the Hans criteria[15]; gene expression profiling data (the gold standard for COO determination[15]) were not collected as this is not routinely performed in standard clinical settings. The primary endpoint was CNS relapse, defined as new involvement of the brain, cranial nerves, leptomeninges, CSF, and/or spinal cord after initiation of frontline therapy, confirmed either histologically or by irrefutable radiographic findings. Progression free survival (PFS) was defined as time from diagnosis to disease progression/recurrence, death, or last follow-up. OS was defined as time from diagnosis to death or last follow-up. Using null rate of 12% baseline CNS relapse risk based on CNS-IPI and alternative rate of 5% for the DLBCL population at large (i.e., hypothesizing prophylactic HD-MTX would normalize risk, but IT would not), we estimated 749 patients per arm would be required to achieve 80% power at a two-sided alpha of 0.05.

Statistical methods

Categorical data were analyzed using multiple techniques, including Chi-square, Fisher exact tests (when $n<5$ in any given subgroup), and logistic regression modeling. Continuous data were assessed using two-

sample T-tests given approximately normal distribution on graphical representation. Variables found to be significant on univariate analyses were included in multivariate comparisons. Kaplan-Meier estimates and log-rank tests were used for time-to-event analyses. Competing risk analyses were performed according to the Fine-Gray method[16], assessing CNS relapse and death as competing events; as those experiencing non-CNS relapse were still at risk for subsequent CNS involvement, this was not considered a competing event.

To minimize selection bias from baseline characteristics between prophylaxis routes (**Table 1**; see below), traditional propensity score matching (PSM) was performed using 1:1 matching without replacement via a greedy 5:1 digit match algorithm[17]. After matching, the group balance was evaluated using standardized differences, with values <0.1 considered negligible[18]. IV versus IT prophylaxis recipients were compared using McNemar's test for paired proportions, with 179 patients for each respective route being successfully matched. Nine of the 11 baseline characteristics were well balanced, with standardized differences <0.1 (**Table 2**). Two variables – B symptoms and chemotherapy regimen – had slight imbalance (standardized difference between 0.1-0.2). All analyses were performed in SAS 9.4 (SAS institute, Cary NC), with associations considered to be significant at a two-sided P value < 0.05.

IV. Results

Patient characteristics

Among 1162 eligible patients, median age was 62 (range 18-86), 60% were male, and 75% had ECOG PS 0-1; 79% had advanced stage (III/IV) at diagnosis and 37% had B symptoms. Serum LDH was elevated in 66% (n=767), including 20% (n=151) at ≥ 3 times upper limit of normal (ULN). Most patients (n=782, 67%) had DLBCL; 305 (26%) had HGBL, of whom 243 (80%) had confirmed double-hit lymphoma (DHL), and 67 (5.8%) had aggressive transformation from either follicular lymphoma (n=59) or other non-CLL indolent histologies (n=8). At least one EN site was documented in 972 patients (83.6%); notable sites included renal / adrenal (12%), bone marrow (11%), sinus (7.4%), and testis (6.2%); 449 patients (39%) had ≥2 distinct EN sites.

In terms of frontline regimen, 536 (47.5%) received RCHOP, 509 (45.1%) received R-EPOCH, and 85 (7.4%) received other regimens. In those with DHL, 209 of 243 (86%) received R-EPOCH, 15 (6.2%) R-CHOP, and 19 (7.8%) other regimens. As most patients had advanced stage disease, median number of chemoimmunotherapy cycles overall was 6; those with limited stage disease had a median of 4 cycles. There was no significant difference in number of cycles by chemotherapy regimen (median of 6 cycles each for RCHOP and REPOCH, p=0.24), including when adjusting for stage or DH status.

In total, 894 (77%) received IT prophylaxis and 236 (20%) received HD-MTX; 32 (2.8%) changed approaches due to toxicity and are assessed below for toxicity only. **Table 1** lists baseline characteristics among single-route prophylaxis recipients.

Overall prognosis by NCCN-IPI was estimated as: low (0-1; n=12, 1.0%), low-intermediate (2-3; n=198, 18%), high-intermediate (4-5; n=495, 43%), or high (≥6; n=302, 30%); 155 (13%) had incomplete NCCN-IPI data. Baseline CNS relapse risk by CNS-IPI was estimated as: low (0-1; n=196, 18%), moderate (2-3; n=546, 51%), or high (≥4; n=321, 30%); 67 (5.9%) had incomplete CNS-IPI data. Using published risk predictions of 0.8, 3.9, and 12% by respective CNS-IPI category[12], the weighted CNS relapse risk for the study population at large was estimated at 5.8%.

Prophylaxis allocation

All patients received methotrexate, with 121 of 894 IT recipients (13.5%) also receiving cytarabine. No other prophylactic agents were reported. HD-MTX was most commonly dosed at 3.5 g/m2 (n=176, 75.5%), with 17 (7.3%) receiving less than 3 g/m2 (range 2.0 -2.75 g/m2) due to baseline renal dysfunction and 4 (1.6%) receiving doses of 4 g/m2 or greater. There were no documented CNS relapses among patients who required dose reduction below 3 g/m2.

Median number of prophylaxis doses was 4 for IT administration (IQR 3-5) and 3 for HD-MTX (IQR 2-4); number of IT prophylaxis doses did not vary by whether patients received MTX monotherapy or MTX plus cytarabine. Delayed initiation of prophylaxis by either route until after completion of all planned

chemotherapy cycles occurred in 130 patients (12%), more commonly among HD-MTX recipients (n=86 vs 44, p<0.0001). Of those receiving delayed IT prophylaxis, 41 of 44 (93%) received MTX monotherapy.

Compared to HD-MTX, IT recipients had a higher proportion with age ≥70 (26 vs 18%, p=0.006), baseline renal impairment (17.8 vs 13.1%, p=0.10), and/or R-EPOCH chemoimmunotherapy backbone (87 vs 13%, p<0.0001). Patients with DHL were also more likely to receive IT prophylaxis (90 vs 10%, P<0.0001), reflecting more frequent R-EPOCH use in this subgroup. In contrast, HD-MTX recipients had higher proportions with testicular involvement (11 vs 4.9%, p=0.001) and increased (≥2 sites) total EN burden (48 vs 34%, p<0.0001).

