LYMPHOMA CANADA

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Frontline Treatment of Diffuse Large B-Cell Lymphoma

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Abstract

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of Non-Hodgkin Lymphoma. Although this is an aggressive disease, most patients respond well to initial treatment. The standard frontline treatment is R-CHOP chemoimmunotherapy for six cycles, however factors such as stage and prognostic features or risk factors may determine if abbreviated therapy may be appropriate. Radiation therapy may be part of a planned treatment course usually as consolidation post-chemoimmunotherapy. Additional or alternative chemotherapy may need to be considered based on high-risk molecular features (presence of *MYC, BCL2* and/or *BCL6* rearrangement), central nervous system (CNS) involvement at diagnosis or if a patient is at high-risk of secondary CNS relapse. In Canada, no unified national guideline exists for the treatment of DLBCL, and the provincial guidelines in existence vary. An evidence-based national treatment guideline supported by Canadian hematologists is warranted to ensure a consistent and optimal approach for the frontline treatment of DLBCL patients. A group of experts from across Canada developed a national evidence-based treatment guideline to provide healthcare professionals with clear guideline and best practices for the management of frontline DLBCL. Results of the current provincial guidelines in existence are presented with consensus recommendations based on available evidence.

KEYWORDS

Diffuse Large B-Cell lymphoma, DLBCL, Treatment, Prognosis, Guidelines, R-CHOP.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a heterogenous group of B-cell malignancies that constitutes 30-40% of all Non-Hodgkin lymphomas and affects over 20,000 Canadians (census data from 1992-2010)[1]. The heterogenous nature of this type of lymphoma can result in diverse clinical presentations and prognosis with a wide spectrum of patient ages and comorbid conditions[2].

Due to the aggressiveness of DLBCL, a rapid diagnosis and initiation of treatment is essential. Overall, frontline chemotherapy cures approximately 80-90% of patients with limited stage and 60-70% of advanced stage disease, depending on the presence of other risk factors[3]. When deciding on initial therapy, it is critical to consider the pathological components of the disease such as its molecular features, which can be determined through testing. Further, other clinical features of the patient may play a role in the length and intensity of the frontline standard of care (SOC) treatment. The current SOC for frontline treatment of DLBCL is R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab). A caveat to SOC would be for the extreme elderly unfit patients, where other treatment options such as reduced dose CHOP or R-mini-CHOP and R-CEOP (cyclophosphamide, etoposide, vincristine, prednisone, rituximab), are all potentially curative approaches. Optimization of frontline treatment for DLBCL requires consideration of disease stage, molecular features, as well as patient factors such as comorbidities.

Across Canada, treatment in the frontline setting is relatively standardized, but differences can occur with the length of treatment or in select cases, alternate rituximab combination therapy based on institutional guidelines. Further, in less common, and less data-driven scenarios such as the presence of cardiac dysfunction, there may be greater challenges in determining a standard treatment approach. Treatment guidelines for DLBCL are not available in all provinces and may differ based on provincial and institutional considerations. As there is currently no Canadian-wide guideline for the standardized management of DLBCL patients in the frontline setting, a group of Canadian DLBCL experts, in collaboration with Lymphoma Canada, have developed a nationwide consensus guideline. This guideline is based on the current best available evidence for the frontline management of patients with DLBCL.

GUIDELINE RECOMMENDATIONS

1. Recommendation for limited stage criteria and treatment;
2. Recommendation for advanced stage DLBCL patients;
3. Recommendation for patients with *MYC* rearrangement;
4. Recommendation for High-Grade B-Cell lymphoma with FISH positive testing for *MYC*, *BCL2* and/or *BCL6* (Double-Hit/Triple-Hit);
5. Recommendation for CNS prophylaxis;
6. Recommendation for pre-phase treatment.

Methodology

An initial web-based search was performed on provincial cancer centers to identify DLBCL management guidelines. DLBCL provincial experts were contacted to verify guidelines and provide insight and input if a guideline could not be located. Once guidelines were collected, information was extracted and differentiated based on common treatment considerations. Following compilation of provincial standards, information was reviewed by a national panel of experts for consensus on the frontline treatment for DLBCL patients in Canada. The National Comprehensive Cancer Network categories of evidence and consensus (**Table 1**) were used to grade the level of evidence and support for the clinician recommendations for frontline treatment[4]. A treatment algorithm was created based on these recommendations.

Table 1: NCCN Categories of Evidence and Consensus

CATEGORY 1	Based on the high-level evidence, there is uniform consensus that the intervention is appropriate.
CATEGORY 2A	Based on the lower-level evidence, there is uniform consensus that the intervention is appropriate.
CATEGORY 2B	Based on the lower-level evidence, there is consensus that the intervention is appropriate.
CATEGORY 3	Based on any level of evidence, there is major disagreement that the intervention is appropriate.

Results

An online search revealed existing DLBCL treatment and management guidelines in four provinces (British Columbia (BC), Alberta (AB), Ontario (ON), Nova Scotia (NS)). Three provinces (BC, AB, NS), had one guideline in existence for the province, while one province (ON) had three DLBCL guidelines. Specialists from the remaining provinces (Saskatchewan (SK), Manitoba (MB), Quebec (QC), Newfoundland and Labrador (NF), New Brunswick (NB), Prince Edward Island (PEI)) and territories (Northwest Territories (NWT), Yukon (YK), Nunavut (NU)) were then contacted. Specialists from all remaining provinces confirmed no official provincial guidelines were in existence. Physicians that do not have guidelines within their own province indicated they refer to BC Cancer (MB, PEI), Alberta Health Sciences (AHS) (SK), Nova Scotia Cancer Care Program (PEI), Princess Margaret Cancer Centre (PMCC) and the National Comprehensive Cancer Network (NCCN) guidelines and adopt these guidelines to what is available locally. Specific guidelines have not been uniformly adopted or endorsed, and feedback from specialists indicated interest in the creation of a national DLBCL treatment guideline for frontline management.

