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New Developments in the Front-line Treatment of Advanced Stage Classic Hodgkin Lymphoma: A Canadian Perspective

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Introduction

Classic Hodgkin lymphoma (cHL) is highly curable, with excellent outcomes achieved through decades of treatment refinement. Recent years have witnessed a paradigm shift in the management of patients with advanced stage disease, driven by the integration of novel therapies into front-line treatment. Minimizing long-term complications remains an important objective, especially for patients in the adolescent/young adult (AYA) age group. Herein, we summarize the latest developments in the treatment of advanced stage cHL through a Canadian lens, focusing on recent clinical trials that have reshaped the therapeutic landscape.

Definition of Advanced Stage in cHL

The definition of advanced stage has varied widely across guidelines and clinical trials worldwide, with potential downstream funding implications. The National Comprehensive Cancer Network (NCCN) and European Organization for Research and Treatment of Cancer (EORTC) define advanced stage as stage 3–4, while the German Hodgkin Study Group (GHSG) also includes stage 2B with risk factors (large mediastinal mass >0.33 of the maximum transverse thoracic diameter on chest X-ray [CXR] and/or extranodal disease) (**Table 1**). In the RATHL study, advanced stage also included high-risk stage 2, defined as stage 2B or 2A with adverse features (bulky disease >0.33 of transthoracic diameter or >10 cm elsewhere; ≥3 involved nodal sites).[1] Similarly, the Children's Oncology Group (COG) AHOD1331 Phase 3 trial evaluated upfront brentuximab vedotin (BV-AVEPC) with ABVEPC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) in patients aged 2–21 years with advanced stage disease, and included stage 2B with large mediastinal mass (>0.33 of the maximum transverse thoracic diameter on CXR or continuous nodal aggregate >6 cm in other sites), but excluded stage 3A.[2] Finally, at BC Cancer, we define advanced stage as 2B, 3, 4, and stage 1 or 2 with bulky mass (≥10 cm in any dimension) or disease determined to be too extensive to encompass in a radiotherapy field.

Evolution of Treatment Strategies for Advanced Stage cHL: From ABVD to PET-adapted Approaches

For many years, the standard front-line therapy for advanced stage cHL was the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine). ABVD has demonstrated high efficacy, with cure rates approaching 80%, though failure can occur in 20–30% of patients, and bleomycin-associated pneumonitis remains a concern.[1,3-9] Dose intensive escBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) has demonstrated improved progression-free survival (PFS) but not overall survival (OS) compared with ABVD, and is associated with long-term toxicity, including secondary malignancies and infertility.[3,4] Early studies with positron emission tomography (PET) scanning suggested that those with a PET2-positive scan have poor outcomes (PFS: 13–28%) if ABVD is continued.[8,10] Thus, several PET-adapted studies have investigated dose escalation (i.e., to escBEACOPP) if PET2-positive[1,11,12] and de-escalation (omission

	EORTC/LYSA	GHSG	COG	NCCN	RATHL	BC Cancer
Early/limited stage						
Risk factors	Large mediastinal mass[a], age ≥50 years, elevated ESR (>50 mm/h without B symptoms, >30 mm/h with B symptoms, involvement of ≥4 supradiaphragmatic nodal areas	Large mediastinal mass[b], extranodal disease, elevated ESR (>50 mm/h without B symptoms, >30 mm/h with B symptoms), involvement of ≥3 nodal areas on both sides of the diaphragm		Bulky disease[d], elevated ESR ≥50 mm/h, B symptoms, involvement of ≥4 nodal sites	Bulky disease[d], ≥3 nodal sites	
Early favourable	Stage 1–2 without risk factors	Stage 1-2 without risk factors	Stage 1A, 2A	Stage 1–2 without risk factors		
Early unfavourable	Stage 1–2 with ≥1 risk factor	Stage 1-2A with ≥1 risk factor, 2B with elevated ESR or ≥3 nodal areas or both	Stage 1A/ 2A with bulky disease[c] ± extranodal disease (E), 1B/2B±E,3A±bulky±E	Stage 1–2 with ≥1 risk factor		
Limited stage						Stage 1, 2A, non-bulky (<10cm)
Advanced stage						
Advanced	Stage 3–4	Stage 2B with large mediastinal mass and/or extranodal disease Stage 3–4	Stage 2B bulky[c] Stage 3B, 4	Stage 3–4	Stage 2A with risk factors Stage 2B Stage 3–4	Stage 2B Bulky mass[e] (≥10 cm) Stage 3–4

Table 1. Definitions of risk and stage groups in clinical trials and practice guidelines in cHL; *courtesy of Jowon L. Kim, MD and Kerry J. Savage, MD.*

B symptoms: fever, drenching night sweats, unexplained weight loss >10% of baseline body weight over 6 months.

Abbreviations: cHL: classic Hodgkin lymphoma; **COG:** Children's Oncology Group; **ESR:** erythrocyte sedimentation rate; **EORTC:** European Organization for Research and Treatment of Cancer; **GHSG:** German Hodgkin Study Group; **LYSA:** Lymphoma Study Association; **NCCN:** National Comprehensive Cancer Network; **RATHL:** Risk-adapted therapy in Hodgkin lymphoma.[1]

a: mediastinum to thoracic ratio >0.35;
b: mediastinum to thoracic ratio >0.33;
c: mediastinal mass >0.33 thoracic diameter, extramediastinal nodal aggregate >6 cm in longest transverse diameter;
d: mediastinum to thoracic ratio >0.33 or >10 cm elsewhere;
e: also includes rare stage 1 with bulky mass.

of bleomycin from ABVD[1] and omission of consolidative radiotherapy (RT) in those with bulky disease[13-16]) if PET2-negative. An alternate approach is to start with escBEACOPP and de-escalate to ABVD if PET2-negative (AHL2011 study; **Table 2**).[17] Since the RATHL study demonstrated comparable PFS with PET2-guided omission of bleomycin[1], this practice has been widely adopted globally. Although subsequent studies (mostly real-world analyses) have demonstrated a higher 2–5 year PFS of 38–64% in PET2-positive patients who continued on ABVD[18-21], PET2-guided dose escalation to escBEACOPP appears to result in a higher PFS of 60-66% (with limitations of cross-trial comparison), but with similar OS.[11,12,22] Thus, with uncertainty of benefit and toxicity concerns with escBEACOPP, practices vary. With the brentuximab vedotin containing alternate BrECADD demonstrating improved efficacy and safety (**Table 3**), use of escBEACOPP will likely diminish.

Integration of Novel Agents in the Front-line Treatment of Advanced Stage cHL

Brentuximab Vedotin (BV)-AVD and Other BV-containing Front-line Regimens

Brentuximab vedotin (BV), an antibody-drug conjugate targeting CD30, initially demonstrated efficacy in a pivotal Phase 2 trial in patients with relapsed/refractory cHL after autologous stem cell transplant, with an overall response rate (ORR) of 75% and a complete response (CR) rate of 34%.[27] The ECHELON-1 trial compared BV-AVD (BV, doxorubicin, vinblastine, and dacarbazine) to ABVD in patients ≥18 years with stage 3–4 cHL.[7] The modified PFS, which included use of subsequent therapy for incomplete response (defined as Deauville [D] score 3–5) by blinded review, was superior for BV-AVD (2-year modified PFS: 82.1% vs. 77.2%; hazard ratio [HR]: 0.77, 95% confidence interval [CI]: 0.6–0.98).[24] However, in subgroup analysis, benefit was confined to those with stage 4 disease only, which led to initial approval restricted to stage 4 by Health Canada and the European Medicines Agency (EMA). However, with longer follow-up, 5-year PFS benefit was observed in stage 3 and 4 (82.2% vs. 75.3%; HR: 0.68, 95% CI: 0.53–0.87)[18], and subsequent 6-year OS benefit was demonstrated in the intention-to-treat population (93.9% vs. 89.4%; HR: 0.59, 95% CI: 0.40-0.88).[7] This resulted in expanded approval to stage 3 by the EMA in October 2023 and endorsement by Canada's Drug Agency (CDA) in September 2024. Simultaneously, the pediatric regimen BV-AVEPC was CDA endorsed in those aged 2–21 years.[2]

Other upfront BV-containing regimens have demonstrated significant benefit in patients with high-risk stage 2 disease (**Table 2**). The landmark GHSG Phase 3 HD21 trial compared BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) and escBEACOPP in patients with advanced stage cHL aged 18–60 years, with two co-primary endpoints (superiority in safety/treatment-related morbidity, and non-inferiority in efficacy/PFS).[26] The omission of vincristine allowed for a higher dose of BV (1.8 mg/kg) in this regimen compared to BV-AVD (1.2 mg/kg). Following results from HD18, a trial amendment introduced PET2-guided treatment, with patients receiving 4 cycles if PET2-negative (D1-3) vs. 6 cycles if PET2-positive (D4-5). PET2-negative status was lower than in other trials (64%), which may highlight a greater frequency of false positives with this regimen. Consolidative RT was recommended in those with end-of-treatment (EOT) PET-positive residual disease and administered in 15% of the escBEACOPP group and 14% of the BrECADD group. BrECADD demonstrated significantly lower treatment-related morbidity (42% vs. 59%; p<0.0001), driven mostly by reduced hematologic toxicity. Although the study was designed to demonstrate non-inferiority for PFS, a superior 4-year PFS was demonstrated (94.3% vs. 90.9%; p=0.035), with similar OS (98.6% vs. 98.2%). Notably, patients <40 years of age derived the greatest benefit (HR: 0.53) from BrECADD, as did those with stage 2 disease (HR: 0.35), which was likely the predominant stage in this younger age group. Study follow-up remains short to evaluate for long-term complications; however, gonadal function recovery by follicle-stimulating hormone levels was observed in 95% of patients with BrECADD vs. 72.5% with escBEACOPP in women and 86% vs. 39% in men, respectively. Successful childbirths were observed, with 62 births among 59 couples with BrECADD, and 46 births among 40 couples with escBEACOPP. BRECADD is currently under CDA review.

The pediatric trial AHOD1331 included patients aged 2–21 years with "high-risk" cHL (**Table 2**), who were randomized to 5 cycles of BV-AVEPC (BV replacing bleomycin) or

standard ABVEPC.[2] Consolidative involved site RT was administered to those with a large mediastinal mass at diagnosis, PET2-positive "slow-responding lesions" (D4-5), and EOT PET-positive (D3-5) lesions, resulting in 53% and 57% receiving RT in the BV and standard arms, respectively. An improved event-free survival (EFS), an endpoint that includes the development of secondary neoplasm, was observed with a 3-year EFS of 92.1% vs. 82.5% (HR: 0.41, 95% CI: 0.25–0.67) in favour of the BV arm, with greater benefit seen in stage 2B bulky disease (HR: 0.09, 95% CI: 0.01–0.69).

Nivolumab (N)-AVD

Reed-Sternberg cells frequently overexpress programmed cell death ligand 1 (PD-L1) and 2 (PD-L2), contributing to immune evasion and making them particularly susceptible to programmed cell death protein 1 (PD-1) blockade. Anti-PD-1 antibodies demonstrated striking efficacy in the relapsed/refractory setting (ORR 64–74%, CR: 12–29%), leading to approval of both pembrolizumab and nivolumab, including in Canada.[27,28,30] The Phase 3 KEYNOTE-204 study confirmed improved PFS (median 13.2 vs 8.3 months, p=0.003) of pembrolizumab over BV in relapsed/refractory cHL (including "transplant ineligible", a definition that includes insufficient response to salvage therapy for those planned for autologous stem cell transplant).[30]

The landmark SWOG S1826 trial compared nivolumab-AVD (N-AVD) to BV-AVD in patients aged ≥12 years with stage 3–4 cHL.[25] At a median follow-up of 2.1 years, N-AVD demonstrated superior PFS compared to BV-AVD (2-year PFS: 92% vs. 83%; HR: 0.45, 95% CI: 0.30-0.65) and similar OS (99% vs. 98%). Importantly, N-AVD showed remarkable efficacy in patients >60 years, with superior 2-year PFS (89% vs. 64%, p=0.001) and OS (96% vs. 85%, p=0.005).[31] N-AVD was better tolerated, and although there was more grade ≥3 neutropenia (48% vs. 26%), febrile neutropenia rates were similar, even though granulocyte colony-stimulating factor (G-CSF) was not mandated in the N-AVD arm (although we would endorse use in this age group regardless).[25] Overall, immune-related adverse events (irAE) were low, with expected hypo/hyperthyroidism more frequent in the N-AVD arm. Consolidative RT to residual metabolically active lesions was allowed if the intent was pre-specified, but not mandated. Excellent outcomes were observed with near elimination of consolidative RT use (0.7% regardless of arm). Minimizing RT use is of particular significance in AYA patients, in whom future secondary cancers and cardiac disease remain a concern. N-AVD is now listed in the NCCN guidelines for stage 3–4 disease. The NCCN guidelines also include both N-AVD (adapted from the Phase 2 study NIVAHL[32]) and BV-AVD (adapted from the Phase 2 study BREACH[33]) for 4 cycles in combination with RT, as treatment options in stage 1/2 unfavourable cHL.[33] Longer follow-up is needed to confirm response durability, long-term side effects, and impact on fertility. N-AVD recently received a positive CDA endorsement in Canada (June 2025) for use in patients ≥12 years of age with stage 3–4 cHL. As of this writing, the CDA endorsed inclusion of high-risk stage 2 patients along with stage 3 and 4 indication and has been funding approved by the pan-Canadian Pharmaceutical Alliance (pCPA) with provinces rolling out their programs over the next few months.