PATIENT OUTCOMES

With a median follow-up of 2.4 years, median PFS and OS have not been reached; 2-year PFS was 71% and 2-year OS was 82%. Sixty-four (5.7%) of 1130 single-route prophylaxis recipients had CNS relapse after frontline therapy. Anatomic site was documented in 53 of 64 CNS relapses, of which 22 were leptomeningeal only, 29 were parenchymal (including 11 with concurrent leptomeningeal involvement), and 2 involved other CNS sites (ocular, spinal cord; n=1 each). With low numbers in each respective subcategory, there was no significant difference in neuroanatomic site(s) of relapse by prophylaxis route (data not shown).

Differences in CNS relapse by baseline risk factors are listed in **Table 3**. By CNS-IPI category, incidence was 5.1% with low risk, 3.8% with moderate risk, and 8.4% with high-risk (overall significance p=0.02). **Figure 1** shows cumulative incidence of CNS relapse according to CNS-IPI and NCCN-IPI scores. Testicular involvement (n=69) occurred predominantly among patients with low (n=29, 42%) or moderate CNS-IPI (n=25, 36%), with 8 (12%) total and 6 (11%) otherwise low to moderate risk patients having CNS relapse after single-route prophylaxis. Excluding patients with testicular involvement from CNS-IPI risk groups, the adjusted CNS relapse rates for low (n=167), moderate (n=521), and high risk (n=306) were 3.6%, 3.7%, and 8.2%, respectively and 5.0% overall. Renal / adrenal involvement (n=133), a component

of the CNS-IPI, was not independently associated with CNS relapse following single-route prophylaxis (OR 1.08, 95% CI 0.50-2.31; p=0.85), though increasing number of EN sites overall was associated with stepwise increase in CNS relapse risk with each successive site (**Figure 2**). In terms of chemoimmunotherapy regimens, CNS relapse rates did not significantly differ between recipients of RCHOP versus REPOCH (OR 1.25, 95% CI 0.51-3.10; p=0.74), including when adjusting for DH status and CNS-IPI (data not shown).

Cell of origin (COO) by IHC was reported in 656 of 782 patients with DLBCL. Of these 656 patients, 32 (4.9%) experienced CNS relapse, more frequently among patients who did not demonstrate germinal center (GCB) origin (6.7 vs 3.2%, p=0.04). Incorporating IHC-based COO estimations into the CNS-IPI as previously reported by Klanova et al.[19], 217 of 656 (33%) were identified as low risk, 303 (46%) moderate risk, and 101 (15%) high risk; 35 (5.3%) had incomplete CNS-IPI data. Ten of 101 high-risk patients (9.9%) experienced CNS relapse, versus a rate of 15% previously reported for high-risk patients under this framework based on gene expression profiling.

CNS relapse by prophylaxis route

There was no significant difference in CNS relapse rates by prophylaxis route: 48 (5.4%) IT versus 16 (6.8%) HD-MTX (OR 1.28, 95% CI 0.71-2.30; p=0.40). This finding persisted when adjusting for differences in number of prophylaxis doses received and backbone chemotherapy regimen (adjusted OR 1.38, 95% CI 0.74-2.57; p=0.31). In terms of prophylactic agent, there was no significant difference between recipients of IT MTX monotherapy versus those receiving IT MTX plus cytarabine (OR 0.91, 95% CI 0.38-2.18; p=0.61), and there remained no difference between routes when comparing HD-MTX versus either respective IT approach (data not shown).

Two hundred twenty-five (20%) patients died during the study period (n=194 IT vs 32 HD-MTX), including 45 following CNS relapse (n=36 IT vs 9 HD-MTX). A competing risk analysis was performed with death as a competing event to CNS relapse **(Figure 3)**, which continued to find no difference between prophylaxis

routes. In terms of dose timing, there was no significant difference in CNS relapse following intercalated versus delayed administration overall (OR 0.79, 95% CI 0.38-1.63; p=0.52) or when adjusted for route of administration (adjusted OR 0.87, 95% CI 0.39-1.95, p=0.74). This may under-report CNS relapses following delayed prophylaxis, as any patient who was intended to receive the latter approach but who experienced CNS relapse before completing their definitive chemotherapy regimen (and thus never having received prophylaxis) would not have met eligibility criteria for this study.

Among 358 PS-matched patients (n=179 per arm; **Table 4**), there were 19 CNS relapses (5.3%), with no difference between prophylaxis routes (5.0% IT vs 5.6% HD-MTX, p=0.81). There remained no significant difference in CNS relapse among matched patients by prophylaxis route when stratified across CNS-IPI and NCCN-IPI categories, nor did DH status appear to be predictive of CNS relapse in this setting.

Timing of CNS relapse

Median time to CNS relapse overall was 7.8 months (IQR 6.1-10.4 months) and was inversely proportional to risk according to CNS-IPI: 7.0 months (high) versus 8.8 months (moderate) versus 9.8 months (low). Timing did not significantly differ across routes: 7.5 months after IT versus 9.5 months after HD-MTX (p=0.86). Fifteen of 64 CNS relapses (23%) occurred 6 months or less from diagnosis, with non-significant trend towards more events among IT recipients (n=13 vs 2, p=0.23). Excluding these early events, CNS relapses remained similar across prophylaxis routes: n=35 (IT) vs 14 (HD-MTX) (p=0.21). **Figure 4** depicts CNS relapse timing, anatomic location, and subsequent overall survival by prophylaxis route; further subgroup analyses were not performed due to low numbers in each respective category.

Prophylaxis-related toxicities

Clinically significant prophylaxis-related toxicity was reported in 134 patients (12%), including 32 (2.8% of total) who switched prophylaxis route due to toxicity. Toxicities overall were more commonly reported among recipients of HD-MTX versus IT prophylaxis (25.4 vs 6%, p<0.0001); individual toxicities by prophylaxis route are listed in **Table 5**. Common events included renal impairment (n=47) primarily after

HD-MTX, delayed MTX clearance (n=27), and post-LP headache (n=18). Low grade mucositis was not captured, though severe mucosal toxicity was reported in 9 HD-MTX recipients and 6 IT recipients. Hematologic toxicities related to prophylaxis were uncommon with either route and resulted in only one patient changing from HD-MTX to IT prophylaxis. Delays in subsequent chemotherapy due to prophylaxis-related toxicity were noted in 37 patients, of whom 34 received HD-MTX and 5 ultimately switched to IT administration due to toxicity. Renal impairment due to HD-MTX was the most commonly cited reason for switching prophylaxis routes (n=8), followed by difficulty with methotrexate clearance (n=6). No patients received glucarpidase during the study period.

