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WELCOME

Dear Canadian Hematology Community,

We hope this current issue of Canadian Hematology Today finds you all doing well. It's been a tremendously busy time of the year with the recent ASCO and EHA meetings, but it's been great to see everyone again and get back to face-to-face meetings and conferences!

As you may recall from our inaugural issue, this peer-to-peer initiative, written by Canadian clinicians for the Canadian hematology community, is meant to serve as an educational and informational resource with the goal of elucidating important and germane topics in the management of hematological disease. With this said, our current issue highlights some fascinating topics from our authors including a Canadian perspective on the use of chimeric antigen receptor T-Cell therapy for relapsed and refractory large B Cell lymphoma, management of side effects with novel treatments in chronic lymphocytic leukemia (CLL), current and evolving roles for immunotherapy in the treatment of Hodgkin lymphoma, the management of multiple myeloma after lenalidomide-based therapy and tailoring therapy in Waldenström Macroglobulinemia.

We hope you find these articles illuminating and we thank you for your continued readership. Feel free to share our registration link at canadianhematologytoday.com with your peers so that, they too, can subscribe to future issues!

And remember that we're actively accepting manuscripts for 2023 right now!

Best wishes,

Peter Anglin, MD *Laurie H. Sehn, MD* *Julie Stakiw, MD* *Darrell White, MD*

TABLE OF CONTENTS

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IMMUNOTHERAPY IN HODGKIN LYMPHOMA: CURRENT AND EVOLVING ROLES

Introduction
Classical Hodgkin lymphoma (cHL) is a very curable form of cancer for the majority of patients that receive standard primary therapy.[1] Many patients will have a second opportunity for cure at the time of first progression using approaches that incorporate high dose chemotherapy and autologous stem cell transplant (ASCT). In the non-curative setting, a group of patients (including patients with advanced age and comorbidities precluding standard therapy approaches and those with lymphoma that persists despite these treatments) will be treated with palliative intent. While these patients have had limited options in the past,[2,3] novel therapies have rapidly become the standard of care in this setting. Antibodies targeting CD30 (the antibody drug conjugate brentuximab vedotin [BV]) and the immune checkpoint through PD1 (nivolumab and pembrolizumab) have now become standard approved treatments for patients beyond second-line treatment. The biology of PD1 appears particularly relevant in cHL, providing a strong clinical rationale for evaluating these agents in this malignancy.[4] Clinicians in Canada now have several choices when making treatment decisions in patients with relapsed or refractory cHL (RR-cHL). Prospective trials are now determining the role of anti-PD1 antibodies in the curative setting.

Current role of Immunotherapy in cHL: Relapsed or Refractory Disease
Both nivolumab and pembrolizumab are currently approved by Health Canada for the treatment of RR-cHL and funding is broadly available across the country for this indication. Both agents were initially evaluated in phase I studies that demonstrated excellent efficacy and a favourable toxicity profile.[5,6] These initial trials were followed by phase 2 studies that included several different patient cohorts.

The CheckMate-205 study evaluated nivolumab in three cohorts of patients post-ASCT, representing a total of 243 patients.[7-10] The cohorts included HL patients that were BV-naïve, patients post-ASCT and subsequently treated with BV, and patients post-BV at any time during their disease course. Protocol-mandated therapy was nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or toxicity. Patients in one cohort (BV before and/or after ASCT) could discontinue treatment after 1 year in persistent complete response (CR) and could resume treatment if they relapsed within 2 years of the last dose. The overall response rate (ORR) was 69% (95% CI, 63-75) and ranged between 65-73% in each cohort while the CR rate was 16%. The median progression-free survival (PFS)

Patients' Characteristics and Key Outcome and Toxicity Measures	Nivolumab	Pembrolizumab
Trial Name/Code	CheckMate 205	KEYNOTE-087
Location	Europe, North America	Europe, North America, Israel,
Dose/Schedule	3 mg/kg every 2 weeks	200 mg every 3 weeks
Duration of treatment	Until PD or unacceptable toxicity §	Until PD or unacceptable toxicity or investigator decision or max of 24 months ¶
Treatment beyond progression	Accepted per early protocol amendment (see text)	Permitted for clinically stable patients if agreed on by investigator and sponsor
Inclusion criteria	3 different clinical scenarios (arms A, B, C) always after autoSCT and after BV in Arms B and, partly, C	3 different clinical scenarios (cohorts 1, 2, 3) after autoSCT (cohorts 1, 3) and after BV (cohorts 1, 2, and partly 3)
Primary endpoint	ORR by IRC	ORR by IRC and safety
Patients (#)	243	210
Age (median [Range])	34 (26–46) †	35 (18–76)
Age ≥ 65 years (%)	6 §§	8.6
ECOG PS 0–1 (%)	100	100
Previous lines of Tx (median [Range])	4 (3–5) †	4 (1–12)
≥ 3 lines of previous Tx (%)	85	87
Ineligible for autoSCT (%)	0	39
Previous ASCT (%)	100	61
Previous BV (%)	74	83
Median follow-up (months)	33.0	27.6
ORR per IRC (%)	71	72
CR rate per IRC (%)	21	28
Progression free survival (PFS)	15 mo (median)	13.7 mo (median)
Duration of response	18 mo (median) ††	16.5 mo (median) ††
Overall survival	~87–88% at 2 yrs	90.9% at 2 yrs
Discontinuation (patient number [%])	26 (11%) ¶	14 (6.7%) ¶
Toxicity		
TRAEs in ≥ 10% of patients	Rash, fatigue, diarrhea, pruritus, nausea, IRRs	Rash, fatigue, hypothyroidism, pyrexia
TRAEs gr. 3/4 in ≥ 2% of patients	lipase elevations, neutropenia, ALT elevations	neutropenia
TRAEs of special interest	hypothyroidism/thyroiditis (12%), pneumonitis (4%), hyperthyroidism (2%) but none gr. 3/4, rash 9%, hepatitis 5% (4% gr. 3/4)	hypothyroidism (16%), pneumonitis (5%), hyperthyroidism (4%) but none gr. 3/4

Table 1 Comparison of patients' characteristics and overall results for nivolumab, pembrolizumab, phase II trials for rr-cHL.

IRC = independent review committee; IRRs = infusion-related reactions; NR = not reported; TRAEs = treatment-related adverse events. NOTE: Comparisons are not meaningful between nivo/pembro because of highly different eligibility criteria and follow-up times. Even toxicities are difficult to compare due to the very different follow-up times.

§ In arm C only, patients were to discontinue nivolumab after one year in persistent CR and treatment could be resumed if relapse occurred within two years from the last dose; ¶ Patients attaining CR could stop treatment after a minimum of six months and 2 doses after CR; †numbers in parentheses are interquartile range (IQR); §§ 60 years; †† median duration of response for CRs versus PRs: for nivolumab 32 versus 13 months and for pembrolizumab not reached versus 10.9 months; ¶ most frequent causes; Nivolumab: IMRAEs including pneumonitis (2%) and autoimmune hepatitis (1%); Pembrolizumab: pneumonitis (3%), IRRs (1%)

in all patients was 14.7 months (95% CI 11.3-18.5 months). The most common serious drug-related adverse events (AEs) included infusion-related reactions (2%); pneumonitis (1%), pneumonia (1%), pleural effusion (1%) and fever (1%). The most common immune-mediated AEs included hypothyroidism/thyroiditis (12%; all grade 1-2), and rash (9% with 4 classified as grade 3 events) while pneumonitis was only 4% (with no grade 3-4 events).

