ABOUT THE AUTHOR

Shannon Murphy, MD

Dr. Shannon Murphy is a Hematologist and Assistant Professor at Dalhousie University and practices at the QEII Health Sciences Centre in Halifax, NS. Prior to joining the Division of Hematology and Hematologic Oncology in Halifax, Dr. Murphy completed her internal medicine and hematology training at Dalhousie University, followed by a 1-year clinical lymphoma fellowship with BC Cancer in Vancouver. Her practice focuses on lymphoma and chronic lymphocytic leukemia.

Author Affiliations:
Dalhousie University, Halifax, NS

FRONTLINE TREATMENT OF AGGRESSIVE B-CELL LYMPHOMA

Introduction

Aggressive B-cell non-Hodgkin lymphoma, which most often manifests as diffuse large B-cell lymphoma (DLBCL), is the most common non-Hodgkin lymphoma, accounting for up to 30% of diagnosed cases. It is responsible for considerable morbidity and mortality worldwide, with a global burden of approximately 150,000 new patients annually.[1] Large B-cell lymphoma encompasses a group of lymphomas with significant clinical and biological heterogeneity. While there are approximately 18 variations of large B-cell lymphoma in the upcoming 5th edition of the World Health Organization classification of lymphoid neoplasms (WHO-HAEM5), for the purposes of this review the aggressive B-cell lymphomas will refer to the most common entity, diffuse large B-cell lymphoma, not otherwise specified (DLBCL), as well as diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBL-MYC/BCL2), and high-grade B-cell lymphoma, not otherwise specified (HGBL,NOS).[2]

More than 60% of patients may be cured of their DLBCL with front-line treatment, a figure that has not increased measurably for decades despite attempts to improve outcomes by adding to or adjusting the established standard of care regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[3] R-CHOP can also be effective in the setting of high-grade B-cell lymphoma (HGBL), but in that context outcomes are worse than those in DLBCL.[3] There is no established standard of care for HGBL, and while there is evidence to suggest that intensified regimens such as dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) may improve outcomes, this has not been tested in randomized controlled trials (RCTs).

Given substantial efforts to improve DLBCL outcomes following first-line therapy, and the lack of a clear standard of care in treatment of HGBL, this review seeks to outline current front-line treatment of aggressive B-cell non-Hodgkin lymphoma.

Diffuse Large B-cell Lymphoma (DLBCL)

While many DLBCL patients may be cured of their lymphoma with front-line R-CHOP, more than 30% of patients will have relapsed or refractory disease leaving significant room for improvement in front-line treatment outcomes.[3] Significant effort has been made to identify drivers of chemotherapy-resistant disease in an attempt to highlight patients unlikely to respond to standard front-line therapy. Cases of DLBCL with rearrangements of MYC and BCL2, and those with high-grade histology without other clearly distinct molecular features, have been recognized by the WHO as distinct disease entities and studies have shown they benefit from a more intensive treatment approach.[2] Gene expression profiling (GEP) studies have identified two main subgroups of DLBCL based on the cell of origin (COO): germinal center B-cell-like (GCB) and activated B-cell-like (ABC); outcomes in ABC DLBCL have been shown to be significantly worse than those of GCB DLBCL following R-CHOP, with five-year progression-free survival (PFS) and overall survival (OS) of 48% and 56% vs 73% and 78%.[4,5] However, COO does not tell the entire story: GEP reveals an “unclassified” category that is missed by the IHC algorithms, such as the Hans algorithm used in routine clinical practice.[2] Using further molecular analysis, researchers are working to define distinct genetic subtypes

of DLBCL which may be better able to risk stratify patients and guide future treatment.[2,6]

Numerous clinical trials have been undertaken to improve outcomes with R-CHOP. Studies, including the GOYA trial, have looked at changing the anti-CD20 antibody from rituximab to obinutuzumab in combination with CHOP chemotherapy. They have shown no significant difference in PFS or OS, and increased toxicity with obinutuzumab.[7] R-CHOP14 was compared to R-CHOP21 to see if more frequent or dose-dense administration resulted in better outcomes; no significant difference was found, but there was an increased need for transfusions in the R-CHOP14 group.[8] The intensified regimen of dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) was compared to R-CHOP in DLBCL patients and no significant difference in PFS or OS was found between regimens; however, significantly increased toxicity was seen in the R-EPOCH arm.[9]

A series of clinical trials, both completed and ongoing, seek to determine whether there is a novel or targeted agent that, when added to the R-CHOP backbone, would more effectively treat the approximately 30% of patients undertreated by R-CHOP alone, without overtreating the R-CHOP-sensitive patients and causing excess toxicity.