The information included in the existing guidelines was reviewed for common themes to determine the methodology for data extraction and compilation to highlight similarities and differences. For frontline treatment, the common themes for treatment determination included limited vs. advanced disease, additional comorbidities and in some cases integrated clinical risk factors. The information is summarized in **Table 2**. Additional characteristics involved in the decision for treatment, including molecular characteristics and CNS involvement, have been summarized in **Table 3**.

Table 2: Summary of Provincial Guidelines for the Frontline DLBCL Treatment

PROVINCIAL GUIDELINES	BRITISH COLUMBIA	ALBERTA	ONTARIO			NOVA SCOTIA
			Sunnybrook Health Sciences Centre	Princess Margaret Cancer Centre	Cancer Centre of Southeastern Ontario	
Limited Stage (zero to low risk factors)	**Stage 1 or 2, no B symptoms, non-bulky (< 10 cm):** R-CHOP x 3 → PET • If PET positive (D3-5) → INRT • If PET negative → 1 more cycle of R-CHOP *Exceptions: Limited stage composite indolent and aggressive lymphoma & limited stage aggressive T-Cell lymphoma → R-CHOP x 3 then INRT*	**Limited and bulk < 7 cm (no risk factors):** R-CHOP x 4 → PET • If CR 14-21 days after 4th cycle → stop • If PR after 4th cycle → continue R-CHOP for total of 6 cycles → ISRT (30-35 Gy) **If patient cannot tolerate > 3 cycles R-CHOP → stop at 3 cycles → ISRT*	**Non bulky-low risk (0-1 FR on stage adjusted IPI):** R-CHOP x 3 → PET • If CR 2-3 weeks after 3rd cycle → ISRT (30 Gy in 15 fractions) • If PR →ISRT (30 Gy in 15 fractions) + boost 6 Gy in 3 fractions • If no response → 3 more cycles of R-CHOP	**Stage I/II, no risk factors:** R-CHOP x 4 → PET • If CR cycle → observe with no RT particularly if a) non-bulky (< 7 cm) presentation; b) prior surgical excision of all gross disease; c) multiple nodal regions involved (> 3), if non-contiguous • If PR or no response → ISRT (35 Gy in 20 fractions)	**Limited stage:** 1. R-CHOP x 3 → ISRT **Or** 2. R-CHOP x 6 → PET; if PET + → RT **Both treatment regimens are acceptable. Decision between the two will involve assessing patient factors (age, comorbidities), patient preference, and potential complications*	**Stage I/II, non-bulky:** R-CHOP x 3 → ISRT (30-50Gy) **If IPI 0-1:** R-CHOP x 4 with 2 x Rituximab **When avoiding ISRT:** R-CHOP x 6
Limited Stage (high risk factors)		**Limited and bulk < 7 cm (risk factors 1-4**):** R-CHOP x 6 → PET • If CR 14-21 days after 4th cycle → no ISRT • If PR after 4th cycle → ISRT (30-35 Gy)	**Limited stage (2+IPI risk factors and/or bulk disease):** R-CHOP x 6 → ISRT	**State I/II, > 1 prognostic factor:** R-CHOP x 6 → PET • If CR → ISRT (30 Gy in 20 fractions if initial bulk ≥ 7 cm)		**Stage I/II bulky ≥ 10 cm:** R-CHOP x 6 → ISRT (30-50 Gy)
Advanced Stage (low risk factors)	**Advanced stage:** R-CHOP x 6 • If PET - (D1-3) CR → Observe • If PET + (D4, 5) with radiation volume → INRT	**Bulk ≥ 7 cm - 0-3 risks or age > 65:** R-CHOP x 6 cycles • If CR → Observe • If no CR → ISRT (30-35 Gy) to site of prior bulk	**Advanced stage:** R-CHOP x 6	**Age < 60:** R-CHOP x 6-8	**Advanced stage:** R-CHOP x 6 • If bulk disease or PET+ → ISRT	**Stage III/IV, with/without bulky disease ≥ 10 cm:** R-CHOP x 6 *ISRT not recommended (discussed on individual basis if concern for symptoms, bone disease or risk structures)* Clinical trials may be considered
Advanced Stage (high risk factors)		**4-5 risk factors and age < 70 :** R-CHOP x 6 • If no CR → high-dose therapy/ASCT **Or** • R-CHOP x 4-6 → high-dose chemotherapy/ ASCT in first remission (especially if PET+ after R-CHOP x 4) • If no CR → ISRT (30-35 Gy)	**Advanced disease** R-CHOP x 6 • If bulky disease or PET + → ISRT	**Age > 60:** R-CHOP x 6 • Bulky masses (> 10 cm), extradural tumour with spinal cord/nerve root compression, impending or actual organ compromise → ISRT **Up to 8 cycles of Rituximab can be funded if required*		**Stage III/IV,** R-CHOP x 6

ABBREVIATIONS: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), ISRT (involved site radiation therapy), INRT (involved node radiation therapy), ISRT (involved site radiation therapy), RT (radiation therapy), CR (complete response), ASCT (autologous stem-cell transplant), PET (positron emission tomography), PR (partial response). B symptoms (fever, drenching night sweats, weight loss), Gy (Gray - unit of ionizing radiation), D1-5 (Deauville 5-point scale for PET scans), IPI (International Prognostic Index).