Older Patients with cHL

Older patients with advanced stage cHL have shown inferior outcomes with conventional therapies, due to higher toxicity and more treatment-resistant tumour biology.[35] In a subgroup of older patients (≥60 years) from the ECHELON-1 trial, although not powered for this comparison, there was no improvement in PFS with BV-AVD (5-year PFS 67.1% with BV-AVD vs. 61.6% with ABVD, p=0.44), and it was associated with increased grade ≥3 neuropathy (18% vs 3%), febrile neutropenia (37% vs. 17%), and more dose modifications (80% vs. 71%).[36] Studies have suggested that HL patients ≥70 years have particularly worse outcomes.[35] A Phase 2 study of sequential administration of BV and AVD (i.e., BV x 4, AVD x 6, BV x 2) in patients >60 years demonstrated improved outcomes (2-year PFS: 84%, OS: 93%) and tolerance compared to historical expectations; however, treatment duration is long and neuropathy still a concern.[35,37,38] Preliminary results from a Phase 2 study assessing BrECADD in patients aged 61–75 years with a median follow-up of almost 2 years demonstrated very encouraging results (2-year PFS: 91.5%) and no treatment-related deaths, although febrile neutropenia occurred in 54% of patients.[39] However, this regimen is unlikely to supplant N-AVD given the excellent tolerance and OS advantage over BV-AVD demonstrated in older patients observed in the SWOG1826 study.[31] Treatment

Trial	Advanced stage definition	Treatment arms	Median follow-up	PFS	OS	Comment
PET2-adapted studies						
RATHL[1,22] n=1,201	Stage 2B-4, 2A with risk factors Age 18–79y	After 2ABVD: PET2-neg (D1–3): 4ABVD vs. 4AVD PET2-pos (D4–5): BEACOPP#	3.4y, 7.3y	**All:** 7y PFS 78.2% **PET2-neg:** • 3y PFS 85.7% with ABVD vs. 84.4% with AVD • 7y PFS 81% with ABVD vs. 79.2% with AVD **PET2-pos:** • 3y PFS 67.5% • 7y PFS 65.9%	**All:** 7y OS 91.6% **PET2-neg:** • 3y OS 97.2% with ABVD vs. 97.6% with AVD • 7y OS 93.2% with ABVD vs. 93.5% with AVD **PET2-pos:** • 3y OS 87.8% • 7y OS 83.2%	Led to widespread practice of dropping bleomycin if PET2-neg post ABVD. The practice of PET2-guided dose escalation to BEACOPP varies.
GITIL/FIL HD0607[11,14] n=782	Stage 2B–4 Age 18–60y	After 2ABVD: PET2-neg (D1-3): 4ABVD PET2-pos (D4-5): 4escBEACOPP (+/- R)	3.6y, 5.9y	**All:** 3y PFS 82% **PET2-neg:** • 3y PFS 87% • Bulky (>5 cm) with PET2/EOT PET-neg scan randomized to RT vs. no RT: 6y PFS 92% with RT vs. 90% without RT (p=0.48) **PET2-pos:** • 3y PFS 60% (vs. PET2-neg, p<0.001) • By D score, 3y PFS 73% with D4 vs. 35% with D5 (p<0.001)	**All:** 3y OS 82% **PET2-neg:** • 3y OS 99% • Bulky (>5cm) with PET2/EOT PET-neg scan randomized to RT vs. no RT: 6y OS 99% with RT vs. 98% without RT (p=0.61) **PET2-pos:** • 3y OS 89%	Established that consolidative RT can be omitted in patients with bulky disease (>5 cm) treated with ABVD if PET2 and EOT PET-neg. Subset with 'classic' bulky >10 cm also showed no impact of omission of RT (6y PFS: 89% vs. 86%, p=0.53).
AHL 2011[17,23] n=823	Stage 2B with large mediastinal mass (>33% maximal thoracic diameter), 2BE, 3, 4 Age 16-60y	After 2escBEACOPP: PET2-neg (D1-3): 4escBEACOPP vs. 4ABVD PET2-pos (D4-5): 4escBEACOPP	4.2y, 5.6y	**PET2-neg:** • 5y PFS 87.5% with 6escBEACOPP vs. 86.7% with 2escBEACOPP + 4ABVD (p=0.67) **PET2-pos:** • 5y PFS: 68.2%	**PET2-neg:** • 5y OS 97.7% in both arms, p=0.53 **PET2-pos:** • 5y OS: 92%	Led to practice of starting therapy with escBEACOPP for 2 cycles and de-escalation to ABVD if PET2-neg in some centres.
Trials incorporating frontline brentuximab vedotin or nivolumab						
ECHELON-1[7,24] n=1,334	Stage 3–4 cHL Age ≥18y	6 cycles of BV-AVD vs. ABVD	2.1y, 6.1y	**All:** • 2y modified PFS 82.1% with BV-AVD vs. 77.2% with ABVD (HR: 0.77, 95% CI: 0.6-0.98) • 6y PFS 82.3% with BV-AVD vs. 74.5% with ABVD (HR: 0.68, 95% CI: 0.53-0.86)	**All:** • 2y OS 96.6% with BV-AVD vs. 94.2% with ABVD (HR: 0.73, 95% CI: 0.45-1.18) • 6y OS 93.9% with BV-AVD vs. 89.4% with ABVD (HR: 0.59, 95% CI: 0.4-0.88)	BV-AVD Health Canada approved in 2017 for stage 4 (CDA endorsed 2020). CDA endorsed for stage 3 in 2024.

Trial	Advanced stage definition	Treatment arms	Median follow-up	PFS	OS	Comment
GHSG HD21[26] n=1,500	Stage 3–4, 2B with risk factors (large mediastinal mass ≥1/3 maximal thoracic diameter, 2BE) Age 18–60y	4–6 cycles of BrECADD vs. escBEACOPP PET2-adapted, 4 cycles if PET2-neg and 6 cycles with PET2-pos (D4-5)	4y	**All:** 4y PFS 94.3% with BrECADD vs. 90.9% with escBEACOPP; p=0.035	**All:** 4y OS 98.6% with BrECADD vs. 98.2% with escBEACOPP	BrECADD improved treatment-related morbidity. Greatest PFS benefit in patients <40y (HR: 0.53) and high-risk stage 2B (HR: 0.35). BrECADD currently under CDA review.
AHOD1331[2] n=587	Stage 2B with risk factors (bulky mediastinal mass >1/3 thoracic diameter on x-ray, or extramediastinal mass >6 cm), 3B, 4 Age 2-21y	5 cycles of BV-AVEPC vs. standard ABVEPC Not interim PET-adapted	3.5y	**All:** 3y EFS 92.1% with BV-AVEPC vs. 82.5% with ABVEPC (p<0.001)	**All:** 3y OS 99.3% with BV-AVEPC vs. 98.5% with ABVEPC	BV-AVEPC CDA endorsed in 2024 in ages 2–21y, 2B bulky, 3B, 4. Greatest benefit in 2B bulky (HR: 0.09).
SWOG S1826[25] n=994	Stage 3–4 Age ≥12y	6 cycles of N-AVD vs. BV-AVD Not interim PET-adapted	2.1y	**All:** 2y PFS 92% with N-AVD vs. 83% with BV-AVD (HR: 0.45, 95% CI: 0.30–0.65)	**All:** 2y OS 99% with N-AVD vs. 98% with BV-AVD (HR: 0.39, 95% CI: 0.15–1.03)	N-AVD a new standard in stage 3–4. Striking results in older adults ≥60y. Extrapolated to early unfavourable disease (with RT) in NCCN guidelines. CDA endorsed June 2025, funding approved.

Table 2. Select clinical trials in advanced stage cHL leading to practice changes in Canada; *courtesy of Jowon L. Kim, MD and Kerry J. Savage, MD.*

#: Either 6 cycles BEACOPP14 (if PET-negative after 4 cycles) or 4 cycles of escBEACOPP (if PET-negative after 3 cycles). Salvage if interim PET-positive after switching to BEACOPP.

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; **ABVEPC:** doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; **BrECADD:** brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone; **BV-AVD:** brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; **BV-AVEPC:** brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; **CDA:** Canada's Drug Agency; **CI:** confidence interval; **D:** Deauville; **EOT:** end of treatment; **escBEACOPP:** bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; **HR:** hazard ratio; **N-AVD:** nivolumab, doxorubicin, vinblastine, and dacarbazine; **NCCN:** National Comprehensive Cancer Network; **Neg:** negative; **OS:** overall survival; **PET:** positron emission therapy; **PET2:** interim PET scan after 2 cycles; **PFS:** progression-free survival; **Pos:** positive; **Pts:** patients; **R:** rituximab; **RT:** radiation therapy; **Y:** years.

Trial	Longest median follow-up	Peripheral neuropathy	Febrile neutropenia	Grade ≥3 toxicity	Treatment-related mortality	Treatment discontinuation due to toxicity	Secondary malignancy	Pregnancy/fertility outcomes
RATHL[1,22]	7.3y	Not reported	5% in ABVD, 2% in AVD, 17% in BEACOPP (G-CSF mandated)	69% with ABVD, 65% with AVD, 81% with BEACOPP	0.9% in ABVD, 0% in AVD, 2% in escBEACOPP	Not reported	**Secondary malignancies at 7y:** 5.1% in ABVD, 5.8% in AVD, 2.5% in escBEACOPP **Secondary AML/MDS:** not observed	Not reported
GITIL/FIL HD0607[11,14]	5.9y	Not reported	Not reported	**Hematologic:** 76% with BEACOPP vs. 30% with ABVD **Infections:** 10% with BEACOPP vs. 1% with ABVD **Pulmonary toxicity:** 1% with BEACOPP vs. 2% with ABVD	<1%	Not reported	**Secondary malignancies:** none with 3.6y follow-up, 2% in 5.9y follow up of pts with LNM (all received RT) **Secondary AML/MDS:** not observed	Not reported
AHL 2011[17,23]	5.6y	23% in standard arm vs. 22% in PET-adapted arm	35% in standard arm vs. 23% in PET-adapted arm (G-CSF mandated with escBEACOPP)	**Neutropenia:** 87% with standard arm vs. 90% with PET-adapted arm **Anemia:** 69% with standard arm vs. 28% with PET-adapted arm **Thrombocytopenia:** 66% with standard arm vs. 40% with PET-adapted arm **Infections:** 22% with standard arm vs. 11% with PET-adapted arm	1% in standard arm vs. <1% in PET-adapted arm	7% in standard arm vs. <1% in PET-adapted arm	**Second malignancies:** 3.2% in standard arm, 2.2% in PET-adapted arm **Secondary AML:** 1% in standard arm, 0.5% in PET-adapted arm	**Pregnancies:** 8.5% in 6escBEACOPP, 12.5% in 2escBEACOPP + 4ABVD **Assisted reproductive technology use:** 20.5% in 6escBEACOPP vs. 10.8% in 2escBEACOPP + 4ABVD
ECHELON-1[7,24]	6.1y	29% with BV-AVD vs. 17% with ABVD	**Serious AE of febrile neutropenia, sepsis, or infections:** 24% with BV-AVD (G-CSF mandated) vs. 9% with ABVD	83% with BV-AVD vs. 66% with ABVD	1% in both arms	13% with BV-AVD vs. 16% with ABVD	**Secondary cancer:** 3.5% with BV-AVD vs. 4.9% with ABVD **Secondary AML/MDS:** 2 in each arm	**Pregnancies:** 114/82 couples with BV-AVD and 81/61 couples with ABVD
GHSG HD21[26]	4y	43% with BrECADD vs. 53% with escBEACOPP	28% with BrECADD vs. 21% with escBEACOPP	**Febrile neutropenia:** 28% with BrECADD vs. 21% with escBEACOPP **Infections:** 20% with BrECADD vs. 19% with escBEACOPP **Organ toxicity grade ≥3:** 19% with BrECADD vs. 17% with escBEACOPP **Grade 4 hematologic AE or infection:** 31% with BrECADD vs. 52% with escBEACOPP	**Treatment-related mortality:** <1% with both arms **Treatment-related morbidity:** 42% with BrECADD vs. 59% with escBEACOPP; p<0.0001	2% with BV vs. 18% with vincristine	**Secondary cancer:** 3% with BrECADD vs. 2% with escBEACOPP **Secondary AML/MDS:** <1% with BrECADD, 1% with escBEACOPP	**Gonadal function recovery (FSH level):** 95% with BrECADD vs. 72.5% with escBEACOPP in women; 86% with BrECADD vs. 39% with escBEACOPP in men **Successful childbirths:** 62/59 with BrECADD, 46/40 with escBEACOPP