The KEYNOTE-087 was a single-arm phase II study that examined the efficacy of pembrolizumab in a multi-cohort that included patients with relapse post ASCT (with or without BV exposure) or with chemoresistant disease.[11] Pembrolizumab was administered with a fixed dose of 200 mg IV every 3 weeks and for a fixed duration of up to 2 years. The ORR was 71.9% (95% CI: 65.3-77.9%) and the CR rate was 27.6%. The median PFS was 13.7 months (95% CI: 11.1-17.0).[12] The most common grade 3 treatment-related AEs were neutropenia and diarrhea. The most common immune-mediated AEs were hypothyroidism (15.7%), pneumonitis (4.8%; none grade 3 or greater) and hyperthyroidism (3.8%). Infusion-related reactions occurred in 5.2% of patients. Quality of life and patient reported outcomes were also studied. Patients reported an improvement in QLQ-C30 functional and symptom scores at 12 and 24 weeks into therapy across all cohorts.[13]

The CheckMate and KEYNOTE trials in RR-cHL both demonstrate consistent patient benefit with favourable efficacy and toxicity although it is important to highlight a few key differences in the trials **(Table 1).** KEYNOTE-087 enrolled a cohort of patients that did undergo ASCT while the CheckMate cohorts only included patients post-ASCT failure. The CheckMate studies generally continued treatment until progression (with one cohort allowed discontinuation of treatment if patients remained in CR for at least one year) while the KEYNOTE studies limited treatment to two years. Treatment administration was every two weeks with nivolumab in the CheckMate study while it was every three weeks for pembrolizumab in the KEYNOTE study. Additional studies in malignancy have demonstrated dosing can be extended to once every 4 weeks with nivolumab (480 mg per dose) and every 6 weeks for pembrolizumab (400 mg per dose). Clinicians should consider these dosing interval differences when selecting a specific antibody for an individual patient.

Confirmatory phase III trials were performed for both antibodies. Unfortunately, CheckMate-812 (NCT03138499) which evaluated nivolumab in combination with brentuximab vedotin versus a control of BV monotherapy was terminated prematurely due to insufficient enrolment. In contrast, KEYNOTE-204 evaluated pembrolizumab in patients with RR-cHL who had relapsed post-ASCT or were ineligible for ASCT. Patients received either pembrolizumab (200 mg IV) or BV (1.8 mg/kg IV) every 3 weeks for 35 cycles or until progression or unacceptable toxicity. Efficacy results have been reported and show that pembrolizumab demonstrated an improvement in PFS over BV (HR 0.65, CI 0.48-0.88, p=0.0027; median PFS 13.2 versus 8.3 months). The overall survival analysis is event driven and results are forthcoming. The overall response rate (ORR) for pembrolizumab was 65.6% (CR 25%) and was 54.2% (CR 24%) for BV but did not reach the pre-defined statistical threshold for superiority. Quality of life was also prospectively evaluated and reported.[14] EORTC QLQ-C30 and EuroQoL EQ5D scales were utilized and demonstrated improved quality of life scores with pembrolizumab compared to worsening scores with BV.

The results from the KEYNOTE-204 study portend a potential new standard of care for patients with RR-cHL that have relapsed post-ASCT or are ineligible for transplantation. Pembrolizumab has shown both favourable efficacy and quality of life when compared to BV in this patient population and supports the use of anti-PD1 antibody therapy as the preferred choice. The potential for the combination of BV and anti-PD1 antibodies is of significant clinical interest which remains, to date, unanswered due to enrolment challenges associated with CheckMate-812. Accepting that patients in Canada are increasingly likely to receive BV earlier in the disease course (either with primary treatment based on the results of the ECHELON-1 study or as maintenance treatment post-ASCT based on the results of the AETHERA study),[15,16] the use of checkpoint antibodies in RR-cHL is a well-established gold standard. Clinicians now have a positive randomized controlled trial and two large phase II trials to guide practice in Canada.

Evolving Role of Immunotherapy in cHL: Curative Disease

The clinical trials that will shed light on the role of both nivolumab and pembrolizumab in the curative setting are currently ongoing. Phase I and II studies have evaluated both antibodies in combination in the frontline and second-line curative setting. Published studies using these therapeutic agents have largely focused on younger patients and patients undergoing salvage therapy with a goal of ASCT.

Salvage therapy studies with nivolumab have been published evaluating combinations with BV and ICE (ifosfamide, carboplatin and etoposide given sequentially after nivolumab monotherapy and in combination with nivolumab) chemotherapy.[17,18] These trials highlight favourable ORR (85-95%) and CR rates (65-90%) and appear to compare favourably with traditional chemotherapy ORR and CR rates.[19] Clinicians should be aware that historical results with regimens such as the

GDP (gemcitabine, dexamethasone, cisplatin) phase II experience in Canada used older outcome measures and CT (not FDG PET) imaging.[20] Similar studies are being performed with pembrolizumab with a published single-arm study describing the combination with GVD (gemcitabine, vinorelbine and liposomal doxorubicin). An impressive CR rate of 92% was noted for patients in the two-cycle cohort.[21] Interpretation of these studies is challenging given the lack of a randomized control arm. The Canadian Cancer Trials Group (CCTG) is currently recruiting for a randomized phase II trial of pembrolizumab and brentuximab vedotin versus GDP, followed by high dose chemotherapy and ASCT for RR-cHL.

In the frontline setting, combinations of anti-PD1 antibodies have been evaluated in combination with AVD (doxorubicin, vinblastine, dacarbazine). Nivolumab has been evaluated in the localized early unfavourable setting by the German Hodgkin Study Group (GHSG) and in an industry-sponsored study in advanced disease.[22,23] Both studies demonstrated the feasibility of nivolumab-AVD in these settings. Currently, a study from the North American Intergroup is currently evaluating nivolumab-AVD versus BV-AVD in a large phase III trial (NCT03907488). Pembrolizumab has also been explored in a single arm feasibility phase II trial with 3 cycles of pembrolizumab followed by sequential AVD in early unfavourable or advanced stage cHL.[24] The combination of pembrolizumab and AVD in untreated cHL is currently being studied in a larger single-arm phase II trial (NCT03331341). It is important to note the cautionary experience of nivolumab in combination with BV in the primary treatment setting for patients that were ineligible for traditional chemotherapy as this study did not meet its primary efficacy endpoint.[25]

Conclusions

Immunotherapy with nivolumab and pembrolizumab has been a major advance in the treatment of RR-cHL based on well conducted clinical trials. Current studies are evaluating these agents in combination with standard therapy for primary treatment and in the second-line curative setting. Frontline trials will require long-term follow-up and consideration of efficacy and late effects to better integrate these agents into this setting.

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TAILORING THERAPY IN WALDENSTRÖM MACROGLOBULINEMIA

Introduction
Waldenström Macroglobulinemia (WM) is a mature B-cell neoplasm categorized as a lymphoplasmacytic lymphoma (LPL) with monoclonal immunoglobulin M (IgM) production.[1] WM comprises a spectrum of clinical manifestations related to (a) excessive infiltration of the bone marrow and/or other organs (lymph nodes, spleen, extranodal organs) by the LPL infiltrate, and (b) the impact of excess IgM on the circulatory and immune systems, and end organs. The latter includes serum hyperviscosity, infection related to suppression of other immunoglobulins, autoimmune cytopenias, cryoglobulinemia, production of anti-myelin-associated glycoprotein antibodies leading to peripheral neuropathy, and occasionally AL amyloidosis with end-organ deposition.