Among the 32 patients who switched route due to toxicity, 30 initially started prophylaxis with HD-MTX. Seventeen of 32 (53%) received R-CHOP and 15 (47%) received R-EPOCH; among the latter, 7 had confirmed DHL. One of 32 (3.1%) experienced CNS relapse, after receiving one dose of HD-MTX at $3.5g/m^2$ and the remainder of prophylaxis via IT MTX monotherapy.

V. Discussion

This study represents one of the largest analyses of CNS prophylaxis recipients with DLBCL in the rituximab era. We identified no significant difference in rate of CNS relapse between routes of prophylaxis administration, using multiple techniques to account for variation in patient eligibility for a given route. Incidence of CNS relapse following single-route prophylaxis varied across numerous clinical and pathologic factors, suggesting heterogeneous benefit and/or baseline predisposing risk.

Features correlating with increased CNS relapse risk despite prophylaxis included testicular involvement, non-GCB subtype DLBCL, and high total burden of EN disease. Conversely, DHL did not appear a major risk factor for increased CNS relapse after single-route prophylaxis, nor did single-site involvement of other conventional high-risk EN sites such as kidneys / adrenals, sinus, or bone marrow. Whether this represents a true preventive benefit following prophylaxis is unclear without a non-prophylaxis comparator. However, despite much higher prophylaxis use in our study population versus cohorts used in the development and validation of the CNS-IPI, CNS relapse rates overall were very similar to these historical benchmarks,

raising the question of whether CNS prophylaxis provided meaningful protection against CNS relapse across settings.

While it has remained common practice until recently, no study to date has clearly demonstrated the utility of CNS prophylaxis for DLBCL patients in the rituximab era, nor has a definitive comparison of prophylaxis route been performed in this context. While recent data are limited regarding IT administration, Eyre and colleagues found that patients over age 70 had similar rates of CNS relapse with or without administration and that IT recipients experienced higher rates of infections warranting inpatient hospitalization during therapy[20]. Similarly, a recent meta-analysis by this same group did not identify a significant decrease in CNS relapse following IT prophylaxis for any of the individual clinical trials included in the study, though analyses of pooled individual patient-level data were not reported[21]. Prior reporting of SWOG 8516, which at the time established CHOP as the standard chemotherapy backbone in DLBCL, likewise found no significant difference in CNS relapse with or without IT prophylaxis, though its use was restricted to patients with bone marrow involvement and results predated the use of rituximab[5].

For HD-MTX, a recent Canadian analysis evaluated the Alberta health system's recommendation for HD-MTX as the preferred prophylactic agent in high-risk DLBCL, defined as CNS-IPI ≥4, DHL, or testicular lymphoma[22]. Incompletely adopted, 35.3% of the 906 patients identified as high-risk between 2012-2019 received prophylaxis, with no significant difference after HD-MTX in CNS relapses in general or by CNS-IPI category. Data were presented at ASH 2021 from a subsequent international retrospective effort which was underway at the same time as our group's study and compared HD-MTX against a prophylaxis-free comparator arm. Lewis et al. evaluated a cohort of 2300 patients across Australia, Europe, and North America with at least one risk factor for CNS relapse (CNS-IPI high, DHL, testicular or breast EN involvement); 410 received HD-MTX (n=145 with concurrent IT prophylaxis), 435 received standalone IT prophylaxis, and the remainder did not receive prophylaxis by either route[23]. The authors found no difference in CNS event rates or CNS-specific 5-year survival with versus without prophylactic HD-MTX,

nor were the findings changed when restricting analyses to patients who achieved CR to frontline therapy or when accounting for concurrent IT MTX. The manuscript for the latter study has not yet been published.

Our data provide a key contribution to the lymphoma literature and to the treatment paradigm for future DLBCL patients, noting that route of prophylaxis does not appear to meaningfully impact the ability to prevent CNS relapse in DLBCL. This is especially important in contexts such as DHL, where escalation beyond R-CHOP is the de facto standard of care and our data show no added benefit to using HD-MTX over IT prophylaxis. Additionally, studies seeking to build upon the RCHOP backbone commonly demonstrate greater rates of hematologic toxicities with the addition of various novel agents – a complication which is also well-described using HD-MTX if perhaps under-reported in this particular retrospective study. Many clinical trials in DLBCL will permit prophylactic intrathecal MTX at investigator discretion, including the recent POLARIX study which demonstrated superior PFS following polatuzumab vedotin (Pola) plus R-CHP over conventional R-CHOP and has established the former as a new standard of care in DLBCL for most patients[24]. Congruently, Pola-R-CHP recipients experienced slightly higher rates of cytopenias as well as neutropenic fever compared to RCHOP recipients, and the use of prophylactic HD-MTX was not permitted on study. It is worth noting, especially in context of recent data, that such hematologic and infectious complications would likely increase if Pola-R-CHP were combined with HD-MTX, without clear benefit in terms of CNS relapse prevention or overall disease control. In fact, whether either route provides protection against CNS relapse in DLBCL has gathered growing skepticism, and the absence of prospective clinical trials to address this question is increasingly apparent.

We do not consider data from this study by itself as sufficient to forego the use of CNS prophylaxis in DLBCL altogether, chiefly because each patient received some form of CNS prophylaxis based on study design. Additional retrospective data have been reported which further question each respective route against a non-prophylaxis comparator, and given the scale and complexity needed to investigate a rare and heterogeneous outcome such as CNS relapse, further study to compare routes of methotrexate administration is likely of diminishing benefit compared to that of other key advances in this space.

Notable among these, emerging CNS-penetrant agents in lymphoma such as lenalidomide and ibrutinib may represent future alternatives to methotrexate as prophylactic agents. These agents have established single-agent activity in primary CNS lymphomas, where recurrent mutations in *MyD88* and *CD79b* have been previously described and appear to be present in at least a subset of patients with CNS relapse after initial systemic presentation[25,26]. These mutations are also notably more frequent in testicular lymphomas and thus may represent a particular phenotype of aggressive NHL with propensity for sanctuary site involvement. Additional study is needed to determine whether these mutations are ultimately predictive of CNS relapse and/or response to targeted agents in larger DLBCL cohorts, both upfront and at time of relapse. Furthermore, how these molecular features and the role of CNS prophylaxis in general interplay with the evolving classifications of DLBCL[27,28] remain to be seen, especially as more tailored treatment paradigms emerge that reflect the biologic heterogeneity of this disease.

