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CANADIAN EVIDENCE-BASED GUIDELINE FOR THE

Treatment of Relapsed/Refractory 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 in North America. While most patients often respond well to frontline treatment, there is a significant proportion of patients (30-40%) that will either be refractory to or relapse following frontline therapy. The standard of care for patients in the relapsed/refractory setting includes salvage therapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) for patients whose disease demonstrate chemosensitivity and who are fit and transplant eligible. However, there is a group of patients that do not demonstrate chemosensitivity to salvage therapy, are ineligible for ASCT, or relapse post-SCT. For this group of patients, there are variable treatment options which may differ across the Canadian provinces due to access and funding. In Canada, no unified national guideline exists for the treatment of relapsed/refractory DLBCL, and the provincial guidelines in existence vary.

A national treatment guideline supported by Canadian hematologists is warranted to ensure that patients with relapsed/refractory DLBCL are treated according to best practice and have equitable access to best available care. A group of experts from across Canada have developed a national evidence-based treatment guideline to provide healthcare professionals with clear guidance on the management of relapsed or refractory 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, Relapse, Refractory.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of Non-Hodgkin lymphoma (NHL) and constitutes 30-40% of all Canadian NHL cases. DLBCL represents a heterogeneous group of aggressive B-cell malignancies that differ in prognosis, clinical and molecular features, and treatment options. Classifying patients by appropriate DLBCL subtype and accounting for additional risk factors are important in establishing the grade of aggressiveness of the lymphoma to determine prognosis. However, this is often difficult in practice and may not necessarily have implications on the treatment and management plan.

Due to the aggressiveness of DLBCL, rapid diagnosis and initiation of frontline treatment are essential. There are specific recommendations for frontline treatment for Canadian DLBCL patients based on high-risk molecular features, central nervous system disease, and risk factors¹. Following treatment with the standard frontline therapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), approximately 30-50% of treated patients will suffer from relapse or refractory disease². For these patients, the standard approach is salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) for those who meet the eligibility criteria and have chemosensitive disease. In contrast, those who do not show chemosensitivity to salvage therapy are not transplant eligible. This group of patients, along with those who relapse following ASCT, are eligible for chimeric antigen receptor (CAR) T-cell therapy. However, provincial funding currently varies and some patients are required to travel out of province or country to access CAR-T therapy. For those that are not eligible for CAR-T therapy or fail treatment, there is no standard treatment approach and treatment will depend on access to clinical trials as well as patient-related factors. Across Canada, several barriers could hinder the availability and timely access to therapies. Such factors can include provincial funding decisions, number and availability of hematologists or oncologists within the province to provide timely access, and number and location of treatment centers. These barriers can result in inequities and delays in treatment for DLBCL patients, especially in the relapse/refractory setting where experimental treatment options may only be available in certain provinces and at certain hospitals through clinical trials.

There are provincial guidelines in existence that distinguish optimal treatment approaches for DLBCL patients based on the presence of comorbid disease, DLBCL subtypes, and in some provinces IPI risk groups. However, guidelines are not universally available in all provinces and thus provinces may differ in their recommendations based on institutional considerations. There is currently no Canadian-wide guideline that provides a roadmap to the standardized management of DLBCL in the relapsed/refractory setting. This indicates a need for an evidence-based guideline. In collaboration with Lymphoma Canada, a group of Canadian DLBCL experts have developed a nationwide consensus-guideline based on the current best available evidence for the management of patients with relapsed/refractory DLBCL.

GUIDELINE RECOMMENDATIONS

1. Proposed high-dose chemotherapy and ASCT eligibility criteria;
2. Recommendation for patients ineligible for ASCT;
3. Recommendation for patients who do not respond to salvage chemotherapy;
4. Proposed chimeric antigen receptor (CAR) T-cell therapy eligibility criteria;
5. Recommendation for patients when CAR-T therapy is not feasible or for those who are ineligible for CAR-T therapy.

Methodology

An initial web-based search was performed on all provincial cancer centers to identify whether DLBCL management guidelines are in existence. DLBCL provincial experts were contacted to verify guidelines and provide insight and input if a guideline could not be located. Once existing guidelines were collected, information was extracted and differentiated based on common treatment considerations. Following compilation of provincial and institutional guidelines, this information was reviewed by the nationally developed panel of Canadian DLBCL experts for the development of recommendations, incorporating important considerations for patients in the relapse/refractory setting. The National Comprehensive Cancer Network categories of evidence and consensus (**Table 1**) was used by the steering committee to grade the level of evidence and support for the recommendations for relapsed/refractory DLBCL patients³. Consensus was achieved based on the level of evidence and support for each recommendation. 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.