Assessment of WM
The assessment of a patient with WM requires 6 steps. **(Table 1).** The first step is to confirm the diagnosis, especially in patients with newly diagnosed disease. The diagnosis requires confirmation of a LPL with its characteristic morphology and immunoprofile, together with a monoclonal serum IgM. The *MYD88 L265P* mutation, typically identified using the polymerase chain reaction or other forms of sequencing in a bone marrow sample, is present in > 90% of patients with WM.[2] The presence of this mutation may help differentiate WM from other lymphoid neoplasms, and is both prognostic and predictive of response to treatment.[3, 4] The impact of several additional recurrent mutations in WM (including *CXCR4*) on the diagnosis, prognosis, and treatment selection for routine clinical practice has not yet been established.[3, 5]

Step	Description
1	Confirm the diagnosis of WM.
2	Evaluate for involvement by WM in hematologic and non-hematologic compartments.
3	Determine whether there is an indication to start treatment.
4	Determine whether there is an indication for immediate plasmapheresis.
5	Select a systemic therapy that incorporates goals of care, genomic findings, and (if applicable) prior therapies.
6	Quantify response to therapy using established criteria. [12] **(Table 2)**

Table 1. Steps in the assessment of a patient with WM in the treatment-naïve and/or relapsed/refractory settings; courtesy of Diego Villa, MD

Group Response Category		Individual Response Category	Monoclonal IgM (serum)	Total IgM (serum) change from baseline	Response in lymphadenopathy and splenomegaly (if present)	Other parameters
ORR	MRR	CR	Absent	Normalization	Resolution	Normal BM morphology
		VGPR	Detectable	≥90% reduction	Resolution	No new signs or symptoms of active disease
		PR		≥50% but <90% reduction	Reduction	
		MR		≥25% but <50% reduction	Reduction or no progression	
		SD		<25% reduction & <25% increase	No progression	
		PD		≥25% increase (from nadir)	Progression	Progression

Table 2. Current response assessment criteria in WM. Table modified from the Sixth International Workshop on WM publication. [12]; courtesy of Diego Villa, MD

BM: bone marrow, CR: complete response, MR: minor response, MRR: major response rate, ORR: overall response rate, PD: progressive disease, PR: partial response, SD: stable disease.

The second step in the assessment of a patient with WM is a thorough evaluation of the various compartments that may be involved directly or indirectly. Such assessment requires a full history and physical examination, comprehensive blood testing including measurements of total/monoclonal IgM and serum viscosity, bone marrow biopsy, and imaging investigations. Patients with neurologic signs or symptoms require brain imaging and cerebrospinal fluid analysis because WM can occasionally involve the central nervous system in the form of Bing-Neel syndrome in which malignant lymphoplasmacytic cells invade the central nervous system.[6, 7] Patients with high serum viscosity or IgM levels require referral to ophthalmology because hyperviscosity can damage retinal blood vessels and impair vision.

Principles of management of WM

The third step in the assessment of a patient with WM is to determine whether there is a treatment indication. The goals of treatment of WM include palliating symptoms, reducing and/or preventing end-organ damage, and improving both quality and quantity of life. Observation is a valid management option in select patients without symptoms or clinically significant findings on initial investigations. This principle holds true in both the treatment-naïve and relapsed/refractory settings. However, most patients with WM require treatment for symptomatic disease or laboratory findings suggesting impending complications (i.e. cytopenias) even when asymptomatic. The International Workshop on WM (IWWM) has established clear treatment initiation criteria.[8]

The fourth step in the initial assessment of a patient with WM is to determine whether plasmapheresis is necessary prior to systemic therapy. Excessive circulating IgM can lead to hyperviscosity syndrome (HVS) which classically presents with mucosal bleeding, retinopathy, and neurologic symptoms. HVS, particularly when associated with ocular or neurologic complications, is considered a medical emergency requiring urgent plasmapheresis. In patients with high IgM or serum viscosity, rituximab administration can cause a hyperviscosity flare.[9] Plasmapheresis and/or omission of rituximab with the first cycle of chemotherapy may reduce the risk of this complication and should generally be considered in patients with serum IgM >50 g/L or viscosity >3.5 centipoise, although there is no definitive threshold. Plasmapheresis is a temporizing intervention and should always be followed by systemic therapy.[10]

The fifth step in the assessment of a patient with WM is to determine the most appropriate treatment option. The interplay between the genomic profile of WM and available therapeutics is progressively informing treatment selection.[3, 4] Specifically, consensus recommendations from the most recent IWWM suggest testing for *MYD88* mutations before starting treatment because patients without *MYD88* mutations are less likely to respond to ibrutinib monotherapy. The same guidelines do not currently recommend the use of *CXCR4* testing to inform treatment decision-making outside of a research setting.[5] The subsequent sections of this review describe therapeutic options for WM.

The sixth step in the assessment of a patient with WM is to determine the clinical response to a particular line of therapy. Response assessment to treatment for WM does not follow traditional criteria for other lymphomas such as the Lugano classification for the initial evaluation, staging, and response assessment of lymphomas[11] because of the specific biology of WM and its response kinetics to therapy. The IWWM criteria for response assessment incorporate additional categories that quantify the degree of response in IgM and qualify response in nodal and extranodal organs, as well as other clinical parameters including symptoms.[12] **(Table 2)**

Rituximab-containing therapy

Over the past 1-2 decades, frontline therapy for WM has included rituximab alone or in combination with cytotoxic chemotherapy. Combinations with alkylators such as bendamustine (BR) are associated with high response rates, a generally acceptable toxicity profile, and prolonged remission in many patients **(Table 3).** An additional advantage of these regimens is their fixed duration, which improves quality of life in responders and provides the option of retreatment in those who relapse after long treatment-free periods.[13-16] The use of maintenance rituximab after chemoimmunotherapy, particularly after BR, is not indicated because it prolongs immune suppression and does not improve progression-free survival (PFS).[15]

Proteasome inhibitors are also active against WM, with phase 2 trials showing high response rates when combined with rituximab **(Table 3).** It is difficult to assess whether the

Reference	n	Therapy	Response rates (%)			Median PFS (months)	Median OS (months)
			ORR	MRR	VGPR		
Rituximab in combination with cytotoxic agents							
Rummel, Blood 2019[15]	109	BR	91	90	s.o.	83*	Median NR
	109	BR+RE				101*	Median NR
Kastritis, Blood 2015[13]	72	CDR	83	74	7	35	95
Laribi, BJH 2019[14]	69	BR	97	96	37	Median NR 2yr 87%	Median NR 2yr 97%
Rummel, Lancet 2013[16]	22	BR	NA	NA	NA	70^	Median NR
	19	R-CHOP	NA	NA	NA	28^	Median NR
Rituximab in combination with proteasome inhibitors							
Dimopoulos, Blood 2013[18]	59	VDR	85	68	7	42	s.o. 82 % à 3 ans
Treon, Blood 2014[20]	31	KDR	87	68	35	46	Median NR
Castillo, CCR 2018[17]	26	IDR	96	77	15	Median NR	NA
Treon, JCO 2009[19]	23	VDR	96	83	13	66	NA

Table 3. Prospective studies of rituximab-containing therapies in the front-line setting; courtesy of Diego Villa, MD

**Difference was not statistically significant (HR 0.80 [95% CI 0.51-1.25], p=0.32)*

^Difference was statistically significant (HR 0.33 [95% CI 0.11-0.64], p=0.003)

B: bendamustine, C: cyclophosphamide, CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone, D: dexamethasone, I: ixazomib, K: carfilzomib, M: maintenance rituximab, MRR: major response rate, NA: not available, NR: not reached, ORR: overall response rage, R: rituximab, V: bortezomib, VGPR: very good partial response