Trial	Longest median follow-up	Peripheral neuropathy	Febrile neutropenia	Grade ≥3 toxicity	Treatment-related mortality	Treatment discontinuation due to toxicity	Secondary malignancy	Pregnancy/fertility outcomes
AHOD1331[2]	3.5y	**Grade ≥2:** 19% in both arms	31% with with BV-AVEPC vs. 33% with ABVEPC	74% with BV-AVEPC vs. 68% with ABVEPC	None	Not reported **Dose modifications:** 13% with BV-AVEPC vs. 23% with ABVEPC	**Secondary cancers:** 1 in both arms (<1%) **Secondary AML:** 1 in BV-AVEPC arm	Not reported
SWOG S1826[25]	2.1y	29% with N-AVD vs. 56% with BV-AVD	**Febrile neutropenia:** 6% with N-AVD vs. 7% BV-AVD (GCSF mandated) **Neutropenia:** 56% with N-AVD vs. 34% BV-AVD **G-CSF use:** 56% with N-AVD (not mandated) vs. 97% with BV-AVD (mandated) **Sepsis:** 2% with N-AVD vs. 3% BV-AVD	**Febrile neutropenia:** 6% with N-AVD vs. 7% with BV-AVD **Infections:** 2% with N-AVD vs. 3% with BV-AVD **Neuropathy:** 1% with N-AVD vs. 8% with BV-AVD **LFT elevation:** 7% with N-AVD vs. 8% with BV-AVD **Possible immune-related AE (all grades):** **Thyroid abnormalities:** 10% with N-AVD vs. <1% with BV-AVD **Rash:** 15% in both arms LFT elevation: 38% with N-AVD vs. 76% with BV-AVD	<1% with N-AVD vs. 1% with BV-AVD	9% with nivolumab vs. 22% with BV	Not reported	Not reported

Table 3. Safety outcomes in advanced stage cHL trials; *courtesy of Jowon L. Kim, MD and Kerry J. Savage, MD.*

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; **AE:** adverse event; **ABVEPC:** doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; **AML:** acute myeloid leukemia; **BrECADD:** brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone; **BV:** brentuximab vedotin; **BV-AVD:** brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; **BV-AVEPC:** brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; **escBEACOPP:** bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; **G-CSF:** granulocyte colony-stimulating factor; **LFT:** liver enzyme; **LNM:** large nodal mass; **MDS:** myelodysplastic syndrome; **N-AVD:** nivolumab, doxorubicin, vinblastine, and dacarbazine; **Neg:** negative; **OS:** overall survival; **PET:** positron emission therapy; **PFS:** progression-free survival; **Pos:** positive; **RT:** radiation therapy; **Y:** years.

was much better tolerated in the N-AVD arm, with less discontinuation (14% vs. 55%), febrile neutropenia (12% vs. 19%; despite mandated G-CSF with BV-AVD), infections (18% vs. 34%), and neuropathy (33% vs. 68%), also allowing delivery in those aged >80 years.[31,40] With even longer follow-up, similar results were observed in a separate phase 2 study of N-AVD in this age group (3-year PFS 79%, OS 97%).[41]

Canadian Landscape

N-AVD now has CDA endorsement and funding negotiations are complete. Some provinces can already access this regimen for advanced stage patients and fortunately, high-risk stage 2 patients were also included. A recent study from BC Cancer suggests this is highly relevant in the AYA group, as these patients frequently present with high-risk stage 2 disease, and when treated with ABVD, have outcomes similar to stage 3 and 4, and more frequent RT use due to incomplete response.[42] BrECADD is still under CDA review but given the level of evidence, it will also be an available regimen for patients. One remaining question is whether there is a very low-risk group with excellent outcomes with ABVD alone (RATHL approach) given the potential for chronic irAE with PD1 inhibitors observed in melanoma.[43]

New challenges will include personalizing therapy choice, managing novel toxicities, sequencing of therapies in patients with relapsed disease post novel front-line therapies, and ensuring equitable access. As PD-1 inhibitors have been shown to synergize with other therapies, there can be re-induction of response at relapse.[44] BV-based regimens may also be appealing in this setting. In Canada, GDP is the only approved combination in the transplant-eligible population with an ongoing Canadian Cancer Trials Group (CCTG) randomized Phase 2 study comparing GDP to BV-pembrolizumab (NCT05180097). Refinement of conventional PET-based interim response assessment with circulating tumour DNA assessment may aid in selecting patients who may benefit from a more intensive approach or who can have shorter therapy duration.[45] Canadian oncologists and policymakers face complex yet exciting decisions to further refine treatment in advanced stage cHL.

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

Christopher Lemieux, MD, FRCPC, DRCPC

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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Unique Toxicities of Novel Myeloma Therapies: Focus on Belantamab Mafodotin, Talquetamab, and Selinexor

Jesse Shustik, MD, FRCPC

Introduction

Recent survival improvements in patients with multiple myeloma are attributable largely to the introduction of three main drug classes, immunomodulatory drugs (IMIDs), proteasome inhibitors, and anti-CD38 monoclonal antibodies.[1] However, the majority of patients will inevitably develop resistance to all three drug classes, and survival in this setting has been historically poor.[2-3]

Several novel therapeutic classes exploiting new mechanisms of action (e.g., chimeric antigen receptor (CAR)-T cell therapy, bispecific antibodies, antibody-drug conjugates (ADC), and selective inhibitors of nuclear export) have shown high levels of activity in relapsed myeloma and promise to transform the treatment landscape.[4-5] However, these therapies have been associated with distinct toxicity profiles, with adverse effects that are uncommonly observed with conventional antimyeloma therapies. Given improvements in long-term disease control and survival with current therapies, treatment-related toxicity represents an increasingly important health burden in patients with myeloma, and the development of effective toxicity management strategies is required to minimize complications and ensure preserved quality of life.

The current article focuses on unique toxicities associated with three agents that have obtained recent approval for use in relapsed myeloma: belantamab mafodotin, an anti-B cell maturation antigen (BCMA) antibody-drug conjugate (ocular toxicity); talquetamab, an anti- G protein–coupled receptor class C group 5 member D (GPRC5D) bispecific antibody (oral and cutaneous toxicity); and selinexor, a selective inhibitor of nuclear export (hematological, gastrointestinal, and constitutional toxicity). Key trials for these agents are summarized in **Table 1**.

Belantamab mafodotin

Belantamab mafodotin (belamaf) is a first-in-class, humanized ADC targeting B-cell maturation antigen, a cell surface receptor ubiquitously expressed on myeloma plasma cells.[5] Phase 1/2 studies of single-agent

Study	Study Type	Population	Treatment	Response rate	PFS	OS	Toxicity
DREAMM-7[8]	Phase 3, randomized, open-label	Relapsed MM, at least 1 prior line of therapy (n=494)	**Standard arm (DVd)** Bortezomib 1.3 mg/m^2 SC, d. 1,4,8,11/21-day cycle), 8 cycles Dexamethasone 20 mg PO, day of/day after each bortezomib dose, 8 cycles Daratumumab 16 mg/kg IV, qweek cycles 1–3, q3 weeks cycles 4-8, q4 weeks cycle 9+, until progression **Experimental arm (BVd)** Bortezomib, per standard arm (above) Dexamethasone, per standard arm (above) Belantamab mafodotin 2.5 mg/kg IV, d.1 of 21-day cycle, until progression	***BVd vs. DVd*** **ORR:** 83 vs. 71% **VGPR:** 66 vs 46% **CR:** 35 vs.17% **MRD-negative rate:** 39 vs. 17%	***Median PFS:*** **BVd:** 36.6 months **DVd:** 13.4 months (HR: 0.41, p<0.001)	***18-month OS:*** **BVd:** 84% **DVd:** 73% (HR: 0.57, p=NS)	***Thrombocytopenia, grade 3–4*** **BVd:** 55% **DVd:** 35% ***Infection, grade 3–4*** **BVd:** 31% **DVd:** 20% ***Ocular adverse events, any-grade*** **BVd:** 79% **DVd:** 29% ***Ocular adverse events, grade 3–4*** **BVd:** 34% **DVd:** 3%
DREAMM-8[9]	Phase 3, randomized, open-label	Relapsed MM, at least 1 prior line of therapy, with previous lenalidomide exposure (n=302)	**Standard arm (PVd)** Bortezomib 1.3 mg/m^2 SC, d. 1,4,8,11/21-day cycle, cycles 1-8, then d. 1,8/21-day cycle, cycle 9 onwards, until progression Pomalidomide 4 mg PO, d. 1–14/21-day cycles, until progression Dexamethasone, 20 mg PO, day of/day after each bortezomib dose, until progression **Experimental arm (BPd)** Belantamab mafodotin 2.5 mg IV cycle 1, then 1.9 mg/kg IV q 4 weeks, cycle 2 onwards, until progression Pomalidomide 4mg PO, d 1–21/28-day cycle, until progression Dexamethasone 40 mg PO weekly, until progression	***BPd vs. PVd*** **ORR:** 77 vs. 72% **VGPR:** 64 vs.38% **CR:** 40 vs.16% **MRD-negative rate:** 32 vs. 5%	***12-mo. PFS*** **BPd:** 71% **PVd:** 51% (HR: 0.52, p<0.001)	***12-mo. OS*** **BPd:** 83% **PVd:** 76% (HR 0.77, p=NS)	***Thrombocytopenia, grade 3-4*** **BPd:** 24% **PVd:** 20% ***Infection, grade 3–4*** **BPd:** 49% **PVd:** 26% ***Ocular, all-grade*** **BPd:** 89% **PVd:** 30% ***Ocular, grade 3–4*** **BPd:** 43% **PVd:** 2%

Study	Study Type	Population	Treatment	Response rate	PFS	OS	Toxicity
MonumenTAL-1[20]	Phase 1–2	Relapsed MM, at least 3 prior lines of therapy, including IMID, proteasome inhibitor, and anti-CD38 monoclonal antibody (n=375)	**Recommended Phase 2 dosing:** Talquetamab 0.4 mg/kg SC qweek **OR** Talquetamab 0.8 mg/kg SC q2weeks	***0.4 mg/kg q week:*** **ORR:** 74% **VGPR:** 59% **CR:** 33% ***0.8 mg/kg q2weeks:*** **ORR:** 69% **VGPR:** 59% **CR:** 40%	**Median PFS 0.4 mg/kg q week:** 7.5 months **0.8 mg/kg q2weeks:** 11.2 months	***12-month OS 0.4 mg/kg q week:*** 76% ***0.8 mg/kg q2weeks:*** 77%	***CRS:*** **all-grade:** 76% **grade 3-4:** 1.5% ***ICANS:*** **all-grade:** 8% **grade 3-4:** 2% ***Infection:*** **all-grade:** 64% **grade 3-4:** 19% ***Dysgeusia:*** **all-grade:** 72% ***Rash:*** **all-grade:** 35% **grade 3-4:** 3.5% ***Non-rash skin toxicity:*** **all-grade:** 65% **Grade 3-4:** 0.3% ***Nail-related:*** **all-grade:** 55.5 ***Weight loss:*** **all-grade:** 40% **grade 3-4:** 3%
BOSTON[26]	Phase 3, randomized, open-label	Relapsed MM, 1-3 prior lines of therapy	**Standard Arm: Vd** Bortezomib 1.3 mg/m^2 SC d.1,4,8,11/21-day cycle, cycles 1-8; 1.3 mg/m^2 SC d. 1,8,15,22/35-day cycle, cycle 9 onward, until progression Dexamethasone 20 mg PO day of/ after bortezomib, until progression **Experimental Arm: SVd** Selinexor 100 mg PO, d. 1,8,15,22,29/35-day cycle, until progression Bortezomib 1.3 mg/m^2 SC, d. 1,8,15,22/35-day cycle, until progression Dexamethasone 20 mg PO, day of/ after each bortezomib dose, until progression	***SVd vs. Vd*** **ORR:** 76 vs. 62% **VGPR:** 45 vs. 32% **CR:** 17 vs. 10%	***Median PFS:*** **SVd:** 13.9 months **Vd:** 9.5 months (HR: 0.7, p=0.0075)	***Median OS*** **SVd:** NR **Vd:**25 months (HR: 0.84, p=NS)	***Thrombocytopenia:*** **grade 3-4:** **SVd:** 39% **Vd:** 17% ***Neutropenia:*** **grade 3-4:** **SVd:** 9% **Vd:** #% ***Fatigue:*** **all-grade/grade 3–4:** **SVd:** 42/18% **Vd:** 13/1% ***Nausea:*** **all-grade/grade 3–4:** **SVd:** 50/10% **Vd:** 8/0% ***Diarrhea:*** **all-grade/grade 3–4:** **SVd:** 32/25% **Vd:** 6/1% ***Weight loss:*** **all-grade/grade 3–4:** **SVd:** 26/12% **Vd:** 2/1%