**IPI risk factors for limited stage as specified in some guidelines can include increased LDH, stage II, ECOG performance status 2-4, age > 60 years.

Table 3: Additional Considerations for the Frontline Treatment for DLBCL patients

PROVINCIAL GUIDELINES	BRITISH COLUMBIA	ALBERTA	ONTARIO			NOVA SCOTIA
			Sunnybrook Health Sciences Centre	Princess Margaret Cancer Centre	Cancer Centre of Southeastern Ontario	
***MYC*-rearranged with no *BCL2* mutation**	R-CHOP x 6	R-CHOP x 6 Considerations: **Age <70, IPI 4-5** R-CHOP x 4 → R-DHAP or RDICEP x1* → HDCT/ASCT **R-CODOX-M/IVAC or DA-EPOCH-R could be considered*	R-CHOP x 6	R-CHOP x 6	R-CHOP x 6	R-CHOP x 6
Double or triple hit lymphoma	DA-EPOCH-R x 6	**For IPI = 0-1** • R-CHOP or with HD-MTX after cycles 2,4,6 • DA-EPOCH-R **For IPI=2-5:** • R-CHOP with HDMTX after cycles 2 (±4) → R-DICEP x 1 → HDCT/ASCT using CNS penetrating regimen (R-BuMel/ASCT or R-MelTBI/ASCT (not BEAM)) • DA-EPOCH-R or R-CODOX-M/IVAC	DA-R-EPOCH x 6	DA-R-EPOCH x 6	DA-R-EPOCH x 6	DA-EPOCH-R x 6
High risk CNS but no disease**	**High risk CNS-IPI ** or testicular, renal/kidney involvement, if tolerable:** CHOP-R + HD-MTX x 3-4 cycles starting cycle 2 may be given post R-CHOP for testicular	Not reported on	**High risk (CNS IPI** > 3 risk factors) + non-GCB phenotype:** • **< 70 years, fit →** HD-MTX (3g/m^2) x 3-4 cycles on day 10 after R-CHOP • **If HD-MTX is not appropriate →** IT MTX/ AraC/ hydrocortisone x 4	**High risk** or stage I-II testis + epidural presentations:** HD-MTX x 2-3 ± IT chemotherapy if tolerable	**High-risk (DSHNHL model)** or those with involvement (kidney, adrenal, testis), if fit:** HD-MTX (3gm/m^2) x 3 during cycles 2,4 and 6 of R-CHOP (around day 5-7)	**High-risk (CNS IPI > 3)** and/or testicular, renal or adrenal involvement:** HD-MTX x 2 post R-CHOP cycles 2,4
Other	N/A	**Pre-phase therapy > 60 years (to decrease toxicity):** G-CSF prophylaxis → Prednisone 100mg/d x 3-7 days prior to cycle 1 of R-CHOP or R-CEOP	N/A	**Chemotherapy sanctuary sites (e.g. testes), or clinically critical sites (e.g. airway or spinal cord compression at presentation):** ISRT **Primary mediastinal large B cell lymphoma/ localized gastric DLBCL:** ISRT (if CR/PR post- R-CHOP)	**Age > 65:** Prednisone 100mg daily for five days prior to R-CHOP + Neupogen prophylaxis for febrile neutropenia **Primary Mediastinal Large B Cell Lymphoma:** • DA-R-EPOCH x 6 → PET If PET+ → ISRT • If less fit → R-CHOP x 6 + ISRT	**Age > 64:** G-CSF → Pre-phase prednisone on case-by-case basis

ABBREVIATIONS: DSHHNHL (German High-Grade Non-Hodgkin's Lymphoma prognostic model), DA-EPOCH-R (dose-adjusted, etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone, rituximab, methotrexate, filgrastim), IT (intrathecal), G-CSF (granulocyte colony stimulating factor), HD-MTX (high-dose methotrexate), CR (complete response), PR (partial response), ISRT (involved-site radiation therapy), PET (positron emission tomography), CNS (central nervous system), R-CEOP (cyclophosphamide, etoposide, vincristine, prednisone, rituximab), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), IPI (International prognostic index), HDCT (high-dose therapy), ASCT (autologous stem-cell transplant), R-CODOX-M/IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine), R-DICEP (rituximab, dose-intensive cyclophosphamide, etoposide, cisplatin), R-BuMel (Rituximab, Busulfan/ Melphalan) or R-MelTBI (Melphalan plus total body irradiation), BEAM (carmustine [BCNU], etoposide, cytarabine, melphalan), AraC (cytarabine).

**CNS IPI risk factors prognostic for CNS relapse include age > 60 years, elevated LDH, ECOG performance status (PS) > 1, advanced stage disease (III, IV), > 1 extranodal (EN) site, adrenal/kidney involvement[5]. In addition, multiple EN sites (> 2), as well as uterine involvement have also been associated with high CNS risk[6]. Less information is known about risk with breast involvement.

Frontline Treatment for DLBCL

Frontline treatment for DLBCL is relatively standardized across Canada with most patients receiving R-CHOP given every 21 days. Considerations to guide therapy include stage of disease, as well as 'double-hit or triple-hit' disease (presence of *MYC* rearrangement typically with *BCL2* or *BCL6* rearrangements). In some provinces, IPI risk factors (age of the patient, ECOG performance status (PS), number of extranodal sites, and lactate dehydrogenase level) can be used to guide treatment. Further, the presence of CNS disease or those at high risk may receive alternate therapy to include CNS penetrant drugs such as high-dose methotrexate (HD-MTX). In those with cardiac dysfunction, etoposide substitution (R-CEOP), or in some cases infusional anthracyclines (DA-EPOCH-R), may be used as an alternative. Data from existing guidelines were compiled and reviewed with recommendations established and consensus achieved amongst the expert panel.