Reference	n		Therapy	Response Rates (%)			PFS	OS
	TN	R/R		ORR	MRR	VGPR		
Treon, JCO 2018 [24]	31	0	Ibrutinib	100	83	20	Median NR 18mo 92%	Median NR 15mo 100%
Treon, NEJM 2015 [25]	0	63	Ibrutinib	91	73	16	Median NR 2yr 69%	Median NR 2yr 95%
Tam, Blood 2020 [23]	18	81	Ibrutinib	93	78	19	Median NR 18mo 84%*	Median NR 18mo 93%
	19	83	Zanubrutinib	94	77	28	Median NR 18mo 85%*	Median NR 18mo 97%
Dimopoulos, NEJM 2018 [21]	34	41	Ibrutinib + rituximab	93	73	23	Median NR 30mo 82%^	Median NR 30mo 94%
	34	41	Rituximab	47	32	4	Med 20 mo 30mo 28%^	Median NR 30mo 92%
Owen, Lancet Haem 2020 [22]	14	92	Acalabrutinib	93	80	9 (R/R)	Median NR 2yr 90% TN, 82% R/R	Median NR 2yr 92% TN, 89% R/R

Table 4. Prospective studies of BTK inhibitors in treatment-naïve and relapsed/refractory WM; courtesy of Diego Villa, MD

**Difference was not statistically significant (HR 0.85 [95% CI 0.43-1.76], p=0.687)*

^Difference was statistically significant (HR 0.20 [95% CI 0.11-0.38], p<0.001)

MRR: major response rate, NR: not reached, PFS: progression-free survival, ORR: overall response rate, OS: overall survival, R/R: relapsed/refractory, TN: treatment naïve, VGPR: very good partial response

long-term outcomes achieved with proteasome inhibitors are comparable to those achieved with BR given the relatively limited sample size of these trials and the lack of head-to-head comparisons.[17-20] The risks and benefits of using proteasome inhibitors should be weighed carefully in patients with peripheral neuropathy which is common in WM. Also, access to these agents, especially in the frontline setting, has historically been limited in Canada.

Bruton Tyrosine Kinase inhibitors

Covalent Bruton Tyrosine Kinase inhibitors (BTKi) have been studied in the frontline and relapsed/refractory settings.[21-25] **(Table 4)** The two largest randomized clinical trials in WM performed to date have evaluated the role of BTKi. The iNNOVATE trial showed the combination of ibrutinib and rituximab both in treatment-naïve and relapsed/refractory WM was associated with a significant improvement in PFS compared to rituximab alone, and led to regulatory approval of ibrutinib in WM.[21] In the ASPEN trial, zanubrutinib was associated with a higher very good partial response rate compared to ibrutinib (28% vs. 19%), although this difference was not statistically significant, and in the end PFS rates were similar with both agents at the 18 month timepoint. Zanubrutinib was associated with a lower incidence of known BTKi toxicities including atrial fibrillation, hypertension, diarrhea, and bleeding.[23] BTKi are known to cross the blood-brain barrier and are the treatment of choice for patients with Bing-Neel syndrome.[26]

Potentially available therapies in Canada with activity against WM

Several classic and novel agents currently used in other malignancies demonstrate activity against WM in phase 2 trials **(Table 5).** Certain agents are associated with significant toxicity limiting their future use in WM including fludarabine (prolonged cytopenias and infection),[27, 28] lenalidomide (severe rapid-onset anemia),[29] and idelalisib (cytopenias, diarrhea, liver toxicity).[30] Other agents with single-agent activity and expected toxicity profiles such as everolimus, venetoclax, daratumumab may be more appropriate for off-label use, although access in Canada remains limited.[31-33] Autologous and allogeneic stem cell transplantation may benefit selected patients with treatment-responsive R/R WM at the expense of significant toxicity, including a high non-relapse mortality rate with allogeneic stem cell transplantation.[34]

Conclusions and future directions

WM is a lymphoid malignancy with a unique biology, natural history, and management considerations. The treatment of WM is becoming increasingly complex as more treatment options become available, and genomic profiling is playing an increasingly important prognostic and predictive role. Despite these advances, WM remains incurable, and patients with disease refractory to chemoimmunotherapy and BTKi face limited options and a poor prognosis. Non-covalent BTKi[35], novel combinations, and immune therapies are currently under investigation and may provide additional opportunities to improve outcomes in WM.

Reference	Therapy and evidence base	Response Rates	Outcomes	Comments
Nucleoside analogs				
Treon, Blood 2009 [28]	Fludarabine + rituximab Phase 2 study, n=43*	ORR 95% MRR 86% VGPR 33%	mTTP 51 months	Expected significant hematologic and infectious toxicity profiles
Tedeschi, Cancer 2012 [27]	Fludarabine + cyclophosphamide + rituximab Phase 2 study, n=43*	ORR 79% MRR 74% VGPR 21%	mEFS 50 months	
Immunomodulatory imide drugs (IMIDs)				
Treon, Blood 2008 [36]	Thalidomide + rituximab Phase 2 study, n=25*	ORR 72% MRR 64%	mTTP 35 months	Dose reductions necessary in all patients, very frequent neuropathy
Treon, CCR 2009 [29]	Lenalidomide + rituximab Phase 2 study, n=16*	ORR 50% MRR 25%	mTTP 19 months	Study stopped early due to acute onset severe anemia
mTOR inhibitors				
Ghobrial, AJH 2014 [33]	Everolimus Phase 2 study, n=60	ORR 73% MRR 23%	mTTP 25 months mPFS 21 months	Expected hematologic and non-hematologic toxicity
PI3K inhibitors				
Tomowiak, Blood Adv 2021 [30]	Idelalisib + obinutuzumab Phase 2 study, n=48	ORR 71% MRR 65% VGPR 10%	mPFS 25 months	High discontinuation rates due to toxicity
BCL2 inhibitors				
Castillo, JCO 2022 [31]	Venetoclax (24 months) Phase 2 study, n=32	ORR 84% MRR 81% VGPR 19%	mPFS 30 months	Frequent PD after stopping venetoclax at 24 months
Anti-CD38 monoclonal antibodies				
Castillo, Blood Adv 2020 [32]	Daratumumab Phase 2 study, n=13	ORR 23% MRR 15%	mPFS 2 months	Generates hypothesis that combinations including dara may be preferred
Hematopoietic stem cell transplantation				
Parrondo, CLML 2020 [34]	Autologous stem cell transplantation	ORR 85% CR 22%	pPFS 55% pOS 76%	1-year NRM 4%
	Meta-analysis of 8 retrospective studies, n=278			
	Allogeneic stem cell transplantation Meta-analysis of 7 retrospective studies, n=311	ORR 81% CR 26%	pPFS 49% pOS 57%	~50% myeloablative; 1-year NRM 29%; Acute GVHD 71% (10% grade 3+)

Table 5. Studies of other therapies in relapsed/refractory WM; courtesy of Diego Villa, MD

**Also included a proportion of treatment-naïve patients.*

CR: complete response, GVHD: acute graft vs. host disease, mEFS: median event-free survival

mTTP: median time to progression (calculated only in responding patients), mPFS: median progression-free survival, NRM: 1-year non-relapse mortality, pPFS: pooled progression-free survival (estimated at 3-5 years given reporting differences between studies), mOS: median overall survival, ORR: overall response rate, pOS: pooled overall survival (estimated at 3-5 given reporting differences between studies), VGPR: very good partial response.

