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Practical Management of Aggressive B-Cell Lymphomas with CD20×CD3 Bispecific Antibodies

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CD20×CD3 bispecific antibodies (BsAbs) have transformed the therapeutic landscape of relapsed or refractory large B-cell lymphoma (LBCL). By redirecting T cells to target CD20-expressing lymphoma cells, these off-the-shelf agents offer high response rates and durable remissions in patients who previously had limited options, including those who relapse after chimeric antigen receptor T-cell therapy. In Canada, epcoritamab and glofitamab are now approved for patients with LBCL after at least two prior lines of treatment. The combination of glofitamab, gemcitabine, and oxaliplatin has been recently approved for patients with relapsed/refractory diffuse large B-cell lymphoma not otherwise specified LBCL after at least 1 line of therapy and who are ineligible for autologous hematopoietic stem cell transplant. This review provides a practical framework for Canadian hematologists: identifying eligible patients, implementing pretreatment evaluation, safely delivering therapy in inpatient and outpatient settings, and managing toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. We will also discuss infection prophylaxis, sequencing with cellular therapies, and future directions for BsAbs in earlier treatment lines.

Introduction

Despite advances with immunochemotherapy, autologous hematopoietic stem cell transplantation, and chimeric antigen receptor (CAR) T-cell therapy, relapsed or refractory (R/R) large B-cell lymphoma (LBCL) remains incurable in more than half of patients.[1-6] Also, approximately 30–40% of patients are not candidates for CAR T-cell therapy because of comorbidities or logistical barriers.[7,8] For these patients, outcomes have historically been poor, with median overall survival measured in months.[9] Unlike CAR T-cell therapy, bispecific antibodies (BsAbs), such as the CD20xCD3 BsAbs glofitamab and epcoritamab, are readily available, can be administered without manufacturing delays, and are feasible in both academic and community settings.[10-12]

Indications and Patient Selection

In Canada, glofitamab is approved for the treatment of adult patients with R/R diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), DLBCL transformed from indolent follicular lymphoma (FL), or primary mediastinal B-cell lymphoma after two or more lines of systemic therapy, for those who have previously received or are unable to receive CAR T-cell therapy.[13] Epcoritamab is approved for the same indications, as well as for high-grade lymphoma, DLBCL transformed from indolent lymphoma, and grade 3B FL.[14]

Both epcoritamab and glofitamab demonstrated high response rates and durable remissions in heavily pretreated populations. In the EPCORE NHL-1 study, epcoritamab achieved an overall response rate (ORR) of 63% with 39% complete responses (CR) in patients who had a median of three prior therapies (range 2–11), including CAR T-cell therapy (38,9%).[15] Responses were durable at two years of follow-up in a significant proportion of responders. Among patients who achieved a CR, 64% remained in CR at 2 years.[16] Similarly, glofitamab showed an ORR of 52% and a CR rate of 39% in its pivotal trial, which included patients previously treated with CAR T-cell therapy (33.1% of patients in the trial), with long-term remissions documented even in those with post–CAR T-cell therapy relapse.[8,17] The populations most likely to benefit from these treatments are those ineligible for CAR T-cell therapy due to comorbidities or age, those relapsing after CAR T-cell therapy, and patients with rapidly progressive disease requiring immediate therapy.[8,18] However, responses are less favourable when relapse occurs within three months of CAR T-cell therapy.[7] In Canadian practice, where CAR T-cell therapy access may be limited for patients living far from an approved CAR T centre, BsAbs provide an important and scalable alternative.

More recently, the combination of glofitamab, gemcitabine, and oxaliplatin (Glofit-GemOx) was approved for patients with R/R DLBCL NOS, after at least 1 line of therapy, who are ineligible for autologous hematopoietic stem cell transplant.[13] This approval represents a major advance for patients who historically had limited therapeutic options when a transplant was not feasible.[19] The STARGLO Phase III trial compared Glofit-GemOx with the standard rituximab, gemcitabine, and oxaliplatin (R-GemOx) regimen in transplant-ineligible patients. Glofit-GemOx demonstrated a clear and clinically meaningful improvement in outcomes. The median overall survival was not reached with Glofit-GemOx versus 13.5 months with R-GemOx, translating into a 24-month overall survival rate of 54.4% versus 33.6%, respectively. Similarly, the median progression-free survival was 13.8 months for Glofit-GemOx and 3.6 months for R-GemOx. Response rates were also superior, with a CR rate of 58% in the Glofit-GemOx arm versus 25% in the R-GemOx arm.[20] These findings establish Glofit-GemOx as a new standard of care for patients with R/R DLBCL who are not candidates for autologous hematologic stem cell transplantation, bridging an important therapeutic gap, and further highlighting the potential of BsAb-based combinations in aggressive B-cell lymphomas.