Table 1. Pivotal trials (belantamab mafodotin, talquetamab, selinexor); *courtesy of Jesse Shustik, MD, FRCPC.*

Abbreviations: BPd: belamaf, pomalidomide, dexamethasone; **BVd:** belamaf, bortezomib, dexamethasone; **CR:** complete response; **CRS:** cytokine release syndrome; **DVd:** daratumumab, bortezomib, dexamethasone; **HR:** hazard ratio; **ICANS:** immune cell-associated neurologic syndrome; **IMID:** immunomodulatory drug; **IV:** intravenous; **MM:** multiple myeloma; **MRD:** minimal residual disease; **NR:** not reached; **NS:** not significant; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; **PVd:** pomalidomide, bortezomib, dexamethasone; **SC:** subcutaneous; **SVd:** selinexor, bortezomib, dexamethasone; **Vd:** bortezomib, dexamethasone; **VGPR:** very good partial response.

belamaf demonstrated significant activity in relapsed/refractory myeloma, though with adoption complicated by frequent ocular toxicity and lack of benefit over standard of care in a randomized trial.[6-7] The pivotal DREAMM-7/DREAMM-8 phase 3 trials demonstrated the benefit of belamaf-containing combination regimens in patients with relapsed myeloma after 1 or more prior lines of therapy, in comparison with standard-of-care regimens.[8-9] In the DREAMM-7 study, BVd (belamaf, bortezomib, dexamethasone) was associated with significant prolongation of progression-free survival (PFS) in comparison with DVd (daratumumab, bortezomib, dexamethasone) (median PFS 36.6 vs 13.4 months; hazard ratio [HR]: 0.41), with evidence of overall survival benefit on updated follow-up.[8,10] In the DREAMM-8 study, BPd (belamaf, pomalidomide, dexamethasone) demonstrated significant improvement in PFS in comparison with the standard-of-care PVd regimen (pomalidomide, bortezomib, dexamethasone) (12-month estimated PFS, 71% vs. 51%; HR: 0.52).[9] The BVd/BPd regimens are approved by Health Canada for use in relapsed multiple myeloma, with specific indications following the eligibility criteria of the DREAMM-7/8 studies.

Corneal epithelial toxicity is a known effect of ADC therapy and occurs frequently in patients receiving belamaf. Common ocular symptoms include dry eye, photophobia, and reduction in visual acuity, and are associated with microcystic changes in the corneal epithelium on ocular slit lamp examination.[11] The exact mechanisms of ocular toxicity remain uncertain, but have been hypothesized to relate to off-target uptake of the ADC in corneal epithelial cells and resultant apoptosis due to intracellular release of the monomethyl auristatin F (MMAF) payload. The incidence of all-grade and grade 3-4 ocular toxicity has ranged from 70–90% and 30–55% of patients, respectively, in prospective belamaf single-agent and combination trials.[6,8-9,12] Of note, pre-existing ocular conditions (e.g., cataracts, glaucoma, baseline visual acuity >20/50) have not been exclusion criteria from belamaf trials, and an association between baseline ocular conditions and an increased risk of ocular adverse events has not been consistently observed.[8-9,13]

Serial ophthalmological examinations were mandatory for patients receiving belamaf-containing regimens on the DREAMM-7/8 studies, and ophthalmic findings were graded based on a Keratopathy and Visual Acuity (KVA) scale incorporating corneal findings on ocular slit lamp exam and measured changes in best corrected visual acuity (BCVA) (**Tables 2 and 3**).[8-9,14] Protocol-based dose modifications in both trials were primarily based on ophthalmic exam findings, with dose delays until resolution and/or dose reduction required for patients with grade ≥2 findings. Overall, dose delays due to ocular toxicity occurred in 78/75% and dose reductions in 44/57% of patients on BVd/BPd, respectively, with the majority of patients experiencing a first event after the first 2 cycles of therapy. Patients commonly experienced multiple episodes of ophthalmic toxicity, with approximately 55% of patients with a grade ≥2 ophthalmic event in both studies experiencing three or more occurrences. However, ocular toxicity was reversible with treatment interruption in the majority of patients. In a pooled analysis of both studies, documented resolution had occurred in 83% of grade ≥2 ophthalmic events at the time of data cut-off with a median time to resolution of 12 weeks.[14] In patients with reduction of visual acuity to 20/50 in the DREAMM-7/8 studies, 85–95% had improvement of vision to baseline acuity, with a median time to resolution of 8–9 weeks; improvement occurred in all patients with reduction of visual acuity to 20/200 (1-2% of belamaf-treated patients in both studies).[8-9,14] Discontinuation of therapy due to ocular toxicity occurred in 9% of patients in both trials.

Belamaf dose delays and modifications led to a progressive lengthening of treatment interval in the DREAMM-7/8 studies, though without appearing to compromise efficacy. In both studies, the median interval between doses increased over time, from the initial protocol-specified intervals of 3–4 weeks to 8–12 weeks after the first 9 months.[14] However, among patients treated with BVd experiencing at least one extended dose delay (>2 cycles), median PFS was 36.6 months, similar to the overall BVd arm in DREAMM-7, and in the DREAMM-8 study, the estimated 12-month PFS was 90% in BPd-treated patients requiring at least one extended dose delay. Among patients requiring extended belamaf dose delays, 85–90% had already achieved at least a partial response prior to the first extended dose delay, with up to 90% subsequently achieving at least very good partial response (VGPR) following the delay.

Practical guidelines have been created for the management of belamaf-associated ocular

	DREAMM-7[8,14]	DREAMM-8[9,14]
Standard belamaf schedule	2.5 mg/kg IV q3 weeks	2.5 mg/kg IV cycle 1, then 1.9 mg/kg IV q4 weeks (cycle 2 onward)
Dose modification (reduced dose level 1)	1.9 mg/kg IV q3 weeks	1.9 mg/kg IV q8 weeks
Grade ≥2 OEF incidence	86%	87%
Median time to onset, first grade ≥2 OEF	6 weeks	5 weeks
Resolution rate, first grade ≥2 OEF	81%	86%
Time to resolution, first grade ≥2 OEF	12 weeks	16 weeks
Visual acuity reduction 20/50, incidence	34%	34%
Visual acuity reduction 20/200, incidence	2%	1%
Resolution rate, visual acuity reduction to 20/50	94%	84%
Time to resolution, visual acuity reduction 20/50	9 weeks	8 weeks
Proportion of time on study with visual acuity <20/50	11%	14%
Ocular toxicity leading to dose delay, incidence	78%	75%
Ocular toxicity leading to dose reduction, incidence	44%	57%
Ocular toxicity leading to discontinuation, incidence	9%	9%

Table 2. Belantamab-related ocular toxicity, DREAMM-7/8 studies.[8,9,15]

Abbreviations: IV: intravenous; **OEFs:** ophthalmic examination findings

toxicity (**Table 3**).[13] Multidisciplinary collaboration between treating physicians and eye care professionals remains an essential component of therapy, and should include shared education strategies, efficient communication pathways, and clear reporting templates for ophthalmic exam findings. Serial ophthalmological evaluation remains obligatory during early cycles of therapy. However, in patients without ongoing toxicity, a vision-related patient questionnaire incorporating ocular symptoms and effects on activities of daily living has been proposed as a screening tool for treating clinicians, eliminating the need for regular eye care specialist assessment in patients without symptoms. In a preliminary evaluation in patients treated in a prospective belamaf trial, patients

	Examination findings per KVA scale	Recommended dose modifications
Grade 1	**Corneal examination finding(s)** • Mild superficial punctate keratopathy[a] **Change in BCVA[b]** • Decline from baseline of one line on Snellen Visual Acuity	• Continue according to belamaf prescribing information • Ophthalmic evaluation may be planned to confirm ocular event(s) do not worsen
Grade 2	**Corneal examination finding(s)** • Moderate superficial punctate keratopathy[c] **Change in BCVA[b]** • Decline from baseline of two or three lines (and Snellen Visual Acuity not worse than 20/200)	• Use Q8W dosing and maintain at new dose interval, provided recovery to Grade 1 • If ocular events remain Grade 2 after 8 weeks **OR** Grade 2 ocular events recur after initial recovery to Grade 1, consider extending dose interval to 12 weeks • If dose interval exceeds 12 weeks, reduce belamaf dose[e]
Grade 3	**Corneal examination finding(s)** • Severe superficial punctate keratopathy[d] **Change in BCVA[b]** • Decline from baseline by more than three lines (and Snellen Visual Acuity not worse than 20/200)	• Reduce belamaf dose[e] AND extend dose interval to at least 12 weeks and maintain at new dose interval, provided recovery to Grade 1 • If dose interval exceeds 16 weeks, further reduce belamaf dose[e]
Grade 4	**Corneal examination finding(s)** • Corneal epithelial defect **Change in BCVA[b]** • Snellen Visual Acuity worse than 20/200	• Consider treatment hold until Grade 1 • If continuing treatment with belamaf is being considered, reduce belamaf dose[e] AND extend dose interval to at least 12 weeks and maintain at new dose interval

Table 3. Recommended belamaf dose modifications following ocular events as defined by the KVA scale; *adapted from Terpos et al., 2024.*

[a] Mild superficial punctate keratopathy (documented worsening from baseline), with or without symptoms.
[b] Changes in visual acuity due to treatment-related corneal findings.
[c] Moderate superficial punctate keratopathy with or without patchy microcyst-like deposits, peripheral sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
[d] Severe superficial punctate keratopathy with or without diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity.
[e] There are limited data on the efficacy of belamaf at doses lower than 1.9 mg/kg; if possible, the administration of doses below 1.9 mg/kg should be avoided.

Abbreviations: BCVA: best corrected visual acuity; **belamaf:** belantamab mafodotin; **KVA:** Keratopathy and Visual Acuity; **Q8W:** every 8 weeks.

monitored with a vision-related anamnestic tool exhibited no difference in rates of high-grade ocular toxicity compared to patients undergoing regular ophthalmological examination.[15] In the current Health Canada product monograph, ophthalmological examination is mandatory prior to each dose for the first 6 cycles of belamaf therapy, but may be reduced thereafter to every 3 months and whenever clinically indicated in patients without corneal or vision changes through the first 6 cycles.[16]

For prevention of ocular toxicity and management of low-grade symptoms, regular use of preservative-free lubricating drops and avoidance of contact lenses from the time of treatment initiation is advised. For grade ≥2

ophthalmic changes, current guidelines recommend dose delay until resolution and subsequent extension of the dosing interval to 8–12 weeks.[13] The use of more extended (8–12-week) belamaf dosing intervals as initial therapy has also been explored in recent combination studies and may become standard of care in the future.[12,17]

Talquetamab

Talquetamab is a first-in-class, humanized IgG4 bispecific antibody with binding to the CD3 receptor on T cells and to GPRC5D, an orphan transmembrane receptor with high levels of expression on malignant plasma cells but limited expression on normal plasma cells and other human tissues.[18] GPRC5D is highly expressed in the bone marrow of patients with myeloma and has been associated with high-risk disease features and adverse clinical outcomes. GPRC5D expression in normal tissues has been evaluated using sensitive analytic techniques, and in addition to plasma cells has been found in keratinized structures, including hair follicles, eccrine glands, and tongue.