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- Avoid use during pregnancy.
- Breastfeeding should be discontinued.
- No overall difference in effectiveness and safety observed in patients ≥65 years of age compared to younger patients. In the combination study (MURANO), patients ≥65 years of age experienced higher incidences of diarrhea, peripheral oedema, dizziness, blood creatinine increased, constipation, pyrexia and fall than those <65 years of age.
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Please refer to the study parameters[†§] and reference list at: **meddocs.ca/CA-VENC-210030.html**.

* V: VENCLEXTA.
‡ The median follow-up at the time of analysis was 28 months (range: 0 to 36 months).
¶ The median follow-up at the time of primary analysis was 24.8 months (range: 0.3 to 37.4 months) in the VENCLEXTA + rituximab arm and 22.1 months (range: 0 to 33.8 months) in the bendamustine + rituximab arm (data cut-off date May 8, 2017).

CLL: chronic lymphocytic leukemia; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; R/R: relapsed/refractory; IRC: independent review committee; ITT: intention-to-treat; G-CSF: granulocyte-colony stimulating factor; CrCl: creatinine clearance.

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MULTIPLE MYELOMA MANAGEMENT: WHAT COMES AFTER LENALIDOMIDE-BASED THERAPY?

Over the past two decades a myriad of new combination strategies and therapeutic agents for the treatment of multiple myeloma (MM) have been developed. Novel drug classes such as proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies have demonstrated very promising efficacy outcomes related to survival endpoints and improvements in quality of life for myeloma patients.[1-7] Data from the United Kingdom shows that over a fifteen year period from 2003 to 2017, 52.6% of patients with myeloma were alive 5 years after diagnosis and 29% after 10 years. Other researchers have evaluated The Surveillance, Epidemiology, and End Results (SEER) database to asses the probability of survival of myeloma patients, comparing treatment strategies between non-novel and novel therapies (e.g; bortezomib, lenalidomide, pomalidomide) **(Figure 1)**.[8] Overall, 7,139 newly diagnosed patients with MM between 2006–2012 were able to link with the social security administration Master Death File for analysis. Patients younger than 65 years old at diagnosis had better survival than those 65 years and older ($P < 0.01$) and 19.5% of MM patients had an autologous stem cell transplantation (ASCT) during the same time period, with an improved survival experience than those without SCT ($P < 0.01$). Among the newly diagnosed cohort in this analysis who received a MM treatment ($n = 4,902$), patients treated with novel therapies within 1 year of diagnosis showed significantly better survival than those with only non-novel therapies ($P = 0.01$).In this large dataset, a greater proportion of MM patients survived for 2 years post diagnosis in 2012 (87.1%) than in 2006 (69.9%), whereas the 2-year survival was consistent for matched control patients without MM (93.9–97.4%) during the same time period).[8]

Despite the improvements in survival outcomes, the addition of these novel agents to the treatment armamentarium for MM has resulted in a corresponding increase in the lifetime cost of MM treatment. In the above-mentioned study, researchers found that total per patient per month (PPPM) all-cause healthcare costs increased from $3,263 PPPM in 2000 to $14,656 PPPM in 2014 among newly diagnosed MM patients, which were primarily driven by costs of outpatient services, such as laboratory, radiology and physician visits, among others.[8] In Canada, even though over 60% [9] of the population has private drug insurance, the heavy costs associated with multiple myeloma therapy do predominantly fall under the publicly-funded system. A Canadian analysis from 2014 in patients ineligible for SCT calculated and compared the total annual drug cost of the two maintenance therapy options. Costs were based on $1.3mg/m^2$ of bortezomib on days 1, 4, 8, 11 every three months, plus 50 mg of prednisone every other day, or 10 mg of lenalidomide on days 1 through 21 of each 28-day cycle. Administration costs including oncology nursing time and pharmacist workload, and pharmacy costs including a 10% markup and dispensing fees were added to the acquisition cost of bortezomib and lenalidomide, respectively. Unit and labour costs were obtained from public Canadian sources. The results of this Canadian cost impact analysis demonstrated that the total annual costs of treatment per patient were $20,106, and $108,741 for bortezomib and lenalidomide, respectively.[10] As such, access to certain drugs or drug combinations is restricted for myeloma patients and Canadian clinicians despite this being an understandable approach from a public resource utilization perspective.

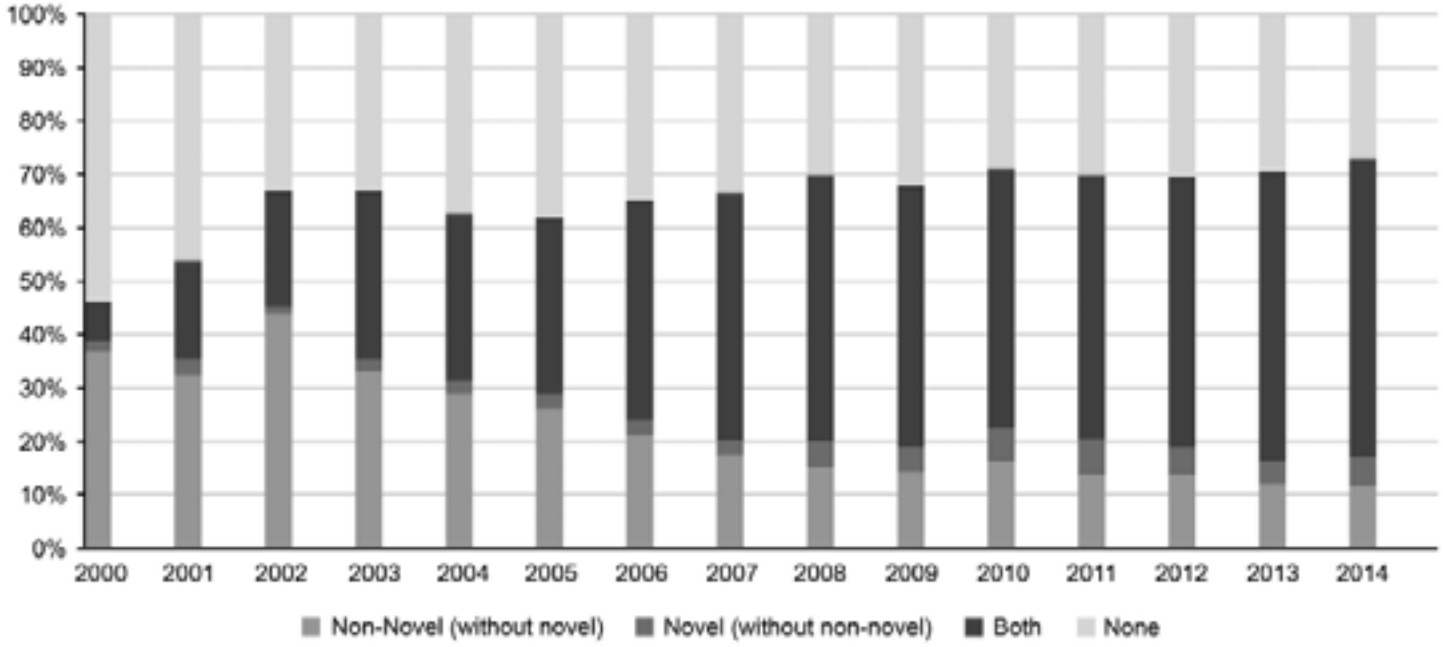

Figure 1. Multiple myeloma treatment used within 1 year after diagnosis, by year of diagnosis. Note: novel treatment include: bortezomib, carfilzomib, lenalidomide, panobinostat, pomalidomide and thalidomide. Non-novel treatment include: arsenic trioxide, bendamustine, busulfan, cisplatin, cyclophosphamide, doxorubicin, etoposide, melphalan, prednisone, dexamethasone, rituximab, vincristine and vorinostat; adapted from Fonseca et al, 2017.

