About the Authors

Colin Stewart, MD

Dr. Colin Stewart is a Hematologist at the Cross Cancer Institute in Edmonton, Canada. He earned his medical degree from the University of Alberta, followed by residency training in Internal Medicine and Hematology at the University of Calgary and a clinical fellowship in Hematology Oncology at the University of Alberta. Dr. Stewart specializes in the treatment of lymphoma and myeloma. His research interests include lymphoma, the re-appraisal of autologous stem cell transplantation, and health economics.

Affiliations: Cross Cancer Institute & University of Alberta, Edmonton, Canada

Robert Puckrin, MD

Dr. Robert Puckrin is a Hematologist and Clinician Investigator at the Arthur Child Comprehensive Cancer Centre, Alberta Blood and Marrow Transplant Program, and the University of Calgary in Calgary, Canada. Having obtained his medical degree from McGill University, he completed Internal Medicine training at the University of Toronto and subsequent training in Hematology and Hematopoietic Cell Transplantation and Cellular Therapy at the University of Calgary. His main clinical and research interests are in lymphoma, cellular therapy, clinical trials, and real-world data.

Affiliations: Arthur Child Comprehensive Cancer Centre & University of Calgary, Calgary, Canada.

doi.org/10.58931/cht.2026.5183

Current Management of Relapsed or Refractory Classic Hodgkin Lymphoma in Canada

Colin Stewart, MD
Robert Puckrin, MD

Introduction

Classic Hodgkin lymphoma (HL) is a rare B-cell malignancy with approximately 1,150 new cases diagnosed annually in Canada.[1] Outcomes have improved substantially over the past several decades, with HL-related mortality declining by 2.2–3.0% annually since 1984, reflecting advances in both first-line and salvage therapies.[1] Despite this progress, 10–30% of patients develop primary refractory or relapsed (R/R) disease, with risk influenced by stage, treatment regimen, and clinical features.[2-4] Relapse rates are further decreasing with contemporary first-line regimens such as nivolumab, doxorubicin, vinblastine, and dacarbazine (nivolumab-AVD) and brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD), and are now estimated at 5–10% in advanced-stage disease.[5,6] Key adverse prognostic factors at relapse include primary refractory disease, relapse within 12 months, and advanced-stage disease.[7-9]

The introduction of novel targeted therapies, including the anti-CD30 antibody-drug conjugate brentuximab vedotin (BV) and the programmed death-1 (PD-1) inhibitors nivolumab and pembrolizumab, has led to improved outcomes in R/R HL.[8] However, in Canada, access to targeted therapies has been constrained by delays in funding and restrictive approval criteria.[10,11] In this review, we address common challenges and outline our approach to the treatment of adults with R/R HL within the contemporary Canadian context.

Second-Line Treatment in Patients Eligible for ASCT

Role of ASCT

In medically fit patients, the management of R/R HL has traditionally consisted of second-line platinum-based chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT). This approach is supported by two landmark randomized trials demonstrating significant improvements in event-free survival, though not overall survival, with ASCT compared to standard chemotherapy.[12,13] Real-world data from the pre-novel agent era confirm durable remissions in approximately 50–60% of patients with R/R HL undergoing ASCT.[9,14,15] ASCT remains an effective curative modality for fit older patients, as well as for those with primary refractory disease and early or late relapses.[16-18]

Selection of Salvage Regimen

Choice of second-line regimen depends on patient fitness, institutional practice, and funding availability. Retrospective Canadian data support the use of gemcitabine, dexamethasone, and cisplatin (GDP), which has achieved overall response rates (ORR) of 62–71%, computed tomography (CT)-based complete response (CR) rates of 7-9%, transplantation rates of 88–96%, and 1.5-to-2-year progression-free survival (PFS) rates of 58–76%.[19,20] The more intensive dose-intensive cyclophosphamide, etoposide, cisplatin (DICEP) regimen, primarily used in Alberta, demonstrated an ORR of 86%, CT-based