Study limitations

Our study has several important limitations, including those intrinsic to its retrospective design. Eligibility was restricted to recipients of single-route prophylaxis, which was heavily skewed towards IT administration and showed imbalances across several key clinical features reflective of clinical practice which affected certain subgroup analyses. Propensity score matching was performed to address those potential confounders which were measured and collected. Despite the large sample size, our comparison of IT and HD-MTX was underpowered for the small number of CNS relapse events observed and the relative imbalances in their respective utilization. Use of dual-route prophylaxis was not assessed, nor was a prophylaxis-free comparator arm. COO was estimated by IHC, which incompletely captures activated B cell subtype DLBCL by gene expression profiling[15] as was utilized in the COO integration to CNS-IPI scores reported by Klanova and colleagues[19]. Given the large number of patients per site, we were unable to collect data points requiring more extensive review of pathology reports, such as double expressor[29] and Epstein-Barr viral status, or additional treatment details such chemotherapy dose levels. While upfront CNS involvement was noted in 15 patients who were excluded on this basis, the incidence of pre-treatment CSF screening more broadly was not routinely captured. Few prophylaxis-related toxicities were reported, which

may be underestimated due to incomplete documentation and/or collection. Community affiliates of each respective site were included, though our findings are likely under-representative of practice outside academic centers.

VI. Development of subsequent studies in CNS prophylaxis

In the months following our abstract presentation and subsequent manuscript publication[30], the lymphoma field has continued to debate the current practice patterns regarding CNS prophylaxis and whether prophylaxis is truly effective. Chief among the known limitations in my own work is the lack of a prophylaxis-free comparator arm. Following its reception at the 2020 ASH annual meeting, I immediately began efforts to develop such an expansion in my own retrospective work.

One important challenge in designing a study in this context is the heterogeneity of CNS prophylaxis use across the broader context of DLBCL therapy overall. If 10-20% of DLBCL patients receive prophylaxis around the time of frontline therapy, screening for eligible patients among a given center's registry – even among those with a limited range of high-risk features – becomes a complex, burdensome, and potentially error-prone task. To help mitigate these concerns, starting around October 2020 I began approaching collaborating centers with established lymphoma patient databases that would include the vast majority of DLBCL patients seen at the respective centers. Automated screening using patient-level criteria (e.g., CNS-IPI score) is generally feasible in such settings and would allow for much larger volumes of retrospective data to be collected with limited workload per site.

By January 2021, I had identified 6 sites in addition to Emory who were interested in participating and had sufficient resources to contribute the level of data required for adequate statistical comparison. I began approaching international colleagues in Canada and the UK, only to learn that an ongoing international effort was ongoing that aimed to compare HD-MTX versus a non-prophylaxis comparator (i.e., Lewis et al, ASH 2021). While my study design would be appreciably different and would benefit from the depth of analyses already reported among CNS prophylaxis recipients, we ultimately abandoned the task of coordinating a retrospective comparison in favor of developing a prospective clinical trial.

Prospective study proposal: lenalidomide-based CNS prophylaxis

Two recent randomized studies evaluated the use of lenalidomide (Revlimid®) plus R-CHOP ("R2-CHOP") compared to RCHOP alone[31,32]. Preliminary reporting suggested a decrease in CNS relapses among R2-CHOP recipients[33], though each respective trial ultimately failed to demonstrate a difference in this regard – again with the limitation of being underpowered for rare CNS events. While a comprehensive comparison of differences between the two randomized studies is beyond the scope of this paper, it is worth noting that each trial utilized a different lenalidomide dosing strategy, where the schedule used in the phase II ECOG 1412 study demonstrated superior efficacy against RCHOP with less hematologic toxicity on cross-trial comparison to that utilized in the industry-sponsored phase III ROBUST study.

Questioning whether a lenalidomide-based approach could overcome the questionable efficacy of MTX-based prophylaxis, in January 2021 I proposed a three-arm randomized phase III study to the ECOG lymphoma committee using the ECOG 1412 R2-CHOP lenalidomide dosing strategy. In this study design (**Figure 5**), enrollment would include DLBCL patients with one or more of the following high-risk features: CNS-IPI high, DHL, or testicular EN involvement. Following screening for occult CNS disease using MRI brain and expanded CSF testing, participants would be randomized 1:1:1 to either lenalidomide, methotrexate (via single administration route, per physician discretion), or no prophylaxis in addition to frontline therapy. Key stratification variables would include select CNS risk factor(s), NCCN-IPI, age (over/under 65 years), and frontline treatment regimen. We hypothesized the following:

1) *No difference* in CNS relapse between prophylactic MTX versus no prophylaxis
2) *Lower CNS relapse* using prophylactic lenalidomide versus either alternative strategy

Power calculations were based on estimates of 12% without prophylaxis based on initial reporting using CNS-IPI high risk, versus 8.2% with MTX-based prophylaxis based on our data noted above, versus a reduction to 5% (i.e., normalization to baseline DLBCL population) with lenalidomide. Setting a two-sided alpha=0.05, we estimated a sample size of 248 per arm would achieve 80% power to detect a decrease in CNS relapse with a lenalidomide-based prophylactic strategy versus no prophylaxis.

I presented this study concept prior to the publication of our retrospective study's primary manuscript, and at the time there was reluctance to pursue a large phase III study without that component. In the months to follow and with the publication of both manuscripts for the above-mentioned randomized studies using lenalidomide in frontline DLBCL, the prior enthusiasm of evaluating lenalidomide as a replacement for prophylactic methotrexate waned substantially. Instead, the conversation nationally was more of increasing skepticism of CNS prophylaxis in DLBCL more broadly. Even following our abstract presentation at ASH 2020, many centers by this point had already eliminated methotrexate-based prophylaxis from standard consideration even among the majority of conventionally defined high-risk patients, despite the limitation that our study did not include a prophylaxis-free comparator arm.

Prospective study proposal: prophylaxis versus no prophylaxis

As debates around CNS prophylaxis continued to evolve, I revisited the possibility of a randomized phase III study with the ECOG lymphoma committee chair, Dr. Brad Kahl. After reviewing several possible trial designs, I developed a second formal proposal which would randomize patients 1:1 to receive either methotrexate-based prophylaxis (via either route of administration) versus no prophylaxis (**Figure 6**). Similar to the first study proposal, enrollment would be restricted to those with at least one risk factor (CNS-IPI high, DHL, and/or testicular lymphoma).