Over the past decade, lenalidomide has become the most widely-used backbone therapy in multiple myeloma (MM), both in the front-line and relapsed settings.[1-7] In Canada, lenalidomide-based therapy is approved for newly diagnosed, transplant ineligible MM patients in combination with dexamethasone or as triplet therapy in combination with bortezomib and dexamethasone (VRd and RVd Lite) or in combination with daratumumab and dexamethasone (DRd).[2-4] In the transplant eligible (TE) setting, lenalidomide is approved as single-agent maintenance therapy post- ASCT once adequate hematologic recovery [ANC ≥1,000/mm^3; platelets ≥75,000/mm^3]) is achieved. It may continue until disease progression or unacceptable toxicity occurs. In some jurisdictions, VRd is funded as a pre-transplant option.

The addition of lenalidomide as maintenance post-ASCT has improved progression free survival (PFS) in TE patients as confirmed by the Canadian Myeloma Research group (CMRG) real world evidence study that included 1256 patients of which 57.6% received lenalidomide maintenance. The median PFS was 58.2 months (95% Confidence Interval [CI]: 52.0–64.0) in the lenalidomide group which was significantly superior to the 34.6 months in the non-lenalidomide group (95%CI: 30.7–37.7, P<0.0001).[11] In Canada, lenalidomide maintenance is conventionally used to progression given the reimbursement limitations in public funding for drug re-utilization. As a consequence, virtually all patients exposed to lenalidomide will inevitably become refractory to the drug, unless treatment is discontinued early due to adverse events. In addition, the sequencing of therapy post-lenalidomide poses another challenge, given that several studies have evaluated the outcomes of anti-myeloma therapy after lenalidomide exposure and after lenalidomide refractoriness, suggesting that outcomes may be better for those lenalidomide exposed but not resistant.[12-14]

In the relapsed setting, the first choice in second line therapy for patients who are lenalidomide-naïve includes a combination of daratumumab, a CD-38 monoclonal antibody, lenalidomide and dexamethasone (DRd). In the pivotal POLLUX trial, 569 patients with multiple myeloma who had received one or more previous lines of therapy were randomized to receive lenalidomide and dexamethasone either alone (control group) or in combination with daratumumab (daratumumab group). The primary end point was progression-free survival. At a median follow-up of 13.5 months in a protocol-specified interim analysis, 169 events of disease progression or death were observed (in 53 of 286 patients [18.5%] in the daratumumab group vs. 116 of 283 [41.0%] in the control group; hazard ratio, 0.37; 95% confidence interval [CI], 0.27 to 0.52; P<0.001 by stratified log-rank test). The Kaplan–Meier rate of progression-free survival at 12 months was 83.2% (95% CI, 78.3 to 87.2) in the daratumumab group, as compared with 60.1% (95% CI, 54.0 to 65.7) in the control group. In a long-term follow up, DRd patients achieved a median progression free survival of 47 months.[6,15]

For patients exposed or refractory to lenalidomide there are several potential options. The OPTIMISMM trial evaluated the impact of pomalidomide, bortezomib and

dexamethasone (PVd) versus bortezomib and dexamethasone (Vd) in patients who had received 1 to 3 prior lines of therapy.[16] In this study, all patients had received a prior lenalidomide-containing regimen for at least 2 consecutive cycles. The median PFS in the pomalidomide, bortezomib, and dexamethasone group was 11.2 months compared with bortezomib and dexamethasone group which was 7.1 months (median 11.2 months [95% CI 9.66–13.73] vs 7.1 months [5.88–8.48]; hazard ratio 0·61, 95% CI 0·49–0·77; p<0.0001).[16] A recent subgroup analysis of the OPTIMISMM trial evaluated outcomes in patients at first relapse (N=226) by lenalidomide-refractory status, prior bortezomib exposure, and prior SCT. Results of this analysis shows that second-line PVd significantly improved PFS vs Vd in lenalidomide-refractory patients (17.8 vs 9.5 months; P=0.0276) and it was slightly better in lenalidomide-nonrefractory patients (22.0 vs 12.0 months; P=0.0491). Significant improvement in overall response rate was also observed with PVd vs Vd in lenalidomide-refractory (85.9% vs 50.8%; P<0.001) and lenalidomide-nonrefractory (95.7% vs 60.0%; P<0.001) patients, with similar results regardless of prior bortezomib use or ASCT. No new safety signals were observed. These data demonstrate the benefit of PVd at first relapse, including immediately after upfront lenalidomide treatment failure.[12]

Another pivotal study is the CASTOR trial which evaluated daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone alone in relapsed MM.[13] In a post-hoc analysis to the original CASTOR trial based on treatment history and longer follow-up, researchers demonstrated that the DVd regimen prolonged progression-free survival (median: 16.7 versus 7.1 months; hazard ratio, 0.31; 95% confidence interval, 0.24-0.39; P<0.0001) and improved the overall response rate (83.8% versus 63.2%; P<0.0001) compared with bortezomib and dexamethasone alone. The progression-free survival benefit of DVd was more pronounced in patients with 1 prior line of therapy (median: not reached versus 7.9 months; hazard ratio, 0.19; 95% confidence interval, 0.12-0.29; P<0.0001).[14] Nevertheless, those refractory to lenalidomide had an unsatisfactory response with median PFS of only 9.8 months.

Other pomalidomide and dexamethasone-based combination regimens are currently under evaluation in phase II and III studies; and include the addition of isatuximab, or carfilzomib, or daratumumab, or cyclophosphamide.[16-18] The vast majority of subjects in these trials included patients who were refractory to lenalidomide after 2 or more prior lines of therapy. The pooled overall response rate across these trials is approximately 70%. However, the pooled median PFS was shown to be around 10 months regardless of the regimen used. Recently, the CMRG presented the results of 73 real-world patients treated post-lenalidomide maintenance. The median PFS for the entire cohort treated with daratumumab-based regimens was 16.96 months (95% CI 11.47-23.44). The median PFS of the individual regimens was reported as follows: DPd 17.65 months, DRd not reached and DVd 11.47 months (p =0.46).[18]

Other MM regimen combinations utilizing Selinexor, an XPO-1 inhibitor have been investigated and show promising results but are currently not publicly funded in Canada but may be available through clinical trials. Emerging agents such as and belantamab mafodotin, a BCMA targeted conjugated monoclonal antibody, cereblon modulators, CAR-T cell therapy and bi specific T-cell engagers targeting various MM cell membrane proteins are currently under investigation.

In summary, the sequencing of therapy in MM is complex. Lenalidomide-based regimens represent the cornerstone of treatment for newly-diagnosed transplant-ineligible MM patients and for transplant eligible patients, and in the maintenance phase. Although there are numerous potential drug combinations to be used in a second line setting and beyond, clinical trial results for patients refractory to lenalidomide are somewhat disappointing conferring a median PFS of only 10 to 12 months. Treatment choices must be carefully considered to take into consideration availability, treatment-related adverse events and potential long-term outcomes.