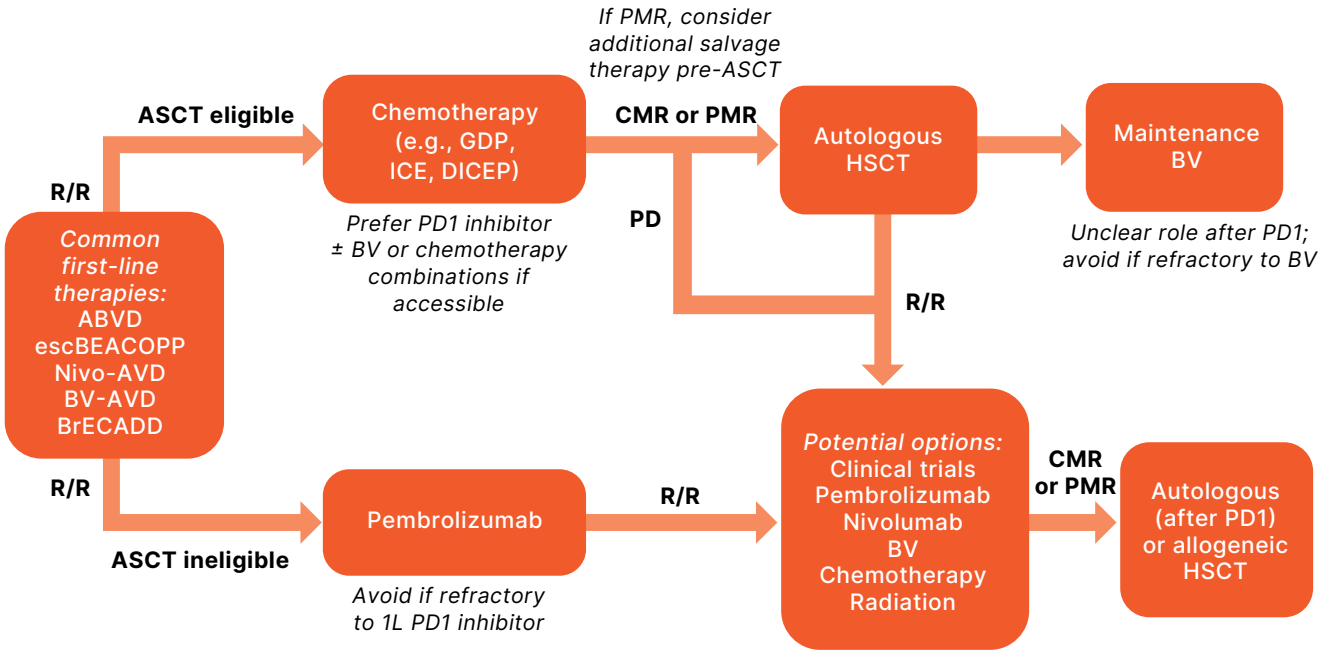

Figure 1. Treatment algorithm for refractory or relapsed Hodgkin lymphoma in Canada; *courtesy of Colin Stewart, MD and Robert Puckrin, MD.*

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; **ASCT:** autologous stem cell transplantation; **BV:** brentuximab vedotin; **BV-AVD:** brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; **BrECADD:** brentuximab, vedotin, etoposide, cyclophosphamide, doxorubicin, daracrbazine, and dexamethasone; **CMR:** complete metabolic response; **DICEP:** dose-intensive cyclophosphamide, etoposide, cisplatin; **escBEACOPP:** bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; **GDP:** gemcitabine, dexamethasone, and cisplatin; **HSCT:** hematopoietic stem cell transplantation; **HL:** Hodgkin lymphoma; **ICE:** ifosfamide, carboplatin, etoposide; **Nivo-AVD:** nivolumab plus doxorubicin, vinblastine, and dacarbazine; **PD:** progressive disease; **PD1:** programmed death-1; **PMR:** partial metabolic response; **R/R:** refractory or relapsed