In order to be more permissive of the expanding list of frontline clinical trials in DLBCL, this study would mirror other key examples in the National Cancer Institute cooperative group setting to function as a secondary protocol to any concurrent investigational or standard-of-care frontline therapy (provided no additional CNS-penetrating agent were prescribed), as opposed to the more prescriptive approach used in my previous lenalidomide prophylaxis concept. This distinction would allow for non-competitive enrollment across multiple frontline studies in DLBCL – for example, a patient could enroll on one study for backbone definitive therapy and on this study for CNS prophylaxis – and may help overcome key barriers in terms of required sample size.

Moving beyond CNS prophylaxis – at least for now

In the editorial accompanying our manuscript in *Blood*, Norbert Schmitz (lead author of the CNS-IPI) noted that while casting substantial doubt on our current practices with regards to CNS prophylaxis, "the retrospective nature of this and other studies does not definitely exclude that the results were influenced by known and unknown confounding factors." [34] Though so commonly called for on this issue, a randomized phase III clinical trial was ultimately considered too logistically challenging to compete with the other trial priorities at the cooperative group level. While other potential avenues remain open to pursuing such a trial, each presents additional barriers in terms of funding and feasibility. Meanwhile, many of the inherent uncertainties around prophylaxis route are likely to be reframed as our standard therapies across frontline and relapsed DLBCL continue to evolve.

One key motivation for prophylaxis, despite its questionable efficacy, has been the continued dismal prognosis in the uncommon patients who experience CNS relapse. While modern chemotherapy regimens have thus far been underwhelming in the latter context, emerging targeted and cellular therapies such as chimeric antigen receptor (CAR) T-cell therapy may offer some hope of improving the outcomes for these patients[35,36]. Additionally, early data using circulating tumor DNA suggest that more sensitive detection methods may allow us to diagnose CNS involvement earlier in the disease course and thus intervene sooner[37,38]. These and other critical advances (including Pola-R-CHP as the new frontline standard of care) are expected to reshape the treatment landscape in DLBCL over the coming years, including in the diagnosis, treatment, and prevention of CNS relapse. Whether it remains such a dreaded complication will depend entirely on how we can leverage these findings to address such a critical unmet need.

VII. Conclusions

This real-world analysis found no difference between IT and HD-MTX in preventing CNS relapse in DLBCL. Relapse rates among high-risk subgroups remain elevated; reconsideration of prophylaxis strategies in DLBCL and of treatment paradigms to improve the dismal outcomes following CNS relapse are of critical need. Future studies should focus less on route of methotrexate administration in favor of how to further leverage understanding of molecular disease features in early detection and risk stratification, as well as the role of more biologically directed therapies in DLBCL across settings.

VIII. Tables and Figures

Table 1. Demographics and baseline clinical features of single-route prophylaxis recipients

Characteristic	Overall (n=1130)		Intrathecal (IT) (n=894)		Intravenous (IV) (n=236)		P-value
Male sex - no. (%)	666	(58.9)	540	(60.4)	126	(53.4)	0.051
Median age - yr (range)	62	(18-86)	62	(18-86)	60	(20-82)	0.02
Less than 70 - no.(%)	852	(75.4)	658	(73.6)	194	(82.2)	Ref
70 and older - no.(%)	278	(24.6)	236	(26.4)	42	(17.8)	0.007
ECOG PS 0-1 - no.(%)	844	(80.8)	669	(80.1)	175	(83.7)	0.24
Baseline renal impairment - no. (%)	172	(16.8)	144	(17.8)	28	(13.1)	0.1
B symptoms - no. (%)	415	(38.3)	314	(36.6)	101	(44.7)	0.03
Serum LDH							
Not elevated	339	(31.3)	262	(30.5)	77	(34.4)	Ref
Elevated, <3x ULN	598	(55.2)	480	(55.8)	118	(52.7)	0.58
Elevated, ≥3x ULN	147	(13.6)	118	(13.7)	29	(13.0)	0.69
Missing / unknown	46	(4.1)	34	(3.8)	12	(5.1)	0.61
Stage - no. (%)							
Limited (I-II)	227	(20.1)	176	(19.7)	51	(21.6)	Ref
Advanced (III-IV)	903	(79.9)	718	(80.3)	185	(78.4)	0.51
Number EN sites							
0	190	(16.8)	174	(19.5)	16	(6.8)	Ref
1	523	(46.3)	415	(46.4)	108	(45.8)	0.051
≥2	417	(36.9)	305	(34.1)	112	(47.5)	<0.0001
EN site(s) involved - no. (%)							
Renal / Adrenal	133	(11.8)	107	(12.0)	26	(11.0)	0.69
Testis	69	(6.1)	44	(4.9)	25	(10.6)	0.001
Breast	34	(3.0)	21	(2.4)	13	(5.5)	0.01
Sinus	82	(7.3)	58	(6.5)	24	(10.2)	0.053
Bone marrow	124	(11.0)	95	(10.6)	29	(12.3)	0.47
CNS-IPI score - no (%)							
0-1 (low)	196	(18.4)	151	(19.2)	45	(19.2)	Ref
2-3 (moderate)	546	(51.4)	432	(51.4)	114	(48.5)	0.33
≥4 (high)	321	(30.2)	245	(29.6)	76	(32.3)	0.67
Histology - no. (%)							
DLBCL	750	(67.0)	575	(65.0)	175	(74.5)	Ref
HGBL	305	(27.2)	270	(30.5)	35	(14.9)	<0.0001
Transformed FL	43	(3.8)	28	(3.2)	15	(6.4)	0.15
Other	22	(1.9)	10	(1.1)	12	(5.1)	0.01
Cell of origin (DLBCL only) - no. (%)							
Germinal center (GCB)	340	(45.3)	258	(44.9)	82	(46.9)	Ref
Non-GCB	316	(42.1)	248	(43.1)	68	(38.9)	0.43
Double-hit status - no. (%)							
DH evaluable	875	(77.4)	687	(78.5)	188	(21.5)	Ref
Confirmed DH / TH[1]	243	(27.7)	223	(32.5)	20	(10.6)	<0.0001
Not DH evaluable	255	(22.6)	207	(23.2)	48	(20.3)	0.36
Frontline chemotherapy regimen							
R-CHOP	536	(47.5)	377	(42.2)	159	(67.4)	Ref
R-EPOCH (+/- dose adjustment)	509	(45.1)	441	(49.4)	68	(28.8)	0.04
Other	85	(7.4)	75	(8.4)	9	(3.8)	0.09

Abbreviations: DLBCL, diffuse large B cell lymphoma. HGBL, high grade B cell lymphoma. FL, follicular lymphoma. iNHL, indolent non-Hodgkin lymphoma. LDH, lactate dehydrogenase. ULN, upper limit of normal. CNS, central nervous system. IPI, international prognostic index. DH, double-hit. TH, triple hit. EN, extranodal. *Notes*: [1]% of DH evaluable patients. Percentages are otherwise referenced within each column. All listed P-values are 2-sided.