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, 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 to confirm the existence of in-province/territory guidelines.

Physicians that did not have guidelines within their own province indicated they referred to BC Cancer (MB, PEI), Alberta Health Sciences (SK), Nova Scotia Cancer Care Program (PEI), Princess Margaret Cancer Centre (PMCC) and the National Comprehensive Cancer Network (NCCN) guidelines and adopted these guidelines to what is available locally and based on institutional regulations. Specific guidelines have not been uniformly adopted or endorsed, and feedback from specialists indicated an interest in the creation of a national DLBCL treatment guideline for both frontline and relapsed/refractory settings.

The information included in the existing provincial guidelines was reviewed for common themes to determine the methodology for data extraction and compilation to highlight similarities and differences. For relapsed/refractory treatment, the common themes for treatment determination included transplant eligible vs. transplant ineligible and beyond second line treatment. The data from the existing guidelines was compiled according to these common themes as shown in **Table 2**.

Table 2: Summary of Provincial Guidelines for Relapse/Refractory DLBCL Treatment Options

PROVINCIAL GUIDELINES	BRITISH COLUMBIA	ALBERTA	ONTARIO			NOVA SCOTIA
			Sunnybrook Health Sciences Centre	Princess Margaret Cancer Centre	Cancer Centre of Southeastern Ontario	
Stem cell transplant candidate	GDP±R → if CR/PR → HDC + SCT	GDP±R → HDC* + in-vivo purge blood of tumour cells + ASCT *R-DICEP or R-MICE	GDP±R → if CR/PR → HDC + SCT	PET+ → biopsy+ → GDP±R → if PR/CR → HDC + SCT	GDP±R → if PR/CR → HDC* + ASCT *GDP, ICE, DHAP, ESHAP, EPOCH	GDP±R → if CR/PR → HDC* + SCT *R-DHAP, R-ICE, R-mini-BEAM
Non-responders to salvage or non-stem cell transplant candidates	CAR T-cell therapy preferred** If ineligible for CAR-T → clinical trial, palliative chemotherapy or RT	CAR T-cell therapy preferred** If ineligible for CAR-T → salvage therapy (DHAP, ICE, GDP, CEPP, MEP) or ISRT to symptomatic sites	CAR T-cell therapy preferred** If ineligible for CAR-T → clinical trial or palliative regimen (cyclophosphamide/ celebrex or VP-16)	CAR T-cell therapy preferred** If ineligible for CAR-T → palliative regimen or clinical trial	CAR T-cell therapy preferred** If ineligible for CAR-T → palliative radiation or chemotherapy	CAR T-cell therapy preferred** If ineligible for CAR-T → salvage chemotherapy, radiation, steroids, clinical trial
Beyond 2nd line including ASCT failure	CAR T-cell therapy preferred** If ineligible for CAR-T → clinical trial, palliative chemotherapy or RT	CAR T-cell therapy preferred** If ineligible for CAR-T → prednisone alone, below dose daily oral, chemotherapy + chlorambucil or etoposide or combination oral therapy (PEP-C) Clinical trial is also an option	CAR T-cell therapy preferred** If ineligible for CAR-T → clinical trial, palliative chemotherapy	CAR T-cell therapy preferred** If ineligible for CAR-T → clinical trial, palliative chemotherapy	CAR T-cell therapy preferred** If ineligible for CAR-T → clinical trial, palliative or chemotherapy	CAR T-cell therapy preferred** If ineligible for CAR-T → salvage chemotherapy, radiation, steroids, clinical trial

**Where CAR T-cell therapy is recommended across the provinces, bridging therapy which can include alternative salvage therapy, radiation, etc., may be required. There is no province-specific bridging therapy.