Limited Stage Disease

Modifications to the standard treatment of R-CHOP for patients with limited stage disease depends on disease factors such as bulk and distribution, and for some guidelines stage modified IPI. The absolute definition of bulky disease can differ. Some groups define it as the largest tumour diameter of ≥ 10 cm, whereas other groups have used more conservative measurements including 5, 7 or 7.5 cm[7]. In addition, a stage-modified IPI may be considered to determine suitability for a limited stage approach (age ≤ 60 years, stage I-II, ECOG status < 2, elevated LDH)[8-10].

All provinces recommend R-CHOP with variations in the number of cycles and use of PET imaging to guide the use of further therapy and radiotherapy (**Table 2**). The number of cycles of R-CHOP prior to the restaging interim PET scan varies per province (between 3-6 cycles), as well as the timing for when to schedule the PET scan. Further, the Deauville five-point scale assessment response may differ per province depending on when the PET scan is scheduled (i.e. interim or post-therapy). As performed in BC, if the interim PET is negative after 3 or 4 cycles of R-CHOP, i.e. CMR (complete metabolic response), the Deauville score associated with this response is 1-2, rather than the standard Deauville 1-3 score[11]. BC uses this more conservative scoring approach as it removes the necessity of further treatment with radiation[12]. A PET positive score in this scenario would be Deauville 3-5 rather than 4-5, as seen in other provinces, and radiation would be administered to include prior disease sites. On the other hand, for patients who receive six cycles of R-CHOP and undergo an end of treatment PET scan, a Deauville 4-5 score would require further treatment with radiation to PET positive areas (consolidation) for all other provinces. As the provinces have slightly different strategies, it is important to consult with a radiation oncologist. The BC guidelines recommend R-CHOP for 3 cycles, with one additional cycle of R-CHOP if PET negative. The NS guideline and ON (CCSEO, SHHC) guidelines also recommend three cycles while other provinces (AB, ON (PMCC), NS) recommend four cycles followed by an interim PET scan. With provinces that divide limited stage treatment based on high risk factors (AB, ON (SHHS, PMH), NS), 6 cycles of R-CHOP is recommended for more high risk patients.

Some guidelines rely on PET imaging results for further treatment decisions. For example, following 4 cycles of R-CHOP, if the interim PET is negative with a complete response, AB and ON (PMCC) recommend observation. On the other hand, ON (CCSEO) and NS guidelines do not rely on PET to guide further treatment; their strategy involves combined-modality chemotherapy with involved-site radiation therapy (ISRT) or involved node radiation therapy (INRT). Guidelines for RT that predated modern imaging and planning techniques used involved fields (IFRT) defined by anatomic landmarks and often encompassed adjacent uninvolved lymph nodes[13]. Modern techniques for conformal RT deliver radiation more precisely based on target volume definitions (ISRT) often using reduced treatment volumes for the effective control of the at-risk involved sites of disease, thereby reducing normal tissue exposure[13]. If PET positive (Deauville 3-5 or 4-5), recommendations from all provinces are to proceed to radiotherapy, except if D5 is accompanied by a new site of disease in which case salvage chemotherapy and stem-cell transplant (SCT) is recommended. BC recommends proceeding to INRT; AB recommends a further 2 cycles of R-CHOP followed by ISRT (30-35 Gy); ON recommends ISRT. Please refer to **Table 2** for the full list of individual provincial DLBCL treatment strategies.

High-risk limited disease was defined by existing guidelines as the presence of risk factors including age > 60 years, stage I/II disease, and > 1 on the age-adjusted IPI. The AB guideline specifies bulk > 7 cm, while NS classifies bulk as ≥ 10 cm. All guidelines, except for BC, which combines low- and high-risk patients together, recommend R-CHOP x 6 followed by PET imaging to assess response. The ON and AB guidelines have similar recommendations following six cycles of R-CHOP, with PET positivity recommending 30-35 Gy ISRT. Specifications have been made (PMCC) for 35 Gy if initial bulk is greater than 7 cm. If localized PET positive following R-CHOP x 6, NS will consider ISRT (30-50 Gy) to convert to a complete response.

Considering these guidelines and current research, options for limited stage disease includes treatment with abbreviated therapy (R-CHOP x 4 plus 2 doses of Rituximab) as proven with the FLYER trial[9], planned combined modality R-CHOP x 3 with ISRT, or PET-guided therapy. If bulky disease is present or the patient is not amenable to radiotherapy, the recommendation is to treat as advanced stage disease.

RECOMMENDATIONS

Definition for limited stage disease: IPI 0-1, no bulky disease (provinces have different definitions of bulk disease), and ≤ 1 extranodal site.

Recommendation for the treatment of limited stage disease: R-CHOP x 3* - 4 cycles, with exceptional 6 cycles, followed by PET scan. There is the option to give response-adapted treatment with PET (groups have different approaches).

*For R-CHOP x 3, proceed with either RT-planned combined modality, or proceed with PET imaging and if negative undergo one additional cycle of R-CHOP.