Table 2: Propensity score matching covariates

Covariate – N (%)	Level	PPx route		Parametric P-value*	Standardized Difference
		IV N=179	IT N=179		
Sex	Male	99 (55.31)	95 (53.07)	0.671	0.045
	Female	80 (44.69)	84 (46.93)		0.045
Number EN sites	< 2 sites	101 (56.42)	104 (58.1)	0.749	0.034
	≥2 sites	78 (43.58)	75 (41.9)		0.034
Renal and/or Adrenal involvement	No	160 (89.39)	162 (90.5)	0.725	0.037
	Yes	19 (10.61)	17 (9.5)		0.037
B symptoms	No	104 (58.1)	95 (53.07)	0.626	**0.101**
	Yes	72 (40.22)	81 (45.25)		**0.102**
	Unknown	3 (1.68)	3 (1.68)		0
NCCN-IPI category	Low	15 (8.38)	12 (6.7)	0.803	0.064
	Low-int.	76 (42.46)	78 (43.58)		0.023
	High-int.	76 (42.46)	73 (40.78)		0.034
	High	12 (6.7)	16 (8.94)		0.083
CNS-IPI category	Low	39 (21.79)	38 (21.23)	0.95	0.014
	Moderate	87 (48.6)	90 (50.28)		0.034
	High	53 (29.61)	51 (28.49)		0.025
Testis	No	162 (90.5)	162 (90.5)	1	0
	Yes	17 (9.5)	17 (9.5)		0

* The parametric p value is calculated by ANOVA for numerical covariates and Chi-Square test for categorical covariates.

Abbreviations: IV, intravenous. IT, intrathecal. EN, extranodal. NCCN, National Comprehensive Cancer Network. CNS, central nervous system. IPI, international prognostic index. Int., intermediate.

Table 3. Univariate analyses of clinical features with CNS relapse among single-route prophylaxis recipients

Characteristic	Overall (n=1130)		CNS relapse (n=64)		No CNS relapse (n=1066)		OR	95% CI	P-value
Male sex - no. (%)	666	(58.4)	39	(5.9)	627	(94.1)	1.09	0.65-1.83	0.78
Median age - yr. (range)	62	(16-86)	61	(21-83)	62	(18-86)	-	-	0.33
Less than 70 - no. (%)	852	(75.3)	54	(6.3)	798	(93.7)	-	-	Ref
70 and older - no. (%)	278	(24.6)	10	(3.6)	268	(96.4)	0.55	0.28-1.10	0.1
ECOG PS 0-1 - no.(%)	844	(74.7)	42	(5.0)	802	(95.0)	0.70	0.37-1.30	0.25
Baseline renal impairment - no. (%)	172	(15.2)	9	(5.2)	163	(94.8)	0.90	0.43-1.87	0.78
B symptoms - no. (%)	415	(36.7)	27	(6.5)	388	(93.5)	1.30	0.77-2.18	0.76
Serum LDH									
Not elevated	339	(30.0)	8	(12.5)	331	(31.1)	-	-	Ref
Elevated, <3x ULN	598	(53.0)	42	(65.6)	556	(52.2)	3.13	1.45-6.74	0.002
Elevated, ≥3x ULN	147	(13.0)	12	(18.8)	135	(12.7)	3.68	1.47-9.20	0.003
Missing / unknown	46	(4.0)	2	(5.7)	44	(4.1)	1.92	0.40-9.36	0.43
Stage - no. (%)									
Limited (I-II)	227	(20.1)	13	(5.7)	214	(94.3)	-	-	Ref

Advanced (III-IV)	903	(79.9)	51	(5.6)	852	(94.4)	0.99	0.53-1.85	0.96
Number EN sites									
0	190	(16.8)	5	(2.6)	185	(97.4)	-	-	Ref
1	523	(46.3)	27	(5.2)	496	(94.8)	2.01	0.76-5.31	0.15
≥2	417	(36.9)	32	(7.8)	385	(92.2)	3.08	1.18-8.02	0.02
EN site(s) involved - no. (%)									
Renal / Adrenal	133	(11.8)	8	(6.0)	125	(94.0)	1.08	0.50-2.31	0.85
Testis	69	(6.1)	8	(11.6)	61	(88.4)	2.36	1.08-5.16	0.03
Breast	34	(3.0)	4	(11.8)	30	(88.2)	2.30	0.79-6.75	0.13
Sinus	82	(7.3)	2	(2.4)	80	(97.4)	0.40	0.10-1.66	0.19
Bone marrow	124	(11.0)	11	(8.9)	113	(91.1)	1.75	0.89-3.45	0.1
CNS-IPI score - no (%)									
0-1 (low)	196	(18.4)	10	(5.1)	186	(94.9)	-	-	Ref
2-3 (moderate)	546	(51.4)	21	(3.8)	525	(96.2)	0.74	0.34-1.61	0.055
≥4 (high)	321	(30.2)	27	(8.4)	294	(91.6)	1.71	0.81-3.61	0.02
Histology - no. (%)									
DLBCL	750	(67.0)	41	(5.5)	709	(94.5)	-	-	Ref
HGBL	305	(27.2)	20	(6.6)	285	(93.4)	1.21	0.69-2.09	0.49
Cell of origin (DLBCL only) - no. (%)									
Germinal center (GCB)	340	(45.3)	11	(3.2)	329	(96.8)	-	-	Ref
Non-GCB	316	(42.1)	21	(6.6)	295	(93.4)	2.13	1.01-4.49	0.047
Double-hit status - no. (%)									
DH evaluable	875	(77.4)	52	(5.9)	823	(94.1)	-	-	Ref
Confirmed DH / TH[1]	243	(27.7)	15	(6.2)	228	(93.8)	1.06	0.57-1.97	0.86
Frontline chemotherapy regimen									
R-CHOP	536	(47.5)	31	(5.8)	505	(94.2)	-	-	Ref
R-EPOCH (+/- dose adjustment)	509	(45.1)	27	(5.3)	482	(94.7)	1.25	0.51-3.10	0.74
Other	85	(7.4)	6	(7.1)	79	(92.9)	0.91	0.54-1.55	0.64
CNS prophylaxis route									
Intrathecal	894	(79.1)	48	(5.4)	846	(94.6)	-	-	Ref
Intravenous (HD-MTX)	236	(20.9)	16	(6.8)	220	(93.2)	1.28	0.71-2.30	0.4