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CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY FOR RELAPSED AND REFRACTORY LARGE B CELL LYMPHOMA: A CANADIAN PERSPECTIVE

Introduction

Comprising approximately 40% of diagnoses, lymphoma is the most common hematological malignancy in Canada, and 80% of lymphoma cases are non-Hodgkin lymphoma (NHL).[1] Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of new NHL cases in Canada. First-line treatment with standard of care chemoimmunotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) results in a cure in approximately 60-70% of patients. Nevertheless, 30%-40% of patients will experience relapse of their disease or are refractory to first-line therapy.[2-5]

Among those patients with relapsed or refractory DLBCL (R/R DLBCL), about 10-15% will exhibit primary refractory disease with either stable or progressive disease despite first-line therapy, while 20-25% will experience relapse after an initial response to treatment.[6] Most relapses will occur within 2-3 years following initial treatment. For these patients, the standard approach is salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) for those who meet the eligibility criteria and have chemosensitive disease.

Salvage Chemotherapy

There is evidence for multiple salvages, or later-line, chemotherapy regimens in the setting of R/R DLBCL. While there are no apparent outliers for optimal response, salvage regimens that include rituximab have historically been associated with slightly better outcomes.[7,8] The CORAL study compared rituximab, dexamethasone, cisplatin, and cytarabine (R-DHAP) to rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) as salvage chemotherapy in R/R DLBCL. Patients received three cycles of either R-DHAP or R-ICE, after which those patients with chemosensitive disease received high-dose chemotherapy conditioning followed by ASCT. Overall response rates (ORR), event-free survival (EFS), and overall survival (OS) were similar for both regimens.[9]

Researchers conducted a phase III trial using a non-inferiority design that compared rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP) to R-DHAP. Again, ORR, EFS, and OS were similar between regimens, but R-GDP demonstrated lower grade 3 and 4 toxicity rates.[7]

Autologous Stem Cell Transplant

Eligible patients who achieve a partial remission (PR) or complete remission (CR) following salvage chemotherapy should proceed to ASCT if they have not been previously transplanted. Evidence for the benefit of ASCT in the R/R setting comes from the PARMA trial, which examined patients with relapsed aggressive lymphoma. Patients who had previously achieved CR with initial therapy received R-DHAP for two cycles and, in the case of chemosensitive disease, were then randomized to either receive additional cycles of R-DHAP or high-dose chemotherapy followed by ASCT. Subjects in the transplant arm had a longer 5-year EFS (46% vs. 12%) and OS (53% vs. 32%).[10] Newer trials have failed to show a similarly robust response, although these trials did show a statistically significant benefit of ASCT.[11] The more modest response demonstrated in these newer trials is likely due to many of the patients in the PARMA trial not having received rituximab as part of their initial therapy, while in more recent years rituximab would have been standard of care for initial therapy in DLBCL. ASCT for patients with R/R DLBCL who had a PR or CR following salvage chemotherapy performs significantly better than salvage chemotherapy alone and constitutes the current standard of care in eligible patients for whom treatment is with curative intent.

In 2018, researchers published encouraging 5-year survival outcomes for patients with R/R DLBCL who had chemosensitive disease and underwent ASCT with R-BEAM conditioning, which consists of a combination of rituximab, carmustine, etoposide, cytarabine, and melphalan. The 5-year disease-free survival (DFS) and OS were 62% and 73%, respectively. In this study, neither cell of origin nor timing of disease relapse were associated with the outcome measures.[12] Patients with primary refractory disease are less likely to respond to salvage chemotherapy and are, therefore, less likely to receive an ASCT.

In contrast to patients who respond to salvage therapy and ASCT, those whose cancer is not chemosensitive to salvage therapy are not eligible for ASCT. This group of patients and those who relapse following ASCT experience exceptionally poor outcomes. The SCHOLAR-1 study retrospectively analyzed outcomes in patients with R/R DLBCL and found a median survival of 6.3 months from the start of salvage chemotherapy, with a 1-year OS of 28% and a 2-year OS of 20%.[13] Early relapse (within 12 months) and refractory disease exhibit a worse prognosis.[6] Of the patients who are refractory or exhibit early relapse, only 30-40% will respond to salvage chemotherapy and have the option to proceed to ASCT, and about 50% will experience a relapse after transplantation. This confers a poor prognosis, particularly for those patients with secondary International Prognostic Index (IPI) scores >2.[13]

Chimeric Antigen Receptor T-cell (CAR-T) therapy

CAR-T therapy involves collecting patient T cells and genetically modifying these to express CARs that include an external antigen-binding domain with heavy and light single-chain variable fragments that direct specificity to an antigen expressed by cancer cells and an intracellular domain consisting of a T-cell receptor signal transduction domain and co-stimulatory domain(s) to provide activation signals to the T-cell. The CARs recognize the specific antigen independently of major histocompatibility complex (MHC) presentation, which overcomes the downregulation of antigen processing and presentation pathways, a common mechanism for immune evasion in tumours.[14]

Two pivotal studies, ZUMA-1 [15] and JULIET [16], studied the outcomes in patients with R/R DLBCL who received anti-CD19 CAR-T cell therapy, and based on those results, the two tested CAR-T cell products, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, were approved in Canada for R/R DLBCL following the failure of two or more lines of therapy **(Table 1)**. The ZUMA-1 trial results were published in 2017, and of the 108 patients studied, the ORR was 82%, with an OS of 52% at 18 months of follow-up.[15] At 27.1 months of follow-up, the progression-free survival (PFS) was 39%, with an ORR of 83% and a CR rate of 58%. More recently updated survival analyses showed a prolonged OS of 44% after four years of follow-up.[17] In a matched propensity score analysis, patients treated with the CAR-T cell therapy axi-cel in the ZUMA-1 trial had significantly longer OS compared to patients in the SCHOLAR-1 trial, with an OS of 50% and 12% at two years of follow-up, respectively.[18] The JULIET trial randomized 93 patients with R/R DLBCL who were either not candidates for, or had contraindications to ASCT, or had relapsed following ASCT, with the CAR-T cell product tisagenlecleucel targeting CD19. Of those patients, 40% achieved a CR and 12% a PR. At 12 months, the RFS rate was 65% (79% among patients with a CR), and the PFS at 14 months of follow-up was 34%.[16] Results of the pivotal studies are summarized in **Table 2**.

In patients who are refractory to chemotherapy, who are not eligible for ASCT, or who relapse after ASCT, consideration should be given to treatment with CAR-T therapy. Patients on salvage chemotherapy in preparation for ASCT who do not demonstrate sufficient response to the chemotherapy should also be considered for CAR-T therapy. **Figure 1** shows the treatment algorithm for relapsed refractory LBCL and where CAR-T cell therapy may be appropriate.

CAR T-Cell Therapy	Description	Indication	Health Canada Approval Date
Tisagenlecleucel (Kymriah)	CD19-directed genetically modified autologous T-cell therapy	Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	September 2018
Axicabtagene Autoleucel (Yescarta)	CD19-directed genetically modified autologous T-cell therapy	Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	February 2019

Table 1. CAR-T Cell Therapies Approved in Canada; from Canadian Evidence-Based Guideline For The Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma; Lymphoma Canada

Additionally, the role of CAR-T therapy was recently explored as an earlier line treatment for patients with R/R DLBCL and LBCL in three prospective randomized studies. In two studies, the ZUMA-7 (DLBCL) [19] and TRANSFORM (LBCL) [20], anti-CD19 CAR-T cell therapy was shown to be superior to standard of care salvage chemotherapy and ASCT in the second-line treatment setting among patients who had primary refractory or early relapsed disease (within 12 months). On the other hand, the BELINDA [21] study (DLBCL) did not show significant differences in outcomes between CAR-T therapy and salvage chemotherapy. **Table 3** provides an overview of the efficacy (objective response rate and event-free survival) as well as toxicities (cytokine release syndrome and immune effector cell-associated neurotoxicity) seen in these three studies.