Advanced Stage Disease

For advanced stage disease which includes stage III/IV, and in some scenarios includes patients with B symptoms (BC) and bulk disease (› 10 cm in BC and NS; AB uses 7 cm cut-off), all guidelines recommend R-CHOP x 6 cycles. One guideline (ON) provides the option for an additional two cycles of R-CHOP if tolerated, however this is uncommon. Several of the guidelines highlight the use of end of treatment PET scan and/or the presence of bulk disease in assessing the need for radiation therapy following chemotherapy. A PET negative scan (Deauville 1-3) following R-CHOP will not require further treatment. If PET negative, but bulk was present at diagnosis, radiation is recommended (SEOCC). If PET positive (Deauville 4-5), the recommendation is radiation therapy (30-35 Gy) if feasible (BC, NS)[14]. Radiation is given to areas of residual positivity. One guideline (NS) recommends a more conservative approach with ISRT in this setting, prompting a discussion to determine critical issues (i.e. spinal cord involvement, age, comorbidities) that would preclude curative intent treatment at relapse.

Advanced stage disease that is high-risk was defined by existing guidelines as an IPI of 3 or higher. All guidelines recommend R-CHOP x 6 cycles. Additionally, with concomitant comorbidities, age and frailty, one guideline (NS) will consider dose adjustment of R-CHOP to R-mini-CHOP x 6 cycles as an option. However, data to support a standard approach in elderly and/or frail patients is lacking. Considering these guidelines and current research including the RICOVER trial[15] and the GOYA trial[16], treatment for advanced stage patients is six cycles of R-CHOP; eight cycles is not justified.

Following R-CHOP, PET negative scans require no further treatment for the patient, while PET positivity recommends ISRT (30-35 Gy). Some guidelines advocate for radiation even with CR following R-CHOP for patients with bulky masses (› 10 cm), bone involvement, extradural tumor with spinal cord/nerve root compression, and impending or actual organ compromise. In BC, if the PET scan is negative after 6 cycles of R-CHOP, patients are observed even with bulky disease. Recent data from this centre demonstrated no difference in outcome in bulky versus non-bulky patients with an end of treatment PET-negative scan[7]. One guideline (NS) does not recommend the use of ISRT following R-CHOP for this patient group.

RECOMMENDATIONS

Recommendation for treatment of advanced stage disease: standard therapy is 6 cycles of R-CHOP. Recommend ISRT if localized responding PET positive (Deauville 4-5) disease at the end of R-CHOP treatment.

*If new site or progression (non-responding), treatment options can include ISRT or other salvage therapy.

Other Considerations for Frontline Treatment

MOLECULAR FEATURES

Molecular characteristics of large B-cell lymphomas can alter prognosis, diagnostic classification, and treatment approach. The most frequent rearrangements include *MYC*, *BCL2*, and *BCL6*. Lymphomas found to have translocations for *MYC* in combination with *BCL2* and/or *BCL6* are no longer classified as DLBCL and are rather classified as High-Grade B-cell lymphoma with double-hit (DH) or triple-hit (TH) features. Though this is seen in only 5-10% of DLBCL cases, it is important for FISH (fluorescence in situ hybridization) testing to be done to identify this patient population in order to receive optimal treatment[17].

RECOMMENDATION

It is recommended that all patients with DLBCL be tested by FISH for *MYC*, with reflex testing for *BCL2* and *BCL6* if *MYC* positive.

MYC REARRANGEMENT (Without Rearrangement of *BCL2* or *BCL6*)

The *MYC* transcription factor is of vital importance to maintaining regular cell function and is the major molecular abnormality in aggressive B-cell lymphomas when rearranged[18]. In DLBCL, *MYC* rearrangement occurs in approximately 10% of cases[19]. Studies have suggested an inferior progression free survival (PFS) and overall survival (OS) for patients with *MYC* rearrangement compared to patients without[20-21]. The prognostic relevance however of single-hit rearrangement remains controversial and has been reported variably. One study suggested that *MYC* rearrangement poses a negative impact to OS only within the first two years following diagnosis, with no difference in survival probability in DLBCL without *MYC* rearrangement after two years[19]. However, rarely does DLBCL relapse after a progression-free timepoint of two years.

Only one guideline (AB) provided a treatment recommendation for single-hit *MYC* rearrangement DLBCL, which was R-CHOP for 6 cycles. However, for those aged <70 years with a high IPI score[4-5], the alternative treatment regimen is 4 cycles of R-CHOP followed by one cycle of either R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin) or R-DICEP (dexamethasone, cyclophosphamide, etoposide, cisplatin). Alternative treatment approaches include R-CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine) or DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab).

RECOMMENDATION

Recommendation for patients with *MYC* rearrangement: 6 cycles of R-CHOP.

DOUBLE-HIT (*MYC* AND *BCL2* OR *BLC6*) OR TRIPLE-HIT (*MYC*, *BCL2*, *BCL6*)

For DLBCL cases with *MYC* rearrangement, it is most often (58-83%) concurrent with dual translocation of *BCL2* or *BCL6*[22]. Double-hit or triple-hit DLBCL is associated with shorter progression-free and overall survival following frontline therapy with R-CHOP[23-24]. It is also associated with a higher risk for CNS relapse[25]. One study assessed whether partner genes associated with *MYC* rearrangement, including either immunoglobulin (IG) heavy chain or light chain or non-IG locus, can affect outcome[19]. When *MYC* is rearranged with an IG partner in double-hit DLBCL, it results in a significantly worse PFS and OS[19]. It is important to note that the outcome of double/triple hit lymphoma with R-CHOP has improved with more comprehensive testing, suggesting that older studies may have a selection bias[26]. However, since we cannot reliably distinguish lower risk patients with current methodology, dose intensified chemotherapy is recommended.