Abbreviations: OR, odds ratio. CI, confidence interval. DLBCL, diffuse large B cell lymphoma. HGBL, high grade B cell lymphoma. FL, follicular lymphoma. iNHL, indolent non-Hodgkin lymphoma. LDH, lactate dehydrogenase. ULN, upper limit of normal. CNS, central nervous system. IPI, international prognostic index. DH, double-hit. TH, triple hit. EN, extranodal. PS, performance status. GCB, germinal center subtype (Hans criteria). *Notes*: [1]% of DH evaluable patients. Percentages are otherwise referenced within each row. All listed P-values are 2-sided.

Table 4: Prophylaxis-related toxicity								
Toxicity - no. (%)	**Total** (n=1162)		**Intrathecal** (n=894)		**HD-MTX** (n=236)		**Switched route*** (n=32)	
Any documented toxicity	134	(11.5)	54	(6.0)	60	(25.4)	32	100
Category:								
Hematologic	23	(2.0)	12	(1.3)	10	(4.2)	1	(3.1)
Renal impairment	47	(4.0)	5	(0.6)	34	(14.4)	8	(25.0)
Mucositis**	17	(1.5)	6	(0.7)	9	(3.8)	2	(6.3)
Delayed MTX clearance[&]	27	(2.3)	0	(0)	21	(8.9)	6	(18.8)
Headache	18	(1.5)	17	(1.9)	1	(0.4)	0	(0)
Other neurologic	12	(1.0)	11	(1.2)	1	(0.4)	0	(0)
Other / Not specified[#]	38	(3.3)	11	1.2	12	(5.1)	15	(46.9)

Abbreviations: HD-MTX, high-dose methotrexate. *Includes switching in either direction between intrathecal and intravenous (HD-MTX) administration. **Excludes low-grade mucositis. [#] Per clinical documentation. [&] No patients received glucarpidase during the study period.

FIGURE 1: Cumulative incidence of CNS relapse, by risk category. CNS relapse and death were analyzed as competing events. (A) CNS-IPI. (B) NCCN-IPI.

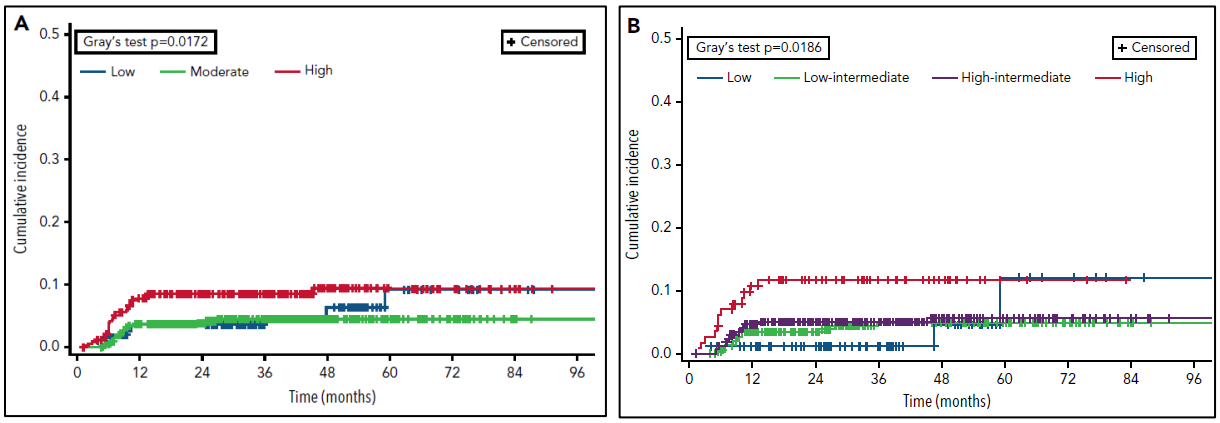


FIGURE 2: Incidence of CNS relapse, by site(s) of extranodal involvement. (A) individual EN site. (B) total number of EN sites.

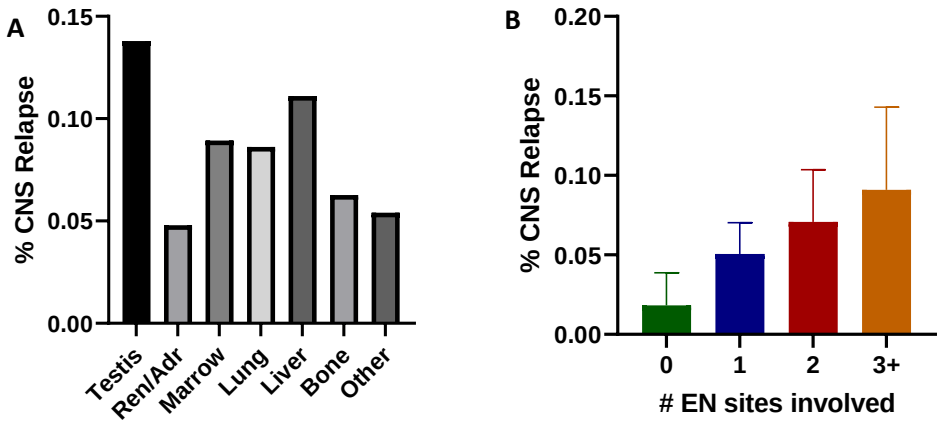


FIGURE 3: Cumulative incidence of CNS relapse, by prophylaxis route. CNS relapse and death were analyzed as competing events.