In the first-in-human, phase 1–2 MonumenTAL-1 study, talquetamab was evaluated in a relapsed myeloma population with extensive previous treatment exposure, with a median of 6 prior lines of therapy, and 75% of patients triple-class-refractory to IMIDs, proteasome inhibitors, and anti-CD38 monoclonal antibodies.[19] In an updated analysis of patients treated at the recommended phase 2 doses (0.4 mg/kg subcutaneously weekly and 0.8 mg/kg subcutaneously every 2 weeks), the overall response rates (ORR) were 74% and 69% for the respective doses, with the majority of responders achieving VGPR or better, and similar rates were observed in a separate cohort of patients previously treated with anti-BCMA T-cell redirecting therapy.[20] Notably, the frequency of infectious complications and use of immunoglobulin replacement therapy was lower than that reported with anti-BCMA bispecific antibodies.

Toxicities associated with talquetamab include immunological events shared with other T cell-redirecting therapies (e.g., cytokine release syndrome [CRS], immune cell-associated neurologic syndrome [ICANS]), and unique 'on-target, off-tumour' toxicities likely related to GPRC5D expression on epithelial structures. Management of CRS/ICANS associated with talquetamab follows standard guidelines for T cell-redirecting therapies. Epithelial toxicities include oral, cutaneous, and nail effects; the incidence and temporal pattern of these toxicities are described in **Figure 1**. These are typically low-grade and rarely lead to treatment discontinuation, but may impact quality of life and require close management to ensure treatment adherence.[18,21]

Oral toxicity, including dysgeusia, dry mouth, and dysphagia, is commonly observed with talquetamab, with taste-related changes reported in approximately 75% of patients in the MonumentTAL-1 study.[20] The mechanism of dysgeusia as an on-target effect of talquetamab remains unclear, as GPRC5D expression on the tongue is limited to filiform papillae, which are not responsible for taste.[21] Taste changes typically develop within 1–2 months of initiation of therapy, are often persistent, and may be accompanied by clinically significant weight loss, occurring in approximately 40% of patients.[21] Various supportive therapies have been employed for dysgeusia, including steroid mouth rinses, zinc and biotin supplements, and salivary substitutes, though with limited evidence for efficacy. Talquetamab dose modifications have been suggested as the most effective mitigation strategy for oral toxicity.[18,21] Patients should be evaluated for oral comorbidities, including oral candidiasis, periodontal disease, and vitamin deficiencies leading to glossitis, and nutritional support may be required to minimize weight loss. In the MonumenTAL-1 study, weight loss was evident early, but with an overall stabilization or slight improvement over time, and cases of grade >3 weight loss (defined as >20% decrease from baseline weight) were rare.[20]

Cutaneous adverse events associated with talquetamab include skin rashes and "non-rash" skin toxicities, such as dry skin, pruritus, and skin exfoliation, most commonly affecting palms and soles.[21-22] Non-rash skin toxicities are more frequent, occurring in approximately two-thirds of patients, and require prophylactic or early use of emollients (e.g., ammonium lactate 12% or urea 10% cream) and sunscreen use for patients with photosensitivity. Skin rashes typically occur within the first month of therapy and resolve in most cases with the use of antihistamines, low-medium-potency topical corticosteroids, or short courses of oral corticosteroids for more extensive rashes. For persistent rashes,

Oral AEs	**Dysgeusia[1]** Incidence: 72.3% Grade 3/4: N/A Time to onset: 13–20 days Resolved: 38.3% Discontinuation: 0.6%	**Dysphagia** Incidence: 24.2% Grade 3/4: 0.9% Time to onset: 21–29 days Resolved: 65.9% Discontinuation: 0%	**Dry mouth** Incidence: 36.0% Grade 3/4: 0% Time to onset: 19–26 days Resolved: 39.0% Discontinuation: 0%
Skin and nail-related AEs (rash and no rash)	**Skin Rash[4]** Incidence: 34.8% Grade 3/4: 3.5% Time to onset: 20-27 days Resolved: 78.9% Discontinuation: 0%	**Skin Non-rash[6]** Incidence: 65.2% Grade 3/4: 0.3% Time to onset: 26-30 days Resolved: 59.4% Discontinuation: 0.9%	**Nail-related AEs[5]** Incidence: 55.5% Grade 3/4: 0% Time to onset: 64-69 days Resolved: 29.5% Discontinuation: 0%
Weight decrease Incidence: 39.5%[2] Grade 3/4: 3.2% Time to onset: 87-91 days[3] Resolved: 38.7% Discontinuation: 0.9%			

Figure 1. Summary of key AEs associated with talquetamab; *adapted from Chari et al, 2024; http://creativecommons.org/licenses/by/4.0/*

[1]Includes dysgeusia, ageusia, hypogeusia, and general taste disorders.
[2]The number of patients with a ≥ 10% decrease in weight from baseline in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts was 37.1%, 32.4%, and 29.4%, respectively.
[3]Time to onset for weight loss is reported for patients with a ≥ 10% decrease in weight from baseline.
[4]Includes rash, maculopapular rash, erythematous rash, and erythema.
[5]Includes nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging.
[6]Includes skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome

Abbreviations: AE: adverse event; **CRS:** cytokine release syndrome; **ICANS:** immune effector cell-associated neurotoxicity syndrome; **QW:** weekly; **Q2W:** every other week.

a dermatology referral for consideration of skin biopsy may be warranted. Nail-related changes occur in 50–60% of patients and commonly persist for the duration of therapy, though rarely lead to dose modification or discontinuation.

Overall, dose modifications were infrequent for oral (7% of patients), skin (5%), and nail (1%) toxicities in the MonumenTAL-1 study, and treatment discontinuation occurred in only 2% of patients collectively for oral and dermatological toxicity.[20-21] However, despite supportive therapies described above, reductions in talquetamab dose or treatment frequency have been suggested as the most effective measure to ensure long-term treatment tolerability in patients with significant oral or cutaneous adverse events.[21] In a MonumenTAL-1 sub cohort, patients achieving at least a partial response prospectively underwent a reduction in talquetamab dose or extended treatment interval; despite dose reductions, all patients maintained responses, with a trend toward reduction in skin and oral toxicities.[23] The development of more refined toxicity grading systems and rational dose modification strategies is currently considered an area of high priority.[18,21]

Selinexor

Selinexor is an oral, first-in-class selective inhibitor of nuclear export with established activity in multiple myeloma. Its mechanism of action is based on inhibition of exportin 1 (XPO1), a nuclear export protein responsible for the traffic of over 200 "cargo proteins" from the cell nucleus to cytoplasm, leading to retention of tumour suppressor proteins in the nucleus and blockade of oncoprotein mRNA transfer to the cytoplasm.[24] Although initial use was based on studies demonstrating ORRs of 25–30% (in combination with dexamethasone alone) in heavily-pretreated patient populations, subsequent development of selinexor has focused on multidrug combination therapy with use in earlier treatment lines.[24-25] In the phase 3 BOSTON trial, weekly selinexor in combination with bortezomib-dexamethasone (SVd) demonstrated statistically higher ORR (76% vs. 62%), ≥VGPR (45 vs. 32%), and median PFS (13 vs. 9.5 months; HR: 0.7; p=0.0075) in comparison with a standard therapy arm of twice-weekly bortezomib-dexamethasone (Vd), in patients with relapsed multiple myeloma after 1–3 prior lines of therapy.[26] Current Health Canada approval of selinexor is for use in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Selinexor has a distinct toxicity profile that includes hematological (thrombocytopenia, neutropenia), gastrointestinal (nausea, diarrhea), and constitutional adverse effects (fatigue, anorexia, weight loss), leading to high rates of early treatment discontinuation in initial studies.[24-25] While these studies employed a more intensive twice-weekly dosing schedule, the use of weekly selinexor dosing was evaluated in subsequent multiagent combination regimens, leading to a chosen selinexor dose of 100 mg weekly in the phase 3 BOSTON study. By consensus, weekly selinexor dosing has reduced the severity of adverse effects,[27] though previous toxicities are still commonly observed. In the BOSTON study, toxicities occurring with higher frequency in the SVd arm included thrombocytopenia (all-grade/grade 3–4: 60/39%), neutropenia (35/9%), nausea (50/8%), vomiting (30/4%), diarrhea (32/6%), fatigue (42/13%), anorexia (35/4%), and weight loss (26/2%).[26]

Aggressive supportive care and liberal dose reduction are the mainstays of selinexor toxicity management, and physician comfort with both strategies is likely to be associated with improved treatment adherence and outcomes.[27-28] Key supportive measures are described below. Although the starting selinexor dose in the BOSTON study was 100 mg weekly, the majority of patients in the SVd arm (65%) required dose reduction, leading to an actual median selinexor dose of 80 mg weekly in this study. In a post-hoc analysis, patients treated with SVd undergoing selinexor dose reduction had improved outcomes in comparison with those who did not (median PFS: 16.6 vs. 9.2 months).[29] In clinical practice, lower weekly doses of selinexor (i.e., 40–80 mg weekly) are commonly effective, and may be justified as initial therapy in the majority of patients. Notably, more recent combination studies with pomalidomide or carfilzomib backbones have employed selinexor doses ranging from 40–80 mg weekly, with promising efficacy.[30-31]

Thrombocytopenia represents the most common hematological toxicity associated with selinexor and has been attributed to inhibition of thrombopoietin signalling during early megakaryopoiesis. The kinetics of selinexor-associated thrombocytopenia are unique, typically occurring 2–3 weeks after treatment, resulting in an approximately 50% reduction in platelet counts, and resolving within 1–2 weeks after drug interruption.[24,27] The use of thrombopoietin agonists or platelet transfusions was required in approximately one-quarter of patients in the BOSTON study, but clinically significant bleeding events were rare.[26] Current guidelines recommend dose reduction for patients with platelet counts of <50,000 and treatment interruption for patients with platelet counts of <25,000, though additional caution may be required in patients with additional bleeding risks, such as concurrent anticoagulant use.[27]

Selinexor-associated nausea is believed to relate to central nervous system effects from drug passage across the blood-brain barrier and requires aggressive antiemetic prophylaxis during initiation of therapy. Routine prophylaxis with an NK-1 inhibitor in addition to a 5-HT3 antagonist (e.g., aprepitant plus ondansetron, netupitant-palonosetron) should now be considered standard; in patients with ongoing nausea or restricted access to NK-1 inhibitors, prophylaxis with olanzapine (2.5–5 mg in the evening for 1–3 days after selinexor) may also be used.[27] The incidence of nausea decreases significantly after the first two months of therapy, and may allow tapering of the antiemetic regimen.

Other frequent nonhematological toxicities include anorexia and fatigue, which may be high-grade in nature. Reduction in oral intake may be associated with weight loss and dehydration, and close nutritional monitoring with high-caloric supplementation and maintenance of adequate oral fluid intake (at least 2L daily) are advised.[27] Hyponatremia occurs frequently and requires close laboratory monitoring during initial cycles, with correction by sodium chloride tablets if present. Fatigue may respond to nutritional optimization and treatment of gastrointestinal toxicities, but for persistent fatigue, the use of methylphenidate has had reported benefit.

Conclusion

Belantamab mafodotin, talquetamab, and selinexor are novel targeted therapies with proven activity in relapsed multiple myeloma and represent attractive treatment options in patients with relapse after treatment with IMIDs, proteasome inhibitors, and/or anti-CD38 monoclonal antibodies. Although these agents are associated with distinct adverse effect profiles, discontinuation due to toxicity is only required in a minority of patients, and further dose optimization after initial approval and increased clinician experience with use are also likely to improve treatment delivery and outcomes. The use of these agents may further evolve as new drug combinations, use in earlier lines of therapy, and fixed-duration approaches are explored.

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Financial Disclosures

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Rational Use of Immunoglobulin in Adult Patients with Secondary Hypogammaglobulinemia in the Setting of Hematologic Malignancy: A Canadian Perspective

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Introduction

Hypogammaglobulinemia is identified by the detection of low serum immunoglobulin (Ig) levels. Secondary hypogammaglobulinemia (SHG) is an acquired state in which circulating Ig levels are reduced due to suppressed antibody production or increased antibody loss.[1,2] Specifically, SHG most commonly refers to low circulating total IgG levels. In contrast, primary hypogammaglobulinemia (PHG) is due to an underlying inborn error of immunity contributing to low or defective Ig production and frequent and/or severe infections.