The REMoDL-B trial studied R-CHOP plus bortezomib vs R-CHOP; to be randomized patients needed to have adequate biopsy samples for GEP in order to stratify by COO.[10] The primary analysis of the trial showed no benefit from the addition of bortezomib, but the five-year follow-up data shows that while there is still no overall benefit, COO analysis demonstrates a PFS and OS benefit in patients with ABC DLBCL.[10,11] Retrospective analysis using a gene-expression-based classifier identified a subset of disease with a high-grade molecular signature which also demonstrated improvement in PFS and OS with the addition of bortezomib.[11]

The PHOENIX trial investigated the addition of ibrutinib to R-CHOP in non-GCB DLBCL and did not demonstrate improved outcomes vs R-CHOP.[12] Interestingly, a subgroup analysis of the PHOENIX trial showed improved event-free survival (EFS), PFS, and OS as well as increased toxicity in patients under age 60. Conversely, patients age 60 or older had inferior EFS, PFS and OS and increased toxicity from the addition of ibrutinib to R-CHOP.[12]

Lenalidomide plus RCHOP (or R2CHOP) has been studied in Phase II and Phase III trials. The Phase 2 ECOG-ACRIN E1412 study encouragingly showed improved PFS and OS in patients treated with R2CHOP vs RCHOP.[13] Unfortunately, the Phase III ROBUST study of R2CHOP vs RCHOP failed to meet its primary end point, with no difference in PFS seen between groups.[14]

The POLARIX trial is the only study to date that demonstrates an overall improvement in PFS vs standard of care R-CHOP. The study examined the addition of the CD79b monoclonal antibody-drug conjugate polatuzumab vedotin to R-CHOP but with vincristine omitted due to overlapping neurologic toxicity - the pola-R-CHP regimen. The researchers compared pola-R-CHP to R-CHOP and found that PFS was improved with pola-R-CHP vs R-CHOP with two-year PFS of 76.7% in the pola-R-CHP arm vs 70.2% in the R-CHOP arm.[15] There was no significant difference in OS and toxicity was similar between arms.[15] Subgroup analysis suggests that pola-R-CHP may not offer incremental benefit to patients 60 years or younger, patients with GCB DLBCL, and patients with lower international prognostic index (IPI) scores.[15]

Based on the available data, R-CHOP remains the front-line standard of care for treatment of DLBCL, although pola-R-CHP could shift the treatment paradigm in Canada. Already adopted as the preferred regimen in some European centres, if polatuzumab is funded for front-line treatment of DLBCL in Canada, it would challenge R-CHOP as the optimal initial therapy for older patients with high-risk non-GCB DLBCL.

Investigation of other novel or targeted agents in combination with R-CHOP such as venetoclax, acalabrutinib, zanubrutinib, and the combination of tafasitamab and lenalidomide are ongoing.

High-Grade B-cell Lymphoma (HGBL)

Although it shares features with DLBCL, HGBL displays higher grade, Burkitt-like morphology but with histologic and genetic features inconsistent with Burkitt lymphoma.[16] The disease entities formerly referred to as "double-" or "triple-hit" lymphoma have been reclassified in order to better reflect their histologic and genetic features. These were initially referred to jointly as HGBL with dual rearrangements of MYC and BCL2 and/or BCL6; the WHO-HAEM5 uses the label diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBL-MYC/BCL2) to include large B-cell lymphomas with MYC and BCL2 rearrangements, composed of large, intermediate, or blastoid cells.[2] DLBCL/HGBL-MYC/BCL2 lymphomas are homogenous and are exclusively GCB by GEP.[2] Lymphomas with rearrangements of MYC and BCL6 are more heterogenous with variable molecular, genetic and GEP features, therefore the WHO-HAEM5 classifies them as either DLBCL, NOS or HGBL, NOS according to their morphological features.[2]

There is no established front-line standard of care treatment for patients with HGBL and outcomes are inferior vs those in DLBCL.[17] Several retrospective analyses have suggested that patients with HGBL experience improved outcomes when treated with intensive regimens vs standard R-CHOP.[18-21] Interestingly, a retrospective, multicentre, pooled analysis conducted in 2023 evaluating 259 patients with DLBCL/HGBL with rearrangements of MYC and BCL2/BCL6 suggested no significant difference in outcomes between intensive regimens and R-CHOP, although the author acknowledges there is a large amount of missing patient data which may impact results.[22] The same authors subsequently conducted a more recently published

systematic review and meta-analysis, again studying retrospective studies of front-line therapy for DLBCL/HGBL with rearrangements of MYC and BCL2/BCL6. The objective was to compare outcomes in patients treated with intensive regimens vs R-CHOP; a review of 876 patients found that PFS and OS were improved with intensified regimens.[23]

The body of existing retrospective data supports intensive front-line treatment over R-CHOP for patients with HGBL, but with very little prospective data on treatment of HGBL, and a lack of randomized, controlled Phase III trials, the intensive regimen associated with the best outcomes is unclear. While there are various intensive treatment regimens described in the literature, the two regimens most frequently reported in this patient population are DA-R-EPOCH and rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate alternating with ifosfamide, etoposide, and cytarabine (R-CODOX-M/R-IVAC), also called the Magrath protocol.