Following review, there are five guidelines that comment on the preferred treatment option for this patient population. DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) x 6 cycles was the preferred method, with consideration for radiation therapy in patients with bulky disease or if PET positive following treatment. One guideline (AB) provides further recommendation based on IPI risk factors. In Alberta, patients with double-hit or triple-hit lymphoma under the age of 70 years should receive more aggressive therapy, possibly including stem cell transplantation. Guidelines advise patients to receive R-CHOP and HD-MTX, then proceed to autologous transplant. This option is not recommended for patients that have previously received an intensified protocol such as DA-EPOCH-R.

RECOMMENDATION

The recommended treatment for double-hit and triple-hit lymphoma is DA-EPOCH-R x 6 cycles.

*May consider HD-MTX at the end of regimen for high-risk CNS patients.

CNS PROPHYLAXIS

The prognosis of DLBCL patients with CNS involvement is poor, with a median survival time of 2-6 months due to both rapid tumor growth and ineffective treatment strategies. CNS involvement, which can manifest in the brain parenchyma, leptomeningeal, spinal cord and eyes, mainly presents within one year of diagnosis and can occur in the following scenarios with respect to the status of systemic disease:

1. Patient is in systemic remission, with isolated recurrence in the CNS;
2. Remission following frontline treatment, but simultaneous systemic recurrence and CNS involvement;
3. CNS involvement while the patient is receiving frontline treatment.

In addition to double-hit and triple-hit lymphoma, certain factors at diagnosis are correlated with a higher risk for CNS involvement including elevated LDH and multiple extranodal sites. Specific extranodal sites impart an elevated risk including kidney, adrenal glands, testes, and possible breast. The CNS-IPI was developed to identify patients at high risk of CNS disease, and incorporates all five IPI factors. Incidence is › 10% in those with a high-risk CNS-IPI and 25-35% in those with advanced stage and testicular or renal/kidney involvement; it remains unknown whether prophylaxis is protective. The optimal prophylactic strategy remains unclear.

The current Canadian guidelines that comment on CNS prophylaxis refer to the German High-Grade Lymphoma Study Group (DSHNHL) to determine patients that are high risk. This includes patients with a high CNS-IPI, kidney/adrenal or testicular involvement, as well as double/triple-hit lymphoma. Consideration is also given to prophylaxis in intravascular lymphoma. All guidelines recommend high-dose systemic methotrexate with leucovorin rescue in young patients with good renal function. The guidelines indicate a range of 2-4 cycles of high-dose methotrexate (3g/m^2). The day of administration is day 10-15 after R-CHOP typically after 2, 4 and 6 cycles, both for fit patients and those under the age of 70 years. Though initial data supports day 15 for better outcomes, recent evidence recommends scheduling before day 10 of R-CHOP cycles. In BC for limited stage testicular involvement, prophylaxis is given after chemotherapy. If issues with scheduling, tolerability or due to treatment delays, one guideline indicates that methotrexate can be administered once R-CHOP is completed, and then 3 cycles of HD-MTX can be performed every 2 weeks. If HD-MTX is not tolerable, another treatment strategy is four doses of intrathecal MTC/AraC/hydrocortisone. Further research on the use of HD-MTX and its benefits in this patient population is warranted.

RECOMMENDATION

Patients at high-risk for CNS involvement could consider receiving prophylaxis with high-dose methotrexate (2-4 cycles, dose of 3g/m^2) in addition to R-CHOP. Patient characteristics and scheduling of HD-MTX administration may differ across institutions.

CARDIAC DISEASE

Curative intent therapy for the frontline treatment of DLBCL is R-CHOP, a chemo-immunotherapy that includes doxorubicin, a known risk factor for cardiotoxicity[30-31]. With an increasingly cumulative dose, R-CHOP can result in cardiac toxicity and in particular congestive heart failure, as a result of the toxic damage to the mitochondria of the cardiomyocytes. One study found that cardiomyopathy could be avoided by keeping a cumulative dose of doxorubicin below 450 mg/m^2 [32]. Additionally, certain established cardiac risk factors such as advanced age, known cardiac disease, prior mediastinal radiation and diabetes mellitus, can increase the risk for anthracycline toxicity. Other methods have been employed to reduce the risk of cardiac toxicity, including the use of anthracycline analogues and alternative methods of drug delivery such as through a continuous slow infusion[33].

Managing cardiac toxicity is an institutionally driven practice with little evidence for a nationally standardized recommendation. Options can include the use of ACE (angiotensin-converting enzyme) inhibitors or dexrazoxane with R-CHOP to prevent cardiomyopathy. Another treatment strategy includes DA-EPOCH-R, as continuous infusional doxorubicin has lower cardiotoxicity. For patients with reduced ejection fraction, substituting the doxorubicin in R-CHOP with etoposide (R-CEOP) or gemcitabine (R-GCVP) have shown promise in retrospective studies[34]. A study from BC demonstrated no reduction in survival when comparing R-CEOP versus R-CHOP, although the study is not powered to show a small difference[35-36].

RECOMMENDATION

Recommendation for patients with cardiac toxicity: In this setting, curative therapy can be delivered. This will likely not involve R-CHOP alone, and may involve additional therapies as per institutional guidelines.

PRE-PHASE THERAPY

Additional recommendations for optimal treatment strategies have been further listed by existing Canadian guidelines such as supportive/ancillary treatments, treatment for intermediary/grey zone DLBCL, and treatment based on specific anatomical tumor locations. Though certain institutional and provincial guidelines comment on intermediary and anatomical tumor locations, these are considered risk factors and do not require specific recommendations. Therefore, consensus was only required on pre-phase and prophylaxis treatment.