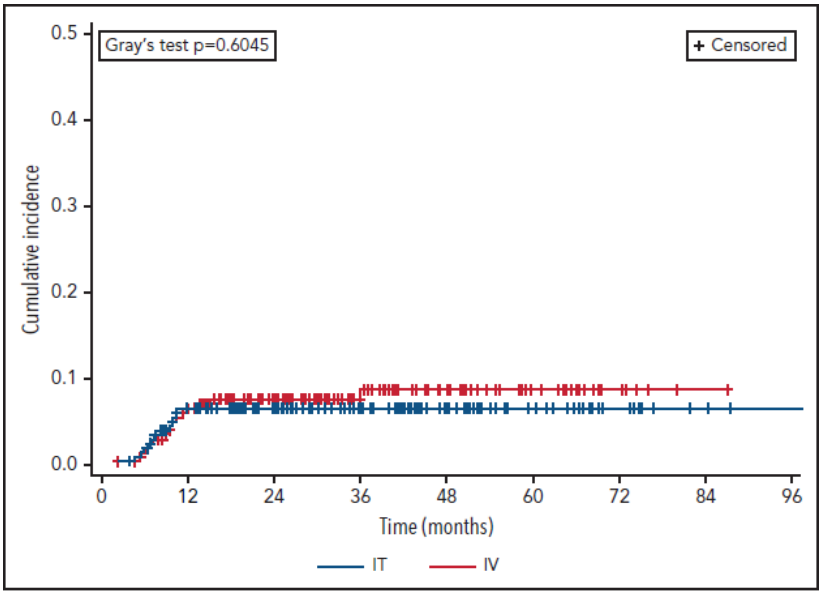


FIGURE 4: Swimmer plot, CNS relapse and subsequent survival, by route of prophylaxis

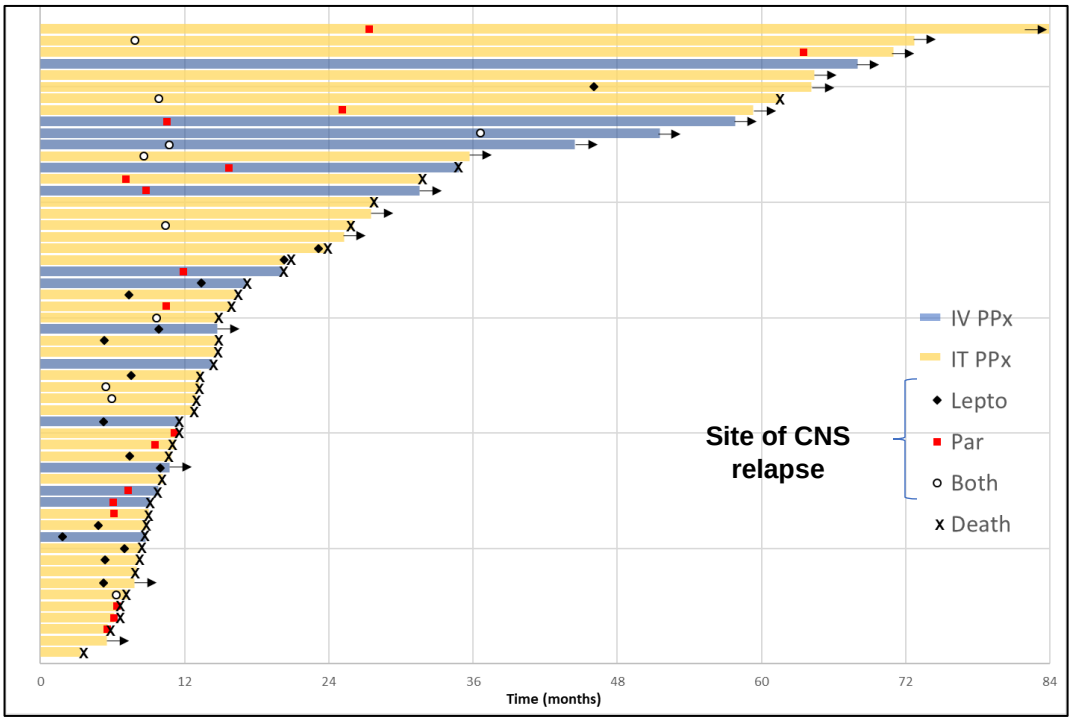
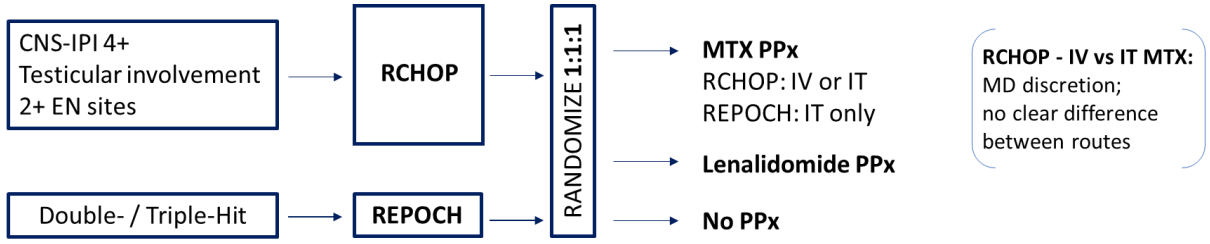
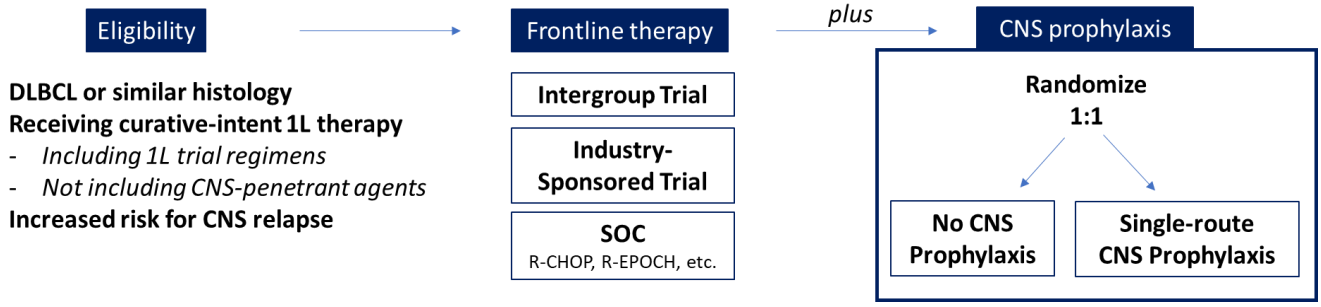


FIGURE 5: Proposed study schema. Presented January 8, 2021 at ECOG Lymphoma Meeting.



Pre-phase steroids+/- cyclophosphamide, OR cycle 1 R-CHOP or R-EPOCH permitted prior to study entry, randomization

FIGURE 6: Proposed study schema. Presented October 26, 2021 at ECOG Fall Meeting.



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