CR rate of 18%, transplantation rate of 95%, and 5-year PFS of 61%.[15] Other established regimens include ifosfamide, carboplatin, etoposide (ICE), dexamethasone, cisplatin, cytarabine (DHAP), etoposide, high-dose cytarabine, cisplatinum (ESHAP), and gemcitabine, vinorelbine, doxorubicin (GVD).[21-23]

Pre-Transplant Response Assessment

Historically, patients with R/R HL could proceed to ASCT regardless of their response to salvage chemotherapy, and durable remissions were observed even among a subset with chemorefractory disease,[15,24] although accurate response assessment was limited by CT-based imaging. In the positron emission tomography (PET) era, achieving a complete metabolic response (CMR) prior to ASCT has emerged as a key prognostic factor, with PET-negative patients demonstrating 15–45% higher PFS compared to those with residual PET positivity.[8,25,26] Notably, several studies have reported comparable PFS among patients attaining pre-transplant PET negativity after one versus two lines of salvage therapy, suggesting a potential role for additional salvage treatment to convert a partial metabolic response (PMR) to a CMR before ASCT.[27,28] However, this approach has not been compared in prospective randomized trials against proceeding directly to ASCT in patients with PMR, and it remains unclear whether PET conversion itself causally improves outcomes or simply reflects more favourable disease biology. As such, it remains reasonable to proceed to

ASCT if an adequate PMR has been achieved particularly if alternative novel salvage regimens are unavailable, as over 50% of patients with a positive pre-transplant PET may still achieve durable remission.[8,26]

Impact of Targeted Therapies Before ASCT

The introduction of BV and PD-1 inhibitors has led to multiple single-arm phase II studies evaluating novel second-line regimens before ASCT. BV-based sequential or concurrent chemotherapy combinations (e.g., BV with bendamustine, gemcitabine, ICE, DHAP, or ESHAP) have demonstrated promising outcomes, with ORRs of 68–100%, CMR rates of 62–81% transplantation rates of 73–96%, and 2-to-3 year PFS rates of 63–82%.[28-32] Importantly, a randomized phase II trial demonstrated that the addition of BV to ESHAP increased CMR rates from 48% to 70%.[33]

PD-1-based strategies have shown particularly promising activity in the pre-ASCT setting, with retrospective data demonstrating superior 2-year PFS among patients undergoing ASCT after PD-1 inhibitor therapy (88%) compared to BV (70%) or chemotherapy (67%).[26] Phase II studies of PD-1 inhibitors ± BV or chemotherapy (e.g., GVD, ICE, gemcitabine and oxaliplatin [GemOx]) have reported ORRs of 85–100%, CMR rates of 67–97%, transplantation rates of 79–95%, and 2-to-3 year PFS rates of 72–96% among all patients and >90% among those undergoing ASCT.[34-39] Intriguingly, favourable 18-month PFS rates of 81% have been observed even among heavily pretreated, chemorefractory patients undergoing ASCT after third- or later-line PD-1 blockade, suggesting a paradoxical synergy between immune checkpoint inhibition and ASCT through deepened responses and/or resensitization to chemotherapy.[40]

Despite these encouraging data, second-line BV and PD-1 inhibitors are not currently funded in Canada for patients eligible for ASCT. Additionally, the future role of BV or PD-1-based salvage regimens is unclear given the increasing incorporation of these agents into the first-line setting.[5,6] Patients who are refractory to a targeted agent-containing regimen may be switched to an alternative novel agent and/or chemotherapy at relapse, whereas those with late relapse may be candidates for retreatment. Indeed, Canada's Drug Agency has endorsed retreatment with BV and PD-1 inhibitors for selected patients who relapse >6-12 months after treatment,[11,41] and small datasets support this approach in R/R HL.[42-44] The phase II CCTG HD11 trial, which randomized patients to BV plus pembrolizumab versus GDP prior to ASCT, has completed accrual and is expected to inform optimal salvage strategies in the Canadian context, including for patients with prior exposure to BV and PD-1 inhibitors.