Pre-phase therapy can be considered a preventative strategy against toxicity such as febrile neutropenia, tumor lysis syndrome, and deterioration of performance status[37]. It can also be used to determine a patient's response to their upcoming chemotherapy regimen. Pre-phase therapy can include a regimen of corticosteroids with or without low dose chemotherapy[38]. Single-agent oral prednisone is the most commonly used regimen. Other regimens include prednisone combined with vincristine and cyclophosphamide or cyclophosphamide alone[38]. Whether all DLBCL patients require pre-phase treatment, or whether there are certain risk factors such as advanced age that preclude its requirement, is still to be established.

For supportive medications during frontline treatment, two guidelines recommend prednisone prophylaxis (100 mg/day) for either 3-7 days (AB) or 5 days (ON) prior to R-CHOP or R-CEOP for patients › 60 years to prevent toxicity to chemotherapy regimen[39]. Another guideline (NS) provided numerous recommendations for supportive treatment. Allopurinol, a drug that prevents the build-up of uric acid, a side-effect of cytotoxic therapies for lymphoma, is recommended for patients at high risk for tumor lysis at a dose of 300mg daily x 5 days for the first cycle only of R-CHOP. As tumor lysis is rare in DLBCL, allopurinol is not commonly used. Granulocyte colony stimulating factor (G-CSF), can be used as a prophylaxis to regulate the production and function of neutrophils in order to accelerate neutrophil recovery time in patients receiving curative regimens[40-41]. This is especially important for patients receiving curative regimens as if there is a delay in receiving cancer treatment due to adverse events such as neutropenia, it could compromise the outcome for that patient. Filgrastim/pegfilgrastim primary prophylaxis are two types of G-CSF recommended for use in patients aged › 65 years, HIV positive patients, or patients felt to be at high risk (› 20%) of febrile neutropenia (open wounds, active infection, bone marrow infiltration by cancer, poor performance status, combined chemo-radiation)[42-46]. Pegfilgrastim is recommended in most cases where HD-MTX is used for CNS prophylaxis; filgrastim should be used to shorten the chemo-free interval and should be stopped 48 hours prior to chemotherapy.

RECOMMENDATION

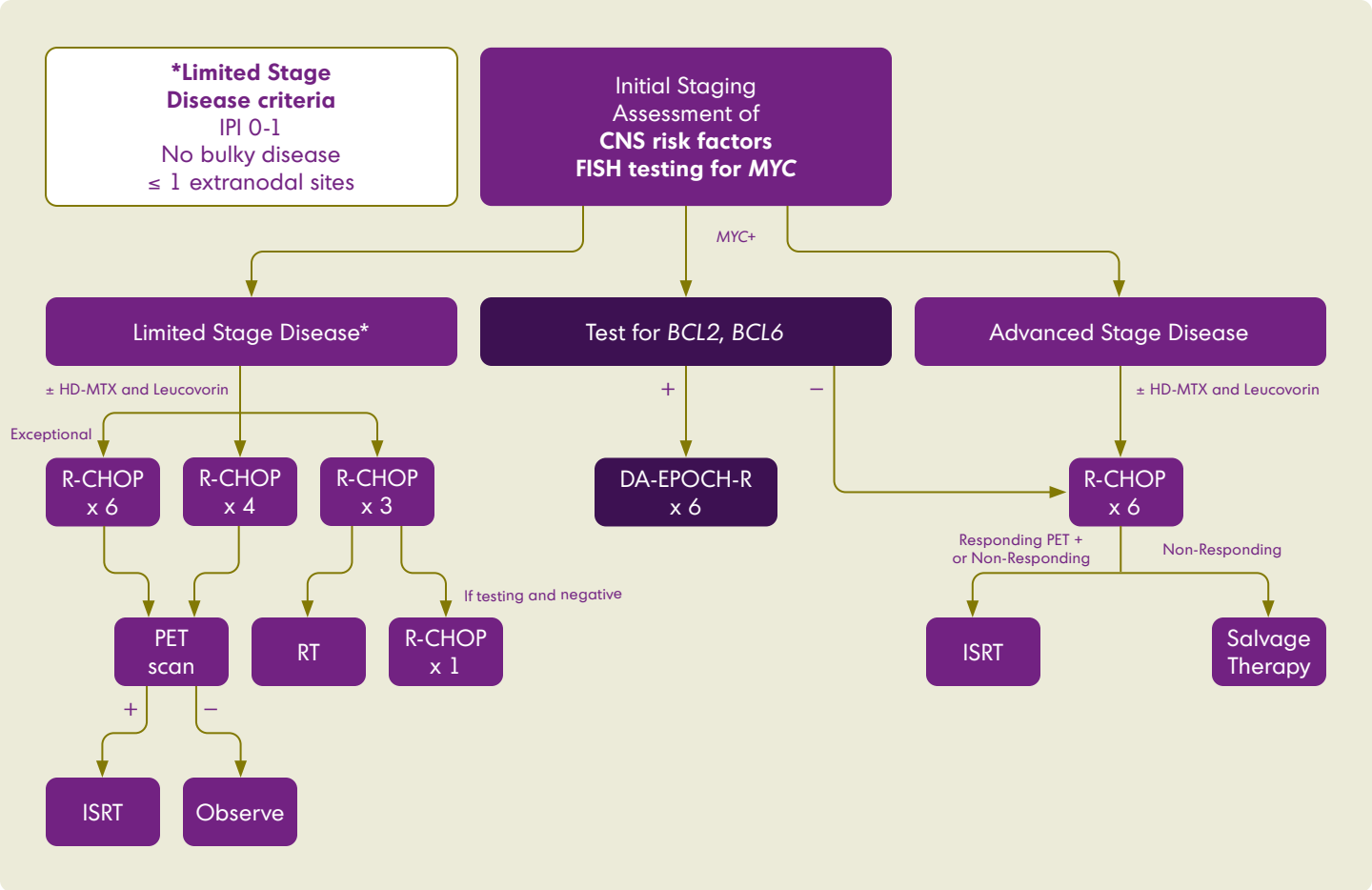
Should consider pre-phase administration of corticosteroids in symptomatic patients and/or older patients (› 60 years), and primary prophylaxis with G-CSF for › 60 years of age receiving R-CHOP or R-CEOP. However, any patient with an episode of febrile neutropenia, regardless of age, should receive subsequent G-CSF prophylaxis.