ABBREVIATIONS: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), ASCT (autologous stem cell transplant), SCT (stem cell transplant), HDC (high-dose chemotherapy), GDP±R (gemcitabine, dexamethasone, cisplatin±Rituximab), ICE (ifosfamide, mesna, carboplatin, etoposide), R-ICE (ICE + rituximab), R-MICE (mitoxantrone, idarubicin, etoposide, cytarabine, rituximab), ISRT (involved-site radiotherapy), CAR-T (chimeric antigen receptor T-cell therapy), DHAP (dexamethasone, cytarabine, cisplatin), R-DHAP (rituximab + DHAP), R-DICEP (dose-intensive cyclophosphamide, etoposide, cisplatin, rituximab), RT (radiation therapy), VP-16 (etoposide, prednisone, vincristine), PET (positron electron tomography) scan, R-mini-BEAM (rituximab, carmustine, etoposide, cytarabine, melphalan), MEP (methotrexate, etoposide, cisplatin), EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), ESHAP (etoposide, cytarabine, cisplatin, methylprednisolone), CEPP (cyclophosphamide, etoposide, procarbazine, prednisone), PR (partial response), CR (complete response), PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide).

Relapsed/Refractory DLBCL Treatment

With the frontline immunochemotherapy regimen R-CHOP, more than 50% of advanced-stage de novo DLBCL patients are expected to be cured^{4,5}. However, there are factors that can prevent this outcome. Between 30-50% of patients with DLBCL will be refractory to R-CHOP or will relapse after achieving a complete remission due to adverse prognostic factors^{4,6,7}. Most relapses will occur within the subsequent 2-3 years after initial treatment. Patients that relapse early (within 12 months), or patients with refractory disease, will have a worse prognosis even with second line therapy⁸.

Salvage Therapy and High-Dose Chemotherapy Followed by ASCT

Autologous stem cell transplantation (ASCT) is the standard treatment approach for DLBCL patients with chemosensitive disease that otherwise meet the eligibility criteria for this therapy. Certain criteria that could exclude patients from stem cell transplant include increasing age and comorbid health conditions. Older age (> 65 years) is not necessarily a contraindication to ASCT, and thus may be feasible in older more fit patients⁹. According to the stem cell transplant guidelines, ineligibility criteria for ASCT includes patients with poor performance status, active CNS involvement, and/or severe concomitant medical or psychiatric illness¹⁰. Patients with HIV seropositivity may be considered for ASCT if well-controlled. Additional ineligibility criteria to assess organ function typically includes bilirubin level > 2xULN, creatinine level > 150 µmol/L, creatinine clearance < 50ml/min, low cardiac ejection fraction (< 50%), and a forced expiratory volume in one second < 50% and/or carbon monoxide diffusion test < 50% of predicted level; these values may differ according to provincial standards¹¹.

Patients with primary refractory disease, which is typically defined as progression on therapy or within three months of treatment completion, are less likely to respond to salvage chemotherapy regimens and as a result will be less likely to benefit from ASCT. The landmark PARMA trial for establishing the role for ASCT over salvage chemotherapy alone showed an increase in event free survival (46% vs 12%) and 5-year overall survival (OS) (53% vs 32%) in the transplantation group over conventional therapy^{12,13}.

Various studies have examined the use of different systemic treatment regimens prior to ASCT to maximize the response rate and OS. These regimens include R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin)¹⁴, ICE (ifosfamide, carboplatin, etoposide)¹⁵, R-ICE (rituximab plus ICE)¹⁶, GDP (gemcitabine, dexamethasone, cisplatin)¹⁷ and R-GEMOX (rituximab, gemcitabine, and oxaliplatin)^{18,19}. Achieving better response to salvage chemotherapy is associated with better outcomes following ASCT, but no salvage regimen has been shown to be superior to another²⁰.

The Canadian provincial guidelines and expert verification all report on stem cell transplant candidacy and salvage regimens in the relapsed/refractory setting for DLBCL patients. AB states the primary eligibility criteria for salvage chemotherapy followed by ASCT includes patients with good performance status.

Age, used in the past as a measurement of performance, has been removed completely from the criteria across provinces, now placing an emphasis on fitness and tolerability of the patient. If residual mass is FDG-avid post-systemic therapy, a biopsy is recommended (ON-PMH; BC), whereby a positive biopsy meets the criteria to proceed with salvage chemotherapy and ASCT. Most guidelines that recommend a specific regimen for high-dose salvage chemotherapy recommend gemcitabine + dexamethasone + cisplatin (GDP), with or without rituximab. GDP is the preferred regimen as it can be given on an outpatient basis and is less toxic than alternatives, with preservation of a better quality of life^{17,21}. To maximize response to ASCT, it is recommended to include rituximab as part of the salvage chemotherapy regimen to in-vivo purge the blood of tumour cells. Certain provinces may currently, or in the past have been, required to consider the availability to use rituximab in combination with salvage chemotherapy with the intent to proceed to ASCT, as funding may only be provided after a certain amount of time has passed from frontline treatment with rituximab-based chemoimmunotherapy. Other provinces provide funding for rituximab combinations with all salvage regimens as required. The provinces have listed alternative regimen options in their guidelines such as DP+R (docetaxel, cisplatin, rituximab), R-DICEP (dose-intensive cyclophosphamide, etoposide, cisplatin, rituximab) or R-MICE (mitoxantrone, etoposide, and cytarabine, rituximab), R-DHAP, R-ICE, R-mini-BEAM (rituximab, carmustine, etoposide, cytarabine, melphalan), ESHAP (etoposide, cytarabine, cisplatin, methylprednisolone) and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin).