Can ASCT be Omitted?

The efficacy of PD-1-based regimens has prompted interest in the potential for omitting ASCT in the era of novel agents. In a provocative phase II study, 24 patients who achieved CMR with pembrolizumab plus GVD received pembrolizumab maintenance without ASCT, resulting in a 2-year PFS of 60%. Outcomes were inferior in patients with stage IV disease, with a 2-year PFS of 37% versus 72% in those with stage I-III disease, although most patients who relapsed were successfully rescued with ASCT.[45] Another prospective trial reported a 2-year PFS rate of 79% among 73 patients with CMR after ESHAP ± BV who received maintenance BV instead of ASCT.[33] In addition, several pediatric studies also reported favourable outcomes with consolidative radiotherapy in lieu of ASCT in selected patients with low-risk relapse.[46-48] Although promising, these findings are preliminary in nature and insufficient to alter standard practice, particularly given the established curative potential of ASCT and its manageable safety profile in a generally fit population. However, ongoing randomized studies are evaluating whether ASCT can be safely omitted or deferred in selected patients.

Maintenance Therapy After ASCT

Post-transplant maintenance with 16 cycles (48 weeks) of BV is funded in Canada based on the AETHERA trial, which demonstrated a significant improvement in 5-year PFS (59% vs 41%) among high-risk patients who received ASCT for R/R HL, including those with primary refractory disease, early relapse within 12 months, or extranodal involvement.[7,49] However, BV maintenance has not been shown to improve overall survival, may represent overtreatment for some patients already cured by ASCT, and is associated with risks of neuropathy (67%), neutropenia (35%), gastrointestinal toxicity (>20%), and premature treatment discontinuation due to intolerance (33%). Its use should therefore be individualized, with the greatest benefit observed in patients with a positive pre-transplant PET or ≥2 enrolment risk factors.

Real-world data suggest the PFS benefit of maintenance BV is maintained despite dose reductions or early discontinuation.[50] Importantly, the AETHERA trial was conducted before the routine incorporation of targeted agents into first and second-line therapy. While there is conflicting retrospective data regarding the utility of maintenance BV among patients previously exposed to targeted agents,[51,52] there is no evidence to support its use among those refractory to BV. Maintenance BV does not appear to be necessary for those undergoing ASCT after PD-1-containing regimens, given the high cure rates with this strategy.[52]

Patients Ineligible for ASCT

Transplant ineligibility may result from advanced age, comorbidities, poor performance status, chemorefractory disease, or inadequate stem cell mobilization. Prior to the availability of BV and PD-1 inhibitors, outcomes for this population with conventional chemotherapy were poor.[53] In the randomized KEYNOTE-204 trial, which enrolled 304 adults with R/R HL who were either ineligible for (63%), or who had relapsed after (37%) ASCT, pembrolizumab was associated with a higher ORR (66% vs 54%) and a significantly improved PFS compared with BV (median 13 vs 8 months).[54] Pembrolizumab now represents the preferred funded second-line option for transplant-ineligible patients without prior PD-1 inhibitor resistance. BV is generally reserved for patients who are intolerant of or refractory to PD-1 inhibitors; however, in most Canadian provinces, its funding is restricted to the post-ASCT setting.