In patients with hematologic malignancies, it is important to evaluate baseline Ig (IgG, IgM, IgA) levels at the time of diagnosis. However, it may be challenging to distinguish whether low Ig levels are attributable to PHG or SHG, if antibody defects are identified in the context of hematologic malignancies (including chronic lymphocytic leukemia [CLL], lymphoma, and multiple myeloma), even before initiation of immunosuppressive treatment.[3] PHG should be considered, especially in younger patients presenting with a hematologic malignancy who have a history of recurrent, severe infections.[1,3]

Treatment of several hematologic malignancies includes anti-CD20 B cell-depleting therapy, which is known to cause the development of SHG. Advancements in lymphoma and myeloma management now incorporate bispecific antibody therapies and chimeric antigen receptor T-cell (CAR T-cell) therapies, which have revolutionized care for patients with disease refractory to conventional treatments. However, the risk of SHG is significant, with rates of ≥70% with bispecific antibody treatments and 20–46% with CAR T-cell therapies.[4,5] Thus, patients with hematologic malignancies have a high rate of SHG attributable to both the underlying disease and associated treatment.

Pooled immunoglobulin products, including intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg), are a source of exogenous IgG that can be administered to replace IgG in patients who have deficient levels. Due to a continuing increase in global demand and a supply dependent on volunteer human donors (most of whom are compensated financially), it is prudent to ensure appropriate stewardship of Ig products. Canada has the third largest consumption of Ig per capita, narrowly trailing behind Australia and the United States,[6] with the annual demand of all countries continuing to increase. Supply sufficiency is a real concern for Canadians who are dependent on American donors and Ig manufacturers to provide approximately 75%–80% of the Ig utilized for patient care.[7]

In this context, we aim to provide a concise summary of when Ig may be considered for the management of SHG in adult patients with hematologic malignancies. Further, we highlight potential risks of adverse reactions due to Ig, the challenges with health system cost and global Ig supply constraints, and areas where further research is required.

Measured serum IgG level

Hypogammaglobulinemia: measured serum total IgG level <7 g/L
• Total IgG level subcategory stratification:
  ◦ IgG 4.0–6.9 g/L
  ◦ IgG 2.0–3.9 g/L
  ◦ IgG <1.9 g/L
• Evaluation of IgG subclasses is not recommended
Duration of low IgG levels subcategory stratification:
• Transient: 3–6 months, 6–12 months, or 12–24 months
• Persistent: more than 24 months

Clinically significant infections:
***Severe infection*—an infection requiring:** • An emergency room visit or hospitalization, and • Intravenous antibiotics, or • A prolonged course or more than 1 course of antibiotic/antiviral/antifungal therapy for the purposes of treatment (not prophylaxis). ***Recurrent* – any of the following occurring in 1 year:** • ≥2 new ear infections, or • ≥2 new sinus infections in the absence of allergy, or • ≥1 pneumonia (for more than 1 year), or • Deep abscesses of the skin or internal organs.

Table 1. Proposed definition of SHG, based on serum IgG levels and clinical infection frequency in adults.[1,8]

SHG Definition

There is a prominent lack of a standardized definition of SHG in the literature, which leads to difficulty in interpreting reported rates of SHG. Serum immunoglobulins that may be measured include IgG (total; subclasses may also be measured), IgA, IgM, and IgE. At present, only IgG-containing replacement therapies are available in Canada. In the context of SHG, limited evidence exists regarding the clinical impact and management strategies of acquired deficiencies of IgG subclasses, as well as total IgA and IgM levels.[1]

In 2022, a standardized definition of SHG, specifically referring to low serum IgG levels and criteria for clinical infection, was proposed by the American Academy of Allergy, Asthma, and Immunology (AAAAI) Primary Immunodeficiency and Altered Immune Response Committees to aid in standardizing future work.[1] Based heavily on primary immunodeficiency (PID) literature, these are summarized in **Table 1**. The listed criteria for severe and recurrent infection are adapted from the Jeffery Modell Foundation's *10 Warning Signs of Primary Immunodeficiency in Adults*, rather than in pediatrics.

In addition to Ig production, vaccination testing has been used as a functional test of the humoral immune system, in which serotype titers are measured before and 4–6 weeks after vaccination. As a pure polysaccharide vaccine, the polyvalent pneumococcal vaccine (Pneumovax 23) has been recognized as provoking a T cell-independent response and has long been used by immunologists.

Unfortunately, Pneumovax 23 is gradually being replaced by a protein-polysaccharide vaccine (Prevnar 20) in many countries, which does not evoke the same type of humoral response. Most other common vaccines, including those against diphtheria and tetanus, are protein-polysaccharide conjugate vaccines and therefore not useful in strictly assessing humoral response. The immunology community is still grappling with how to address this impending void in functional testing.[9]

In the context of SHG due to hematologic malignancy, vaccination testing is not routinely performed. If there is uncertainty around the patient's immune function and vaccination testing is a consideration, consultation with an immunology specialist is recommended.

Ig Replacement Therapy

The decision regarding when to start Ig replacement therapy (IgRT) in the setting of SHG varies, as there are no clear criteria as to when it should be initiated. Published recommendations generally recommend consideration of multiple patient factors, including low IgG levels and a history of serious or recurrent bacterial infections.[1,2] There is no evidence to support the use of IgRT in patients with low IgM or IgA in the context of a hematologic malignancy. It is important to make the distinction between bacterial and viral infections, as the efficacy of IgRT in preventing viral infections has not been proven.[10]

IgRT may include subcutaneous Ig (SCIg) or intravenous Ig (IVIg), and the decision regarding the administration modality must be considered based on resource availability, cost, and individualized patient factors. The cost of IVIg and SCIg is relatively equivalent per gram of IgG. SCIg self-administration at home may be a more convenient option for the patient and has been demonstrated to have a markedly lower health system cost impact than IVIg infusions in an ambulatory care setting, with the average administrative cost of SCIg per patient year being about $5,500 lower than IVIg administered in a hospital clinic.[11] A shared decision-making approach between the patient and multidisciplinary clinical care team is essential, given that the decision to initiate IgRT can be complex.[1]

There is even less clarity around the decision to initiate IgRT as primary versus secondary infection prophylaxis.[1,2] With the advances in hematologic malignancy treatments for relapsed and refractory disease, it remains unclear whether Ig should be initiated as a means of primary infection prophylaxis (i.e., before the development of any infections in the setting of documented low IgG levels), or if daily antibiotics may confer an equivalent protection in certain settings.[12] IgRT has most commonly been used for secondary prophylaxis (ie, to prevent additional severe or recurrent infection development), though proposed criteria to standardize IgRT eligibility based on IgG levels and clinically significant infection have been relatively recent.[1,8] Furthermore, if IgRT is initiated, an optimal IgG level required to achieve adequate infection prophylaxis has not been determined, especially if Ig is initiated prior to the development of a clinically significant infection.[2]

The half-life of total IgG from IVIg administration has been reported to be 26 days[13]; thus, it is not fully eliminated until at least 5 months after administration. Following baseline serum Ig monitoring at the time of disease diagnosis, monitoring of trough IgG levels should occur immediately prior to the next IVIg administration, or at any time during SCIg administration (steady-state) levels. Although a precise target IgG level in this context has not been defined, extrapolating from PID literature, an IgG level of 7–8 g/L is likely reasonable to mitigate against severe or recurrent bacterial infection. Expert opinion suggests that an even lower target trough IgG level in some patients with SHG may be adequate.

Assessment of individual patient factors is necessary to determine when a trial of an IgRT taper or discontinuation may be undertaken. To determine the endogenous patient Ig baseline, circulating Ig levels should be checked no sooner than 3 months following the last IgG dose. By 6 months after the last Ig dose, all replacement IgG will have been eliminated to reflect the patient's baseline Ig levels.[14]

Within Canadian jurisdictions, evidence-based clinical criteria for accessing IgRT have been developed to improve stewardship of this publicly funded resource. A summary of clinical criteria for accessing IgRT in the setting of SHG with hematologic malignancies is presented in **Table 2**.[15-19] A reference comparison of clinical criteria from Australia and the United Kingdom is included in **Table 3**.[20-21] All clinical criteria documents endorse using adjusted body weight (ABW) IgRT dosing.

Ig Preparations and Procurement

Human-source, purified preparations predominantly contain a polyclonal blend of IgG (no clinically significant replacement amount of IgM or IgA protein is included in preparations of IgRT available in Canada). The decision to initiate IVIg versus SCIg depends on the clinical indication for which IgRT is necessary, patient values, an informed discussion about the risks and benefits, and the administration modality related to each product. All brands of IVIg and SCIg available in Canada are approved for IgG replacement in the setting of SHG in adults.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
British Columbia (2024)	Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with hematological malignancies or post-HSCT. **Qualifying Criteria** • Serum IgG must be measured on two separate occasions (at least one sample taken when the patient does not have an active infection, ideally for 4-6 weeks) Baseline serum levels of IgA and IgM should be obtained with the second IgG for assessment of immune recovery Consider pre-existing primary immunodeficiency, if not excluded previously, especially if there is a family history or other non-immunoglobulin deficiency infectious findings Significant hypogammaglobulinemia with serum IgG <5g/L. If paraprotein confounds the serum IgG level (such as in MM), then the indication for starting Ig can exclude the serum IgG level **AND EITHER:** 1. At least one life threatening bacterial infection in the last 12 months (ICU admission) 2. At least two serious bacterial infections in the last 6 months requiring more than standard courses of antibiotics (e.g., hospitalization, intravenous or prolonged antibiotic therapy) **WITH BOTH:** 1. Infections unrelated to chemo/radiotherapy, including neutropenia or mucosal/epithelial toxicity 2. Infections confirmed to be due to encapsulated bacteria and/or are clinically consistent with encapsulated bacteria	Antibiotic therapy may be indicated in addition to Ig therapy. **Loading Dose (IVIg)** - One loading dose of 0.4 g/kg (ABW) in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. **Maintenance Dose (IVIg)**- 0.4–0.6g/kg (ABW) every 4 weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range initially. Trough levels are to be measured within a week before the next infusion, with target trough IgG levels generally at 7-10 g/L (and/or the minimal dose required for clinical effectiveness). SC administration of Ig should be considered as an alternative to IVIg allowing homecare rather than a medical daycare unit or infusion clinic. **Maintenance Dose (SCIg) -** 0.1-0.15g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range initially.	Ig should only be continued or renewed if there is a demonstrated clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. The lowest dose possible that achieves the appropriate clinical outcome for each patient is to be used. The goal of Ig in immune deficiency is to minimize infections, as completely eliminating risk of infections is not a feasible target.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Prairie Collaborative (Saskatchewan, Manitoba, Alberta) (2022)	Ig replacement is recommended for secondary prevention of recurrent, severe infection due to hypogammaglobulinemia (excluding paraprotein) related to other diseases or medical therapy in patients who have a history of infections. It is not recommended for routine replacement of Ig as primary prophylaxis against infections in the setting of an isolated low IgG level without infection. The decision to use Ig should be made in consultation with a physician with recognized expertise in immunodeficiency disorders. Hypogammaglobulinemia secondary to underlying disease or medical therapy (including HSCT) with all of the following: • Serum IgG less than the lower limit of the reference range on two separate occasions **AND** **At least one of the following:** • One invasive or life-threatening infection (e.g., pneumonia, meningitis, sepsis) in the previous year • Recurrent, severe infections • Clinically active bronchiectasis confirmed by radiology • Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from Ig replacement	**Maintenance:** 0.4 to 0.6 g/kg adjusted body weight IVIg every 4 weeks, or SCIG 0.1-0.15 g/kg (ABW) weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. **Loading:** One additional dose of 0.4 g/kg (ABW) may be given in the first month of therapy if the serum IgG level is markedly reduced. *Chronic suppurative lung disease:* 0.4 to 0.8 g/kg (ABW) IVIg or equivalent SCIg dose may be given if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. *Disseminated enterovirus infection:* One dose of 2 g/kg (ABW) (IVIg or SCIg) divided over 2 to 5 days at any stage is permitted (in addition to the maintenance dose).	Continued use of Ig should be based on objective measures of effectiveness established at the outset of treatment. The following outcome measures should be recorded: • IgG level every 3 to 6 months; AND • number of infections and hospital admissions for infection If clinical effectiveness has not been achieved, Ig treatment should be discontinued. Cessation of Ig treatment may be possible depending on the status of the underlying disease.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Ontario (2025)	Hypogammaglobulinemia acquired secondary to hematological malignancies. Ig replacement is recommended for secondary prevention of recurrent, severe infection due to secondary hypogammaglobulinemia (excluding paraprotein) in patients who have a history of infections. It is not recommended for routine replacement of Ig as primary prophylaxis against infections in the setting of an isolated low IgG level without infection. **Qualifying Criteria** • Hypogammaglobulinemia secondary to underlying disease or medical therapy (including HSCT) with all the following: • Serum IgG less than the lower limit of the reference range on two separate occasions **AND** **At least one of the following:** • One invasive or life-threatening infection (e.g., pneumonia, meningitis, sepsis) in the previous year • Recurrent, severe infections • Clinically active bronchiectasis confirmed by radiology • Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from Ig replacement	**Maintenance:** 0.4-0.6 g/kg (ABW) IVIg every 4 weeks, or SCIg 0.1-0.15 g/kg (ABW) weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. **Loading:** One additional dose of 0.4 g/kg (ABW) may be given in the first month of therapy if the serum IgG level is markedly reduced. *Chronic suppurative lung disease:* 0.4-0.8 g/kg (ABW) IVIg or equivalent SCIg dose may be given if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. *Disseminated enterovirus infection:* One dose of 2 g/kg (ABW) (IVIg or SCIg) divided over 2 to 5 days at any stage is permitted (in addition to the maintenance dose).	**Review Criteria** The following outcome measures should be recorded: • IgG level within 3 to 6 months; and number of infections and hospital admissions for infection • Cessation of Ig treatment may be possible depending on the status of the underlying disease.
Atlantic Provinces (Nova Scotia, New Brunswick, Newfoundland and Labrador, Prince Edward Island) (2022)	Patient has/had recent life-threatening or recurrent clinically significant infection(s) related to low levels of polyclonal Ig.	**IVIg dose:** 0.4-0.7 g/kg every 3 to 4 weeks. **SCIg dose:** 0.1-0.23 g/kg every week.	None.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Québec (2025)	Secondary hypogammaglobulinemia due to a hematological cancer or its treatment. **Secondary prophylaxis if the following 3 criteria are met:** • IgG <4 g/L OR on a case-by-case basis if IgG is ≥4 g/L and <6 g/L; • Biologically active cancer treatment OR incomplete immune reconstitution; • Severe, unusual, or recurrent infections	**Initial dosage:** • **IVIg dose:** 0.4 to 0.6 g/kg. • IVIg is generally administered every 3 to 4 weeks. **Maintenance dosage:** Adjust to achieve a residual IgG level at least equal to the lower limit of the reference range according to age or based on clinical efficacy. **Subcutaneous Immunoglobulin (IgSC) and Facilitated Subcutaneous Immune Globulin** **Initial dosage:** 0.1 to 0.2 g/kg. IgSC can be administered daily, weekly, or every two weeks. Facilitated IgSC can be administered weekly initially, then the dose should be gradually adjusted to achieve administration every 3 to 4 weeks. **Maintenance dosage:** Adjust to achieve a residual IgG level at least equal to the lower limit of the reference range according to age or based on clinical efficacy. **Note:** In the case of a severe or life-threatening infection, the initial dose may be higher.	**Duration:** until remission OR immune reconstitution, depending on the clinical situation. **Discontinuation:** yes, after confirmation of remission OR immune reconstitution, depending on the clinical situation.