In determining the response rate to ASCT, there are a few notable studies. The CORAL study, which examined the role for ASCT in the setting of early relapse following frontline treatment with R-CHOP, demonstrated similar response rates between the R-ICE and R-DHAP regimens¹⁴. Further, DLBCL patients with early rituximab failure were found to have a higher risk of disease relapse within the first year of transplantation¹³. With this information, this calls for a further need to understand the prognostic indicators that can identify *r/r* DLBCL patients that are unlikely to benefit from ASCT in order to investigate alternative therapies. One study reported that the presence of at least two of three risk factors (primary progressive disease, *MYC* rearrangement, intermediate-high NCCN-IPI) predicted a poor 2-year OS²².

RECOMMENDATIONS

Based on high-level evidence, uniform consensus was achieved among the steering committee members on appropriate eligibility criteria for high-dose chemotherapy and ASCT:

- Fit patients (with no applied age restriction)
- Chemosensitivity disease
- Good performance status (ECOG \leq 2)
- No active CNS involvement
- Adequate organ function as defined per institutional guideline
- IPI 0-1, no bulky disease (provinces have different definitions of bulk disease), and \leq 1 extranodal site

Based on high-level evidence, uniform consensus was achieved among the steering committee for the recommendation for stem cell transplant eligible chemosensitive patients to receive:

salvage chemotherapy* followed by high-dose chemotherapy and autologous stem cell transplantation.

*Recommend GDP \pm R x3 cycles. R-ICE or R-DHAP may also be used with similar efficacy. R-DICEP is also an alternative.

Non-Stem Cell Candidates and Further Treatment Options

The prognosis of relapsed DLBCL patients who do not undergo high-dose therapy and ASCT is poor. Patients may either not meet the eligibility criteria to undergo ASCT, or not respond to salvage chemotherapy. Among patients who progress following frontline treatment, only 30-40% will respond to salvage chemotherapy and proceed with ASCT^{5,14,17,23}. Even for those patients that respond to salvage chemotherapy and undergo ASCT, 50% are likely to relapse following transplantation^{5,24,25}. The SCHOLAR-1 study among other similar studies, demonstrated that DLBCL patients that are refractory to second-line therapy or relapse within < 12 months post-ASCT have poor outcomes^{5,23,26,27,28}. In Canada, the standard approach for r/r DLBCL patients not responding to salvage chemotherapy or not eligible for ASCT is CAR T-cell therapy²⁰. Some provinces have funding and FACT (Foundation for the Accreditation of Cellular Therapy) accredited centers, and thus are able to administer manufactured CAR-T treatment locally. Other provinces will fund CAR-T therapy but will send their patients to receive treatment in other provinces or even to the United States. There are some provinces that also have new in-house CAR-T products available to patients through clinical trials. A list of current CAR T-cell therapies available to patients in Canada can be found in **Supplementary Table 1**.

Depending on the patient's health and fitness, treatment options for those that are ineligible for stem cell transplant, do not respond to salvage chemotherapy or relapse post-ASCT, include CAR T-cell therapy if appropriate, clinical trials, or palliative chemotherapy¹⁰ or radiotherapy²⁹. There are numerous chemotherapy options, but response rates are generally low and remission duration is short, however studies on the combination of these therapies are underway³⁰. Polatuzumab vedotin, bendamustine and rituximab (Pola-BR) demonstrated improved PFS (7.5 vs 2.0 months), OS (12.4 vs 4.7 months), and time to first response and CR compared with bendamustine and rituximab^{31,32,33}. This treatment provides a promising option for Canadians in this setting, as it is currently HC approved and recently obtained a positive CADTH recommendation for reimbursement. With high CR rates and prolonged disease control, Pola-BR is a beneficial stand-alone treatment and may even provide an important bridge in the future to consolidative therapies including SCT or CAR-T.