Pretreatment Evaluation

Safe delivery of BsAbs requires a thorough pretreatment assessment. Histologic confirmation of CD20-positive LBCL is recommended. Loss of CD20 is reported in up to 12 % of patients.[21] Repeating a biopsy prior to BsABs might be useful even after documentation of the loss of CD20, as one report has shown the reoccurrence of the expression of CD20.[22] Laboratory work should include complete blood count, renal and hepatic function, lactate dehydrogenase, and baseline immunoglobulins.[10] All patients require Hepatitis B virus (HBV) serologies (HBsAg, anti-HBc,

anti-HBs). HBsAg-positive or anti-HBc–positive patients should begin antiviral prophylaxis before the first BsAb dose.[23] Screening for Hepatitis C (HCV) and human immunodeficiency virus (HIV) is recommended, and vaccination history should be reviewed. Prophylaxis against *Pneumocystis jirovecii* and herpesviruses is recommended. Intravenous immunoglobulin (IVIG) may be needed to prevent recurrent infections or treat hypogammaglobulinemia. Institutional readiness is crucial; tocilizumab must be stocked, staff should be trained in toxicity recognition and cytokine release syndrome (CRS) and immune effector cell-associated toxicity syndrome (ICANS) management protocol should be considered.[10]

Administration and Toxicity Management

Treatment with both glofitamab and epcoritamab uses step-up dosing to reduce the risk of cytokine release syndrome (CRS). Epcoritamab is administered subcutaneously, with weekly doses during the initial cycles, after which it is administered less frequently.[14] Glofitamab is given intravenously following a pre-dose of obinutuzumab, with treatment limited to 12 cycles.[13] The first higher step-up dose is often administered in a hospital or under extended observation, especially in patients with bulky disease or comorbidities.[13] Emerging evidence, including from the EPCORE NHL-6 study, supports outpatient administration in selected patients with structured monitoring pathways.[24] Premedication with dexamethasone has significantly reduced the incidence of CRS and should now be considered the standard of care for BsAbs CRS prophylaxis.[25]

CRS is the most common adverse event, affecting 30–60% of patients, usually in cycles 1–2.[15,18,20] Most CRS events are grades 1 or 2. Management follows the American Society for Transplantation and Cellular Therapy (ASTCT) consensus: supportive care for grade 1, tocilizumab for grade ≥2, and corticosteroids for persistent cases.[26] Immune effector cell-associated neurotoxicity syndrome (ICANS) is less frequently observed but clinically important. Symptoms include confusion, aphasia, or seizures. Corticosteroids are the mainstay of management.[10,26] Cytopenias and infections are also common, and may require granulocyte colony-stimulating factor (G-CSF) support, antimicrobial prophylaxis, and sometimes IVIG.[10] Standardized toxicity algorithms have been published and adapted by Canadian centres.[12] Outpatient administration is increasingly used to address resource limitations, with structured protocols ensuring safety through careful patient selection, standardized premedication, and early toxicity monitoring. With dedicated infusion pathways, rapid access to acute care, and robust patient education, many centres now manage most patients entirely as outpatients, preserving inpatient capacity while maintaining safety.[12]

Sequencing with CAR-T and Transplant

BsAbs demonstrate activity after CAR T-cell relapse, though outcomes are worse after an early relapse.[7,15,18] Importantly, prior BsAb exposure does not appear to compromise later CAR T-cell therapy efficacy.[27] For younger patients who achieve remission with a BsAb, allogeneic hematopoietic stem cell transplantation may be considered as consolidation in select cases.[28]

Conclusion

BsAbs represent an effective therapeutic option in R/R LBCL. Combined with GemOx, glofitamab now constitutes a new standard of care for patients ineligible for autologous hematopoietic stem cell transplant. With careful patient selection, structured monitoring, and standard toxicity management, these therapies can be delivered safely across Canada. They also complement CAR T-cell therapy therapy and are likely to play an increasing role in front-line therapy.

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