Table 2. Comparison of approved jurisdictional criteria to access immunoglobulin replacement therapy (IgRT) in the setting of hypoammaglobulinemia secondary to hematologic malignancies within Canadian provinces and territories.[15-19] Prescribers are required to include the indication for IgRT on forms that are reviewed in accordance with provincial policy to ensure Ig request compliance with Ministry of Health-endorsed criteria within each jurisdiction. The territories have not yet endorsed the use of a specific IgRT criteria document; *courtesy of Oksana Prokopchuk-Gauk, MD, FRCPC, DRCPSC, Kathryn Webert, MD, MSc, FRCPC, and Jennifer Grossman, MD, FRCPC.*

*The most current versions of the criteria for prescribing IgRT are included in this summary. However, as documents may periodically be updated, prescribers should confirm the most current version of criteria for accessing IgRT within their jurisdictions when prescribing Ig for patient care.

Abbreviations: ABW: adjusted body weight; **HSCT:** hematopoietic stem cell transplantation; **ICU:** intensive care unit; **Ig:** immunoglobulin; **IVIg:** intravenous Ig; **MM:** multiple myeloma; **SCIg:** subcutaneous Ig.

International Criteria (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Australian National Blood Authority (NBA) (2025)	Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with hematological malignancies or post-HSCT. **Qualifying Criteria** • Serum IgG to be measured on two separate occasions (at least one sample taken when the patient does not have an active infection). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. • Significant hypogammaglobulinemia with serum IgG <4 g/L (excluding paraprotein) regardless of the frequency and severity of infections **OR** • Serum IgG (excluding paraprotein) >4 g/L but less than the lower limit of the age-related reference range with at least one life threatening infection in the last 12 months **OR** • Serum IgG (excluding paraprotein) >4 g/L but less than the lower limit of the age-related reference range with at least 2 serious infections in the last 6 months requiring more than standard courses of antibiotics (e.g., hospitalization, intravenous or prolonged antibiotic therapy) Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.	**Loading Dose (IVIg and SCIg):** one loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. **Disseminated Enterovirus Dose (IVIg and SCIg):** one dose of 2 g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. **Maintenance Dose (IVIg):** 0.4–0.6g/kg every 4 weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any 4-week period. **Maintenance Dose (SCIg):** 0.1-0.15 g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any 4-week period. **Supplementary Dose (IVIg and SCIg):** One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	Initial review is required within 6 months by any specialist with ongoing reviews at least annually to assess clinical benefit. In principle, Ig should be continued or renewed only if there is a demonstrated clinical benefit; therefore, documentation of clinical effectiveness is necessary for continuation of Ig therapy. Clinical effectiveness of Ig therapy may be assessed by monitoring of serum immunoglobulin levels (IgG, IgA, and IgM) and any history of infection. There should be regular consideration of a trial period of cessation of Ig (at least every 12 months) for the purposes of immunological evaluation unless medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis, and/or suppurative lung disease) or severe hypogammaglobulinemia persists where no significant improvement has occurred in the underlying condition. Trial cessation is best commenced in September or October.

International Criteria (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
National Health Service Blood and Transplant (NHSBT), UK (2025)	**Qualifying Criteria** • Underlying cause of hypogammaglobulinemia cannot be reversed, or reversal is contraindicated. **OR** • Hypogammaglobulinemia associated with drugs, including emerging bispecific antibody therapies, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20/CD19 agents, daratumumab, etc.) post-HSCT, NHL, CLL, MM or other relevant B-cell malignancy confirmed by hematologist **AND** • Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months • IgG <4 g/L (excluding paraprotein) • Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge **Notes:** • In patients developing hypogammaglobulinemia associated with B-cell aplasia as a consequence of CAR T-cells targeted against B cell or plasma cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate • Use of Ig post-CAR T-cell therapy in B-ALL: because of the severity of B-cell aplasia and the longer time required for reconstitution, it is anticipated that virtually all patients (children and adults) with B-ALL will initially require Ig replacement following CAR T-cell therapy. As with the use of Ig post-CAR T-cell therapy in B-cell lymphoma, continued use of IVIg should be reviewed at regular intervals based on B-cell recovery, serum immunoglobulins and burden of infection • Use of Ig post-CAR T-cell therapy in B-cell lymphoma: The need for Ig replacement in patients receiving CAR T-cell therapy for B-cell lymphoma is variable, ranging between 31% and 64% in published studies, highlighting faster B-cell recovery in this group in contrast to patients with B-ALL • Use of Ig at inception of bispecific antibody treatment in patients with myeloma and B-cell lymphoma: many patients in these disease groups will have a low serum IgG at baseline due to previous chemo-immunotherapy, including CD20 and CD38-depleting agents. The prophylactic use of Ig would be appropriate in patients with a serum IgG <4g/L at the time of commencement of a bispecific antibody	0.4–0.6 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range	6 monthly reviews (compared to baseline) • Raised trough IgG level • Reduction in number of infections • Reduction in number of treatment courses of • antibiotics • Reduction in number of days in hospital

Table 3. Comparison of criteria to access immunogbulin replacement therapy (IgRT) in the setting of hypoammaglobulinemia secondary to hematologic malignancies from selected countries where Ig products are funded through public healthcare arrangements.[20,21] Prescribers are required to comply with these criteria to access IgRT within their jurisdictions; *courtesy of Oksana Prokopchuk-Gauk, MD, FRCPC, DRCPSC, Kathryn Webert, MD, MSc, FRCPC, and Jennifer Grossman, MD, FRCPC*.

Abbreviations: B-ALL: B-cell acute lymphoblastic leukemia; **CAR-T:** chimeric antigen receptor T cell; **CLL:** chronic lymphocytic leukemia; **HSCT:** hematopoietic stem cell transplantation; **Ig:** immunoglobulin; **IVIg:** intravenous Ig; **SCIg**: subcutaneous Ig; **MM:** multiple myeloma; **NHL:** non-Hodgkin lymphoma

In Canada, Ig products are procured by Canadian Blood Services for all provinces and territories except Québec, which receives products from Hema-Québec. A Request for Proposal process is executed to determine Ig supply vendors for defined periods, to ensure the lowest feasible product cost. IgRT is funded through provincial/territorial tax dollars as a part of the Canadian universal healthcare system. Thus, IgRT utilization appropriateness is carefully monitored within Canadian provinces and territories to ensure accountability.[22] All Ig products are expected to meet utilization appropriateness criteria as defined by respective regional guidelines endorsed by provincial/territorial Ministries of Health.[23] IgRT preparations currently available in Canada are considered equivalent in terms of their potency and efficacy based on concentration, regardless of indications listed within the approved product monograph.[24] The list of currently available Ig products from Canadian Blood Services is listed in the **EFormulary**, and products available in Québec are listed on the **Héma-Québec website**.

Potential Adverse Reactions to Ig

As human blood product concentrates, IgRT products may cause potential adverse transfusion reactions. Expressed informed consent must be obtained by authorized prescribers prior to the administration of IgRT products.

Infection transmission from Ig products is considered theoretical, given the extensive donor screening, testing, and pathogen reduction manufacturing processes. Significant non-infectious risks of Ig must be discussed with the patient as a part of the informed consent process. Risks of IVIg administration and rates occurrence include[25]:

- Non-serious flu-like symptoms (chills; headache; chest, back, or abdominal pain; nausea/vomiting) and hypotension or hypertension in up to 1:5 recipients[26];
- Clinically significant red blood cell hemolysis in up to 1:5 non-group O recipients (due to passive anti-A and anti-B), occurring with within 10 days of IVIg infusion[27];
- Thromboembolic events in up to 1:100 recipients[28];
- Aseptic meningitis in 1:1500 recipients[29]; and
- Anaphylaxis in less than 1:10000 recipients

The risk of local site injection reactions is more common with SCIg (pain, local site irritation). Systemic reactions are less common overall in comparison to IVIg, making SCIg a safer option from the perspective of adverse reaction risk.

Isolated reactions may be idiosyncratic, associated with the blend of donor proteins within a particular product lot number, which do not recur with exposure to a different lot number of the same brand. Recurrent reactions to the same Ig brand may be associated with non-Ig components of the product and warrant trial of a brand switch. Consultation with the local Transfusion Medicine Physician is recommended to discuss product options if serious or recurrent reactions to Ig develop.

SHG and IgRT in Specific Hematologic Malignancies

Multiple Myeloma (MM)

Patients with MM may have SHG at the time of diagnosis as a consequence of their disease. However, in the setting of relapsed or refractory MM, there is a further increased risk of SHG due to both the underlying MM pathology and therapeutic exposures.[30]

Bispecific antibody and CAR T-cell therapies are now available to patients who have received at least 3 prior lines of treatment. Infections are common with bispecific antibody therapy, with rates reported to be 32–76% (any grade), and severe Grade 3–4 infections reported in up to 45% of cases.[31] This infection risk may be related to the bispecific antibody dose and frequency, as dose reductions appear to confer a reduction in infectious risk.[32]

The overall infection risk in patients receiving CAR T-cell therapy for MM was comparable to that of bispecific antibody therapy, with rates of 9–70% reported (any grade); however, the risk of severe grade 3 or higher infections was lower, reported in up to 30% of cases.[4] Interestingly, IgG levels were not measured in all CAR T studies; in the

two studies where IgG levels were measured, SHG with IgG levels under 4 g/L was observed in up to 23.5% of patients.[33,34]

The preventative role of Ig in patients undergoing MM therapy is an area of ongoing investigation. It is prudent to check IgG levels at diagnosis (excluding the monoclonal protein total). Due to the high infection risk with bispecific antibody therapy, current consensus guidelines recommend routine monitoring of IgG levels for SHG. It would be reasonable to check IgG levels every 6 months and whenever significant or recurrent infections occur.[1] Initiation of prophylactic IgRT replacement may be considered if serum IgG levels are under 4 g/L during treatment and thereafter, or in the setting of severe or recurrent infections with higher IgG concentrations.[31] A dose of 0.4 g/kg IVIg administered every 4 weeks[4] or 0.1 g/kg SCIg weekly may be considered with the intent to achieve a minimum effective dose.