Another promising agent evaluated in combination with polatuzumab vedotin was obinituzumab, with a PFS and OS of 6.3 and 10.8 months respectively at median follow-up³⁴. However, in comparison with Pola-BR, there was no indication of benefit of obinituzumab over rituximab in this setting³³. Another therapy combination includes lenalidomide and tafasitamab, which demonstrated a modest ORR, with 43% having a CR, and is currently FDA approved and awaiting review by HC^{35,36}. Neither of these regimens thus far are provincially funded, nor are their backbone therapies BR and lenalidomide, respectively. Other combination regimens are still in testing including ibrutinib, lenalidomide and rituximab, showing an ORR of 44%³⁷. Chemotherapy options for fit patients can include R-ICE, R-GemOx (rituximab, oxaliplatin, cytosine arabinoside, dexamethasone)³⁸, and R-DHAX/rituximab, oxaliplatin, cytosine arabinoside, dexamethasone (ROAD)^{39,40,41}. Palliative strategies can also be employed and should be simple to use, not require intravenous administration, and allow for outpatient administration⁴². Options tested but not all currently available in Canada include oral agents (prednisone, etoposide, procarbazine, cyclophosphamide) used alone or in combination (i.e. PEP-C)⁴², or intravenous therapy including GEPD (gemcitabine, etoposide, cisplatin, dexamethasone), DHAP, ESHAP, and EPIC (etoposide, prednisolone, ifosfamide, cisplatin)⁴³.

Rarely, patients can have late relapses and may be eligible to receive curative intent therapy in the absence of transplant. Localized disease should be treated with combined modality therapy, while for advanced stage disease, combination chemotherapy may be appropriate especially with a low secondary IPI; this may be a curative approach in a minority of patients¹². However, for the majority of transplant ineligible patients, as well as for those who have relapsed following transplant, the first consideration is eligibility for CAR-T treatment. For those that are ineligible for CAR-T, options are broad but may include further palliative chemotherapy or radiotherapy, or clinical trials. Clinical trials are the favoured approach if patients meet the eligibility criteria and are interested in participating. Although rare, patients with good performance status may be suitable for further combination chemotherapy including R-GDP, and less commonly R-ICE. For less fit patients, single agent chemotherapy may be used. Of note, these regimens can also be used as bridging therapy for CAR T-cell therapy. Other options for symptomatic management for this patient group at the time of palliation, or beyond second relapse, can include low dose daily oral chemotherapy with chlorambucil (0.1mg/kg/day) or etoposide (50 mg/day), prednisone, palliative regimen (cyclophosphamide/Celebrex or VP16/prednisone) or combination oral therapy (i.e. PEP-C), as detailed and endorsed by specific Canadian guidelines. This shows a high unmet need for reliable and effective treatment options for patients that are ASCT ineligible or progress following ASCT, where CAR-T may not be an option.

Four of the six Canadian guidelines available (AB, ON, NS, BC), more recent in their versions, present the option of CAR-T therapy for patient's ineligible for ASCT, have refractory disease post-frontline treatment and following two lines of therapy, or relapse following ASCT. However, CAR-T is employed across the country, even though provincial guidelines in existence may not have been recently updated with this information. For example, though CAR-T is available as a treatment option locally in Quebec, no provincially published treatment guideline is available stating this. CAR-T treatment provides a potentially curative approach in this patient population where cure was largely not possible. Results from the ZUMA-1 and JULIET trials were pivotal for understanding the role of CAR-T therapy in the setting of contraindications for ASCT or relapse following ASCT. With CAR-T, about 40% of patients achieved a CR and 12% achieved a PR⁴⁴.

Though higher among the CR patients, at 12 months the rate of RFS was 65%⁴⁴. Currently, CAR-T is approved in Canada for DLBCL patients that are disease refractory or have relapsed following two or more lines of therapy. If this option is not appropriate due to ineligibility criteria which can include decreased performance status, organ dysfunction (renal, cardiac, pulmonary) and active CNS disease, patients will typically be considered for clinical trials or palliative treatment options⁴⁵. It is recommended that CAR-T is preferred over allo-SCT, and allo-SCT may be an option in some provinces if the patient relapses after CAR-T.