The prospective LY10 trial studied the efficacy of the intensive Magrath protocol without rituximab (CODOX-M/IVAC) in patients with Burkitt lymphoma and DLBCL/HGBL.[24] The two-year PFS and OS for the high-risk patients were 54% and 62% respectively, and subgroup analysis showed the patients with Burkitt lymphoma had significantly better outcomes than those with high-risk DLBCL/HGBL.[24] A Phase II study conducted in the United Kingdom examined the Magrath protocol including rituximab (R-CODOX-M/R-IVAC) in patients with high-risk DLBCL and HGBL. It demonstrated good outcomes with four-year PFS and OS of 66.9% and 72.8% respectively, although only 52% of patients underwent cytogenetic studies and only 12% of patients had confirmed rearrangements of MYC, BCL2, and/or BCL6.[25] Toxicity is high with this intensive regimen with frequent grade 3 and 4 adverse events, most commonly neutropenia, thrombocytopenia and infections, and these events were more often observed in older patients.[24,25]

In addition, there is some prospective evidence supporting the use of R-EPOCH in HGBL, with a Phase II study of R-EPOCH in HGBL with MYC rearrangements at 48 months achieving EFS and OS of 71% and 77%, respectively.[26] A small, prospective study examined R-EPOCH followed by consolidative autologous stem cell transplant and found similar outcomes in terms of PFS and OS with no additional benefit offered by consolidative transplant.[27] A retrospective analysis of the use of DA-R-EPOCH in DLBCL/HGBL patients, including those expressing MYC and BCL2 by IHC, as well as those with rearrangements of MYC and BCL2/BCL6, had particularly good outcomes. It demonstrated two-year PFS and OS of 74% and 84%, respectively. However, the study included a population of low-risk patients and some who had DLBCL, NOS with no high-grade features; therefore, efficacy may be exaggerated.[28] A recently published real-world analysis of treatment trends and patient outcomes in DLBCL and HGBL in the United States showed that the patients with rearrangements of MYC and BCL2/BCL6 who received R-EPOCH as first-line treatment had significantly longer OS vs those receiving R-CHOP.[29] DLBCL patients without those cytogenetic findings who were treated with R-CHOP or R-EPOCH had no difference in OS.[29]

There is a body of evidence supporting the use of intensive regimens like DA-R-EPOCH and R-CODOX-M/R-IVAC as front-line treatment for HGBL with a suggestion of improved outcomes over R-CHOP in these patients. However, this has not been proven in RCTs and the intensive regimens have not been compared to each other. There remains no standard of care for front-line treatment of HGBL. DA-R-EPOCH is a commonly described intensive regimen which may improve outcomes over R-CHOP for patients with HGBL. R-CODOX-M/R-IVAC may also be a reasonable choice, although, given the increased toxicity, this may be most appropriate for select younger, fit patients.

Summary

Aggressive B-cell lymphoma is the most commonly diagnosed lymphoma with a significant burden of disease globally. The classification of aggressive B-cell lymphoma continues to evolve as we continue to delineate subtypes based on genetic features. Despite our improved understanding of the disease, we have yet to make substantial improvement in treatment outcomes.

R-CHOP remains the preferred front-line treatment for DLBCL, although pola-R-CHP demonstrates an improvement in PFS over R-CHOP. It may be a preferred initial treatment if it becomes available for this indication in Canada, especially for patients over 60 years of age with non-GCB DLBCL.

Trials investigating therapies in HGBL are limited by the rare nature of the disease, and much of the available evidence for treatment is retrospective or pulled from subgroup analyses. Despite these limitations, there is evidence supporting intensive regimens over R-CHOP as front-line treatment for HGBL. There is no established standard of care in this setting, but DA-R-EPOCH and R-CODOX-M/R-IVAC are both reasonable intensive treatment regimens for HGBL in front-line, with DA-R-EPOCH most frequently described. Additional prospective data and RCTs are needed to confirm the optimal front-line approach in HGBL.

As we continue to advance our knowledge of the molecular landscape of DLBCL and HGBL beyond COO into detailed genetic analysis with next generation sequencing, we may be able to identify the impact of these detailed disease genetics on treatment outcomes, and perhaps target treatments on the basis of molecular classification.[5,6] We await further evidence from clinical trials to inform this approach.

Correspondence:

Dr. Shannon Murphy
Email: Shannon.Murphy@nshealth.ca

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