Summary of Recommendations for DLBCL Treatment

- Definition for limited stage disease: IPI 0-1, no bulky disease (provinces have different definitions of bulk disease), and ≤ 1 extranodal site.
- Recommendation for limited stage disease: R-CHOP x 3* - 4 cycles, with exceptional 6 cycles, followed by PET scan. There is the option to give response-adapted treatment with PET (groups have different approaches).
  - *For R-CHOP x 3, proceed with either RT-planned combined modality, or proceed with PET imaging and if negative undergo one additional cycle of R-CHOP.
- Recommendation for advanced stage disease: standard therapy is 6 cycles of R-CHOP. Recommend ISRT if localized responding PET positive (Deauville 4-5) disease at the end of R-CHOP treatment.
  - *If new site or progression (non-responding), treatment options can include ISRT or other salvage therapy.
- It is recommended that all patients with DLBCL be tested by FISH for *MYC*, with reflex testing for *BCL2* and/or *BCL6* if *MYC* positive.
- Recommendation for patient with *MYC* rearrangement: 6 cycles of R-CHOP.
- The recommended treatment for double-hit and triple-hit lymphoma is DA-EPOCH-R x 6 cycles.
  - *May consider HD-MTX at the end of regimen for high-risk CNS patients.
- Patients at high-risk for CNS involvement could consider receiving prophylaxis with high-dose methotrexate (2-4 cycles, dose of 3g/m^2) in addition to R-CHOP. Patient characteristics and scheduling of HD-MTX administration may differ across institutions
- Recommendation for patients with cardiac toxicity: In this setting, curative therapy can be delivered. This will likely not involve R-CHOP alone, and may involve additional therapies as per institutional guidelines.
- Should consider pre-phase administration of corticosteroids in symptomatic patients and/or older patients (› 60 years), and primary prophylaxis with G-CSF for › 60 years of age receiving R-CHOP or R-CEOP. However, any patient with an episode of febrile neutropenia, regardless of age, should receive subsequent G-CSF prophylaxis.

Based on these recommendations, a treatment algorithm for DLBCL patients undergoing frontline treatment provides the optimal treatment path(s) based on the patients' disease stage, molecular status and CNS and cardiac risk factors (**Figure 1**).

Figure 1. Treatment Algorithm for Frontline Treatment Options for DLBCL Patients



ABBREVIATIONS: IPI (International Prognostic Index), ISRT (involved site radiation therapy), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), CNS (central nervous system), HD-MTX (high-dose methotrexate), DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), RT (radiation therapy), PET (positron emission tomography), FISH (Fluorescence in situ hybridization).

Conclusion

Despite the widespread standardization of R-CHOP for the frontline treatment for DLBCL, there is still variability in the number of cycles of R-CHOP recommended, use of interim PET, and use of radiation consolidation. There are numerous patient factors to consider when determining the final treatment course. The guidelines in this report categorize treatment strategies based on limited and advanced DLBCL, while also considering other factors such as molecular features, CNS involvement, pre-phase treatment and cardiac toxicity. Molecular testing is recommended for all DLBCL patients. If patients are *MYC* positive, reflex testing for *BCL2* and/or *BLC6* will determine the frontline treatment approach. For *MYC* positive patients, accepted therapy includes R-CHOP x 6 cycles. If the patient tests positive for double-hit or triple-hit DLBCL, the optimal treatment strategy is DA-EPOCH-R.

For patients that test negative for molecular features, treatment strategy is based on limited versus advanced stage disease. For limited stage disease patients, risk factors may play a role in the number of R-CHOP cycles depending on the institution and province. Patients may undergo R-CHOP x 3, 4 or 6 cycles followed by a PET scan to assess response. There is the option to response-adapt with PET. Evidence supports patients receiving three cycles of R-CHOP to either undergo pre-planned RT combination modality or PET-guided treatment with one additional R-CHOP cycle if PET negative. For patients with advanced stage disease, the recommendation is for 6 cycles of R-CHOP followed by ISRT if there is localized residual disease.

Other important considerations include patients at risk for CNS involvement, patients with cardiac disease, and pre-phase treatment for patients at risk. For patients at risk for CNS involvement, there is the option to receive prophylaxis with high-dose systemic methotrexate in addition to leucovorin alongside R-CHOP. For patients with cardiac disease, curative therapy can be delivered through different treatment additions to R-CHOP as per institutional guidelines. For patients that are › 60 years of age that are symptomatic, corticosteroids could be considered, and primary prophylaxis with G-CSF should be considered in patients › 60 years of age.

Conflict of Interest Disclosures

The following represents disclosure information from the authors within the last two years related to the subject matter of this guideline.

MS: Novartis, Kite/Gilead, BMS; **MB:** Novartis, Kite/Gilead; **JK:** Kite/Gilead, BMS, Novartis; **KS:** Kite/Gilead, BMS, Merck, Roche; **PS:** Novartis, BMS; **MMK:** Roche; **RT:** n/a

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