Bridging therapies are used if there is a concern for or evidence of progressive disease, causing symptoms or worsened clinical status. Therapies include single-agent treatment with cyclophosphamide, cytarabine, gemcitabine, GDP±R, DHAP±R, ICE±R, localized radiation therapy for bulky or symptomatic disease, steroids (dexamethasone or methylprednisolone), or GemOx±R²⁰.

RECOMMENDATIONS

Based on high-level evidence, uniform consensus was achieved among the steering committee for the recommendation for patients that are eligible for intensive therapy following failed salvage therapy or failed SCT to receive: CAR T-cell therapy.

Based on high-level evidence, uniform consensus was achieved among the steering committee for CAR-T eligibility criteria:

- Patient has received 2 or more lines of systemic therapy
- Good performance status (ECOG \leq 2)
- Not received prior adoptive T-cell immunotherapy
- No active CNS disease
- No significant compromise to vital organ function (as defined per institutional guidelines)

Based on lower-level evidence, uniform consensus was achieved among the steering committee to recommend relapsed/refractory patients ineligible for CAR-T to receive: palliation therapy or treatment through clinical trials.

*Recommend GDP \pm R x3 cycles. R-ICE or R-DHAP may also be used with similar efficacy. R-DICEP is also an alternative.

Summary of Recommendations for Relapsed/Refractory DLBCL Treatment

- High-dose chemotherapy and ASCT eligibility criteria:
 - Fit patients (with no applied age restriction)
 - Chemosensitivity disease
 - Good performance status (ECOG ≤ 2)
 - No active CNS involvement
 - Adequate organ function as defined per institutional guideline
- Recommendation for stem cell transplant eligible chemosensitive patients is to receive salvage chemotherapy* followed by high-dose chemotherapy and autologous stem cell transplantation.
 - *Recommend GDP \pm R x3 cycles. R-ICE or R-DHAP may also be used with similar efficacy. R-DICEP also is an alternative.
- Recommendation for patients eligible for intensive therapy following failed salvage therapy or failed SCT is to receive CAR T-cell therapy.
- CAR-T eligibility criteria:
 - Patient has received 2 or more lines of systemic therapy
 - Good performance status (ECOG ≤ 2)
 - Not received prior adoptive T-cell immunotherapy
 - No active CNS disease
 - No significant compromise to vital organ function (as defined per institutional guideline)
- Recommendation for relapsed/refractory patients ineligible for CAR-T is palliation therapy or treatment through clinical trials
 - New options may become available in this setting such as Pola-BR
- Based on these recommendations, a treatment algorithm for relapsed/refractory DLBCL patients provides optimal treatment path(s) (**Figure 1**).

Conclusion

Despite the progress in frontline therapy response rates for DLBCL patients, patients still experience disease relapses or are refractory to frontline treatment. The standard recommended therapy for this patient population is salvage therapy followed by high-dose chemotherapy and autologous stem cell transplantation. Though this treatment option does have a positive outcome in a large percentage of r/r DLBCL patients, there is still a group of patients that are ineligible for ASCT, are not responsive to salvage chemotherapy, or relapse post-ASCT. This patient group has a poor prognosis and is in need for effective treatment approaches. With CAR T-cell therapy being approved in Canada, this provides patients an encouraging prognosis.

The recommendation for patients in this group is to receive CAR-T, with bridging therapy if required. For patients that are not eligible for CAR-T or relapse post-CAR T-cell therapy, the recommendation includes palliative therapies and clinical trials. New options may become available in this setting once funded, such as Pola-BR. These are the recommendations issued by the national steering committee of leading hematologists and oncologists across Canada for patients with relapsed/refractory DLBCL.

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 (formally Celgene); **MB:** Novartis, Kite/Gilead, BMS (formally Celgene); **JK:** Kite/Gilead, BMS, Novartis; **KS:** Kite/Gilead, BMS, Merck, Roche; **PS:** Novartis, BMS; **ME:** Kite/Gilead, BMS/Celgene, Novartis.

Supplementary Table 1. CAR T-Cell Therapies Approved for Use in Canada

CAR T-CELL THERAPY	DESCRIPTION	INDICATION	HEALTH CANADA APPROVAL DATE
Tisagenlecleucel (Kymriah)	CD19-directed genetically modified autologous T-cell immunocellular therapy.	adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.	September 2018
Axicabtagene Autoleucel (Yescarta)	CD19-directed genetically modified autologous T-cell immunotherapy.	adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	February 2019

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