Chronic Lymphocytic Leukemia (CLL)

SHG is a well-known complication of CLL in the context of this underlying B-cell disease, with evaluation of baseline serum Ig levels recommended at diagnosis as a part of routine patient work-up.[35] Treatments, including immunosuppressive regimens and B cell-targeted therapies have the potential to exacerbate the degree and duration of SHG; thus, experts have recommended that clinical follow-up of infection history and serum Ig level evaluation should occur at a minimum every 6 months.[36]

There is a strong body of literature demonstrating that IgRT confers a decrease in the frequency of bacterial infections, including major bacterial infections in patients with CLL and SHG. However, no survival benefit with IVIg use has been demonstrated.[37] Clinical practice guideline recommendations vary, though there is consensus to initiate IgRT in patients with SHG with repeated infections at immune replacement doses, including 0.4 g/kg IVIg or 0.1 g/kg SCIg; prophylactic use of IgG to prevent primary infection is not endorsed.[38,39]

Lymphoma

The prevalence of SHG appears to be lower in patients at the time of B-cell lymphoma diagnosis than in patients with MM and CLL. Thus, confirming patient serum Ig levels at the time of lymphoma diagnosis is appropriate to establish a baseline. The risk of SHG is known to increase with B-cell-targeted therapy, including rituximab.[1] SHG has been observed in nearly 40% of patients after a rituximab-based therapy; however, only a minority are of clinical significance (non-neutropenic infections requiring IgRT).[40] Variability in definitions of SHG, inconsistencies in the measurement frequency of IgG levels among lymphoma trial participants, and the evolution of lymphoma diagnosis and treatment has led to challenges in the evaluation and management of SHG in this population.

Management of more intensive diffuse large B-cell lymphoma may include autologous stem cell transplantation, bispecific antibody therapy, and CAR T-cell therapies. More intensive treatments like bispecific antibody therapy and CAR T-cell therapies may increase the risk of SHG in patients with relapsed or refractory disease, but its incidence and duration can be variable.[41,42]

Presently, there is no definitive role for prophylactic IgRT during lymphoma treatment, regardless of the underlying diagnosis and measured serum IgG levels, in the absence of severe or recurrent infections.

Recommendations regarding the frequency of Ig measurement in patients receiving lymphoma treatment are not specific, though it may be reasonable to consider evaluating serum IgG levels every 6 months or as required based on recurrent or severe infections.[1] A precise management strategy for SHG in the context of lymphoma treatment has not yet been clearly defined due to the lack of randomized, controlled trial data.[1,5] Following CAR T-cell therapy, it is reasonable to consider IgRT in adults with serious or recurrent infections with encapsulated organisms and IgG levels under 4 g/L.[42] An immune supportive dose of 0.4 g/kg IVIg or 0.1 g/kg SCIg may be initiated in this context. At this time, no clear role for prophylactic IgRT has been defined in adult CAR T-cell therapy recipients who have not developed an infection.

Hematopoietic Stem Cell Transplantation (HSCT)

To date, a definitive clinical benefit of Ig replacement for prevention against bacterial infections in the setting of autologous and allogeneic bone marrow transplantation has not been demonstrated. Establishing a pre-transplant IgG level is prudent to establish a baseline. Monitoring for infection is essential throughout the patient's treatment course.

In 2018, Canadian and American HSCT experts collaborated to develop five Choosing Wisely recommendations with the aim of reducing unnecessary healthcare resource utilization while providing optimal patient care. Given the absence of high-quality evidence demonstrating infection prevention and overall survival, plus commentary that IgRT may predispose patients to a higher risk of complications and adverse effects, the recommendation "*don't routinely give Ig replacement in adult HSCT recipients in the absence of recurrent infections regardless of Ig level*" was included.[43]

European bone marrow transplant best practice recommendations reaffirm that late infection prevention (more than 100 days following transplantation) against encapsulated bacterial infection includes oral antibiotic prophylaxis as a first-line strategy. Initiation of IgRT may also be considered at an immune supportive dose in patients with serum IgG levels of less than 4 g/L. Finally, vaccination should be initiated with immune recovery.[44]

A Proposed Approach to SHG Management in Hematologic Malignancies

The decision to initiate Ig prophylaxis in patients with SHG with hematologic malignancies is complex and multifactorial. We have adapted a framework recently proposed by experts[14], based on current literature (with an acknowledgement of existing limitations)[27], as summarized in **Figure 1**. Shared decision-making between patients and healthcare providers remains an essential component of determining the right time to initiate Ig replacement therapy, balancing the risks and benefits of this treatment, relative to potential alternative strategies for infection prevention, in the context of potential global Ig supply limitations.

Future Ig Sustainability

In Canada, the demand for Ig is expected to increase by approximately 10% each year for the next 5 years. SHG is expected to be the fastest-growing area for immunoglobulin use in Canada, with the potential for growth for this indication estimated to be closer to 15% over the next 5 years. This growth is mostly due to factors such as the increased availability and use of new immunosuppressant therapies, the increasing prevalence of diseases such as leukemias, MM, and lymphoma, and the fact that patients who may require IgRT are living longer with disease due to improvements in treatments and supportive care.[45]

This rapid growth in demand for Ig products is also seen internationally, in both developed and developing countries, leading to global shortages and related impacts on pricing. This has prompted many jurisdictions to significantly increase the collection of plasma, the critical material from which Ig drugs are made, to meet population needs. In Canada, Canadian Blood Services and Héma-Québec are exploring ways to expand and accelerate plasma collection and promote immunoglobulin production within domestic borders.

While Canadian patients' needs for IgRT are currently being met, the ongoing global shortage of Ig has raised concerns about sustainability and the possibility of a Canadian Ig shortage. Because of this, the *Canadian National Advisory Committee for Blood and Blood Products*, through the support of Health Canada and provincial/ territorial Ministries of Health, recently developed the *National Plan for the Management of Shortages of Immunoglobulin Products (The Ig Plan)*.[46] The specific purpose of the national Ig Plan is to maximize the effectiveness of a response to any crisis that impacts the adequacy of the overall Ig supply in Canada. The Ig Plan acknowledges that difficult decisions will need to be made about allocating Ig product in the event of a shortage. It also emphasizes the use of alternative therapies to Ig, where applicable. Criteria to guide clinical decisions and triage of Ig products, as well as an ethical framework, are provided to guide decision making and to assist with doing as little harm as possible.

Additional high-quality studies that utilize standard definitions for SHG and severe or recurrent infection are needed in the setting of hematologic malignancies to better understand the role of IgRT for primary or secondary infection prevention. Currently, there are limited data to inform when IgRT should be started, when it can be stopped, how it should be dosed, and the role of alternatives like antibiotic use for infection prevention. The RATIONAL platform trial at several sites in Canada is aimed at helping answer some of these questions. This investigator-initiated, international (Australia, New Zealand, Canada), Phase II/III randomized controlled trial has three domains: the START domain will compare prophylactic antibiotics to standard dose IgRT for patients eligible to start IgRT; the STOP

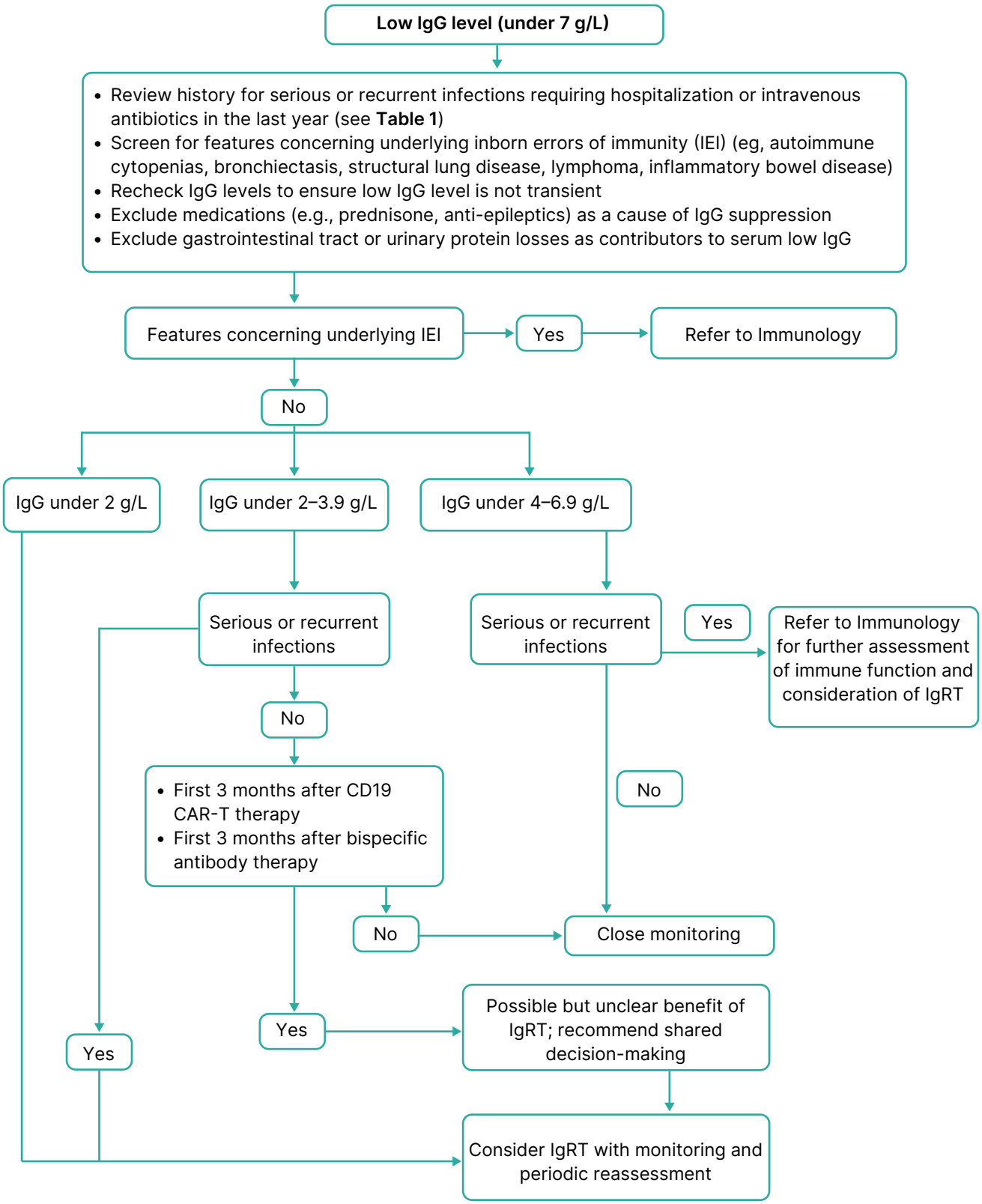


Figure 1. A proposed approach for evaluating SHG in hematologic malignancies, based on presented evidence; *adapted from Pendergrast et al., 2021.*[14]

Abbreviations: CAR-T: chimeric antigen receptor T cell; **Ig:** immunoglobulin; **IgRT:** Ig replacement therapy.

domain will compare stopping IgRT with either prophylactic antibiotics or antibiotics on demand, to continuing standard dose IgRT; and the DOSE domain will compare low dose and standard dose IgRT.[47]

Summary

The decision to initiate IgRT in patients with hematologic malignancies is complex and must consider both patient and healthcare system impacts. To obtain IgRT, clinicians in provinces and territories are required to comply with the clinical criteria for Ig, endorsed within their regional jurisdictions. Current evidence supports close patient monitoring and IgRT initiation at immune supportive doses in the setting of severe or recurrent infections with documented significantly reduced IgG levels. SCIg is an important IgRT option that is more convenient and less resource-intensive. Additional guidance is needed to better understand when to decrease or stop IgRT. It is essential to maintain stringent Ig use, as current product utilization trends will be unsustainable into the future. Exploration of alternatives to Ig for infection prevention in the setting of SHG must be prioritized.

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Financial Disclosures:

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