Of note, response assessment during PD-1 therapy may be challenging due to false-positive PET findings and pseudoprogression related to immune cell infiltration.[55] In cases of equivocal response, treatment continuation with repeat imaging and/or biopsy is appropriate to clarify disease status.[55] Data also support continuation of PD-1 blockade beyond progression in selected patients with asymptomatic, indolent relapse to maximize the clinical benefit of this therapy.[56,57]

Multiply Relapsed Disease

Post-ASCT Relapse

Outcomes for patients relapsing after ASCT have improved in the current era of PD-1 inhibitors and BV, with 4-year overall survival rising from 43% to 71%.[8] Both agents are broadly funded in Canada for patients relapsing after ASCT, and the superiority of PD-1 inhibitors over BV was confirmed in post-ASCT relapses in the KEYNOTE-204 trial.[54] While the median PFS with these agents is in the range of 9–15 months, long-term follow-up demonstrates 5-year PFS rates of 14–22%, suggesting a curative potential in a subset of patients.[58-60] Among patients who relapse while off treatment, rechallenge with PD-1 inhibitors or BV is associated with an ORR of >50–60% and a median PFS of 6–13 months.[44]

Double-Refractory Disease

Ultimately, a subset of patients develop resistance to both BV and PD-1 inhibitors ("double-refractory disease"), representing an area of high unmet need with limited evidence to guide therapy. Radiotherapy can be an effective option for localized relapses, although most patients will eventually relapse outside the irradiated field.[61] Emerging data suggest that epigenetic therapies may restore sensitivity to PD-1 inhibitors.[62] Other palliative-intent strategies include chemotherapy (e.g., bendamustine, vinblastine, gemcitabine) or everolimus, though responses are typically partial and short-lived.[63-65] Whenever possible, enrolment in clinical trials should be sought, as there are encouraging results from early-phase studies of CD30-directed CAR T-cell therapy, allogeneic natural killer cells, bispecific antibodies, and novel antibody-drug conjugates and immune checkpoint inhibitors.[66-69]

Contemporary Outcomes of Allogeneic HSCT

Allogeneic hematopoietic stem cell transplantation (HSCT) remains an underappreciated but important curative option for patients with multiply relapsed disease who have exhausted other options. Several contemporary studies have reported remarkably high PFS rates of 69–84% following allogeneic HSCT after PD-1 therapy in heavily pretreated patients, suggesting a PD-1-mediated enhancement of the graft-versus-lymphoma effect.[70,71] The safety profile of allogeneic HSCT has improved with the adoption of reduced-intensity conditioning and post-transplant cyclophosphamide.[70,72,73] However, because pre-transplant exposure to PD-1 therapy has been associated with increased risks of acute graft-versus-host disease, a washout period of 4–12 weeks is recommended prior to transplantation owing to the long half-lives of these agents.[72,74]

Given the prognostic importance of achieving adequate disease control prior to allogeneic HSCT,[70,72] the timing of transplantation should be individualized, taking into account the disease course, patient preferences, and anticipated availability of bridging therapies. Referral for allogeneic HSCT is recommended by the time of initiation of a second targeted therapy in multiply relapsed patients. Patients with high-risk features, such as refractory disease or short remission durations, may benefit from consolidation with allogeneic HSCT while responding to a second targeted agent, whereas others may defer transplantation until progression on both agents, followed by re-induction with chemotherapy prior to transplant. Donor lymphocyte infusion may be considered in the setting of post-transplant relapse, with reported ORR of 56–79%.[75,76]

Conclusions

Outcomes in R/R HL have become increasingly favourable due to the integration of targeted therapies across multiple lines of treatment. However, this progress has introduced new uncertainties, including the impact of novel first-line regimens on salvage strategies, the evolving role of ASCT, and the optimal management of patients with double-refractory disease.

In Canada, the most immediate challenge remains access. Despite robust evidence, targeted therapies are inconsistently funded, particularly in the pre-transplant and transplant-ineligible settings, creating a gap between evidence and practice. Addressing these disparities will be essential to ensure that advances in therapy translate into meaningful improvements in patient outcomes.

Correspondence

Robert Puckrin, MD
Email: Robert.Puckrin@albertahealthservices.ca

Financial Disclosures

C.S.: Honoraria: Sanofi, GSK, Roche, and AstraZeneca.
R.P.: Honoraria: Abbvie, AstraZeneca, Beigene, Eli Lilly, Incyte, Kite, Janssen, Merck, Pfizer, Roche, and Seagen

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