Variable	ZUMA-1 (axi-cel [KTE-C19])	JULIET (t-cel [CTL019])	JULIET Package Insert (t-cel [CTL019])	TRANSCEND-NHL-001 (full cohort; liso-cel [JCAR017])	TRANSCEND-NHL-001 (core cohort; liso-cel [JCAR017])
No. pheresed	111	165	160	134	NR
No. treated	101	111	106	114	NR
No. evaluable	101	93	68	102	73
No. never treated (%)	10 (9) of 111	50 (31) of 161	49 (30) of 160	20 (15) of 134	NR
Bridging treatment, %	0	92	90	NR	NR
ORR, %	82	52	50	75	80
CR, %	54	40	32	55	59
6-Month ORR, %	41	37*	NR	NR	47
6-Month CR, %	36	30*	NR	NR	41
ITT ORR (%)	83 (75) of 111	48 (30) of 161	N/A	77 (63) of 122	NA

Table 2. Efficacy of Anti-CD19 CAR T Cells in Aggressive B-NHL; adapted from Caron, A. et al, 2019

Abbreviations: axi-cel, axicabtagene ciloleucel; B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; CR, complete response; ITT, intent-to-treat; liso-cel, lisocabtagene ciloleucel; NA, not applicable; NR, not reported; ORR, objective response rate; t-cel, tisageneleucel.

**Numbers reflect an earlier presentation of the JULIET trial.[8]*

	ZUMA-7 [19]	TRANSFORM [20]	BELINDA [21]
Number of patients	359	184	322
Primary refractory (N)	74	73	66
crossover	No	Yes	Yes
ORR (CAR T)	83	86	46
EFS (in months)	8.3	10.1	3
CRS (N)	92	49	59
ICANS (N)	60	12	10

Table 3 Overview of efficacy and toxicities in three pivotal anti-CD19 CAR-T cell therapy trials; courtesy of Mahmoud Elsawy, MD, MSc

CAR: chimeric antigen receptor; CRS: cytokine release syndrome; EFS: event-free survival; ICANS: immune effector cell-associated neurotoxicity; ORR: objective response rate

Real-world results

Several real-world and registry data have replicated the results reported in the above-described pivotal trials. Among 298 patients who underwent leukapheresis for CAR-T manufacturing in several US centers, 275 (92%) actually received an anti-CD19 CAR-T cell therapy product. The best ORR and CR rates observed in infused patients were 82% and 64%, respectively. At a median follow-up of 12.9 months from the time of CAR T-cell infusion, the median PFS was 8.3 months, and the median OS was not reached.[22]

Practical considerations for anti-CD19 CAR-T cell therapy

Eligibility criteria

Recently, a group of Canadian lymphoma and cell therapy specialists published a consensus recommendation on the eligibility criteria for anti-CD19 CAR-T cell therapy. The consensus recommendations included that patients eligible for intensive therapy following failed salvage therapy or failed stem cell transplant, should receive anti-CD19-targeted CAR-T cell therapy according to the criteria listed below.[23]

Indications for ICU admission for patients with CRS and/or ICANS[26]	High-risk patients for severe CRS and ICANS	General management guidelines in ICU
SBP < 90 mmHg requiring vasopressors; OR • Hypoxia/respiratory distress with increasing oxygen requirement (≥6L O^2/min) or need for ventilatory support, OR • Clinically significant arrhythmias or acute coronary syndrome with positive troponin; OR • ICE-score ≤6 points, signs of raised ICP or seizures; OR • Team concern particularly for high-risk patients	• Older age (≥65 yrs) • Early onset CRS (<24 hr) • Coexisting comorbid conditions (e.g. renal, CVS) • High tumor burden • High pretreatment LDH • High pretreatment inflammatory markers (ferritin, CRP)	• The use of tocilizumab (anti-IL6R) and/or steroids should be done in close consultation with the transplant team • Supportive management of organ toxicities as per standard guidelines • Assess for infection (blood/urine cultures, chest x-ray, ICANS: lumbar puncture, and start empiric antibiotic therapy if not already started • Laboratory: creatinin, urea, LFTs, WBC, LDH, ferritin, and CRP daily until 72 hrs after symptom improvement • Consider formal echocardiography (recommended for prolonged severe CRS >72h) • ICANS: CT/MRI, EEG, neuroprotective care, consider ICP monitoring • Neurology team should be closely following patients with ICANS

Table 4. Intensive care indication, risks, and general management for patients experiencing CRS or ICANS; courtesy of Mahmoud Elsawy, MD, MSc

CRP: c-reactive protein; CRS: cytokine release syndrome; CT: computed tomography; EEG: electroencephalogram; ICANS: immune effector cell-associated neurotoxicity; ICE: immune effector cell encephalopathy; ICP: intracranial pressure; LDH: lactate dehydrogenase; LFT: liver function test; MRI: magnetic resonance imaging; SBP: systolic blood pressure; WBC: white blood cell count

ELIGIBILITY CRITERIA

- Patient has received ≥2 lines of systemic therapy
- Good performance status (ECOG </=2)
- Not received prior adoptive T cell immunotherapy
- No active central nervous system (CNS) disease
- No significant compromise to vital organ function (as defined per institutional guidelines)

Additionally, as per Health Canada approved indications for CAR-T therapies, patients must meet the following criteria [23] :

HEALTH CANADA APPROVED INDICATIONS FOR CAR-T CELL THERAPIES

- R/R DLBCL of the following subtypes, after ≥2 lines of systemic therapy:
- DLBCL, not otherwise specified
- High-grade B-cell lymphoma
- High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement
- DLBCL arising from follicular lymphoma
- Primary mediastinal large B-cell lymphoma (PMBCL)

** Relapsed disease is defined as partial or complete response to the last line of therapy and subsequent progression*

** Refractory disease is defined as progressive or persistent disease as the best response to the previous therapy*

Bridging therapy

Patients undergo leukapheresis before CAR-T therapy and manufacturing of CAR-T cells usually takes several weeks. During this time, if there is a concern for, or evidence of, progressive disease that is causing symptoms or worsening of clinical status, patients would likely benefit from bridging therapy while awaiting CAR-T treatment. Agents to consider for bridging to CAR-T therapy include [6] single-agent treatment with cyclophosphamide, cytarabine, gemcitabine, or other salvage regimens. Localized radiation therapy may also be beneficial for bulky or symptomatic disease. Furthermore, single-agent steroids could also be utilized. Currently polatuzumab vedotin with bendamustine and rituximab is approved as an effective bridging regimen prior to CAR-T cell therapy.[24]

Considerations for toxicity management

CAR-T cell therapy is associated with two unique acute toxicities, which can be severe and even life-threatening. Cytokine release syndrome (CRS), the most frequently occurring toxicity, can present with low-grade constitutional symptoms or a high-grade syndrome associated with life-threatening multiorgan dysfunction; rarely, severe CRS can evolve into fulminant hemophagocytic lymphohistiocytosis. Immune effector cell-associated encephalopathy syndrome (ICANS) is the second most common adverse event and can occur concurrently with or after CRS. These adverse events require intensive monitoring, accurate grading, and prompt management with aggressive supportive care, anti-IL-6 receptor therapy, and/or corticosteroids.[25]

Prompt recognition and urgent aggressive intervention for the management of CRS or ICANS are key elements for successful outcomes and lead to shorter ICU stays. Almost all CRS/ICANS are reversible with adequate and timely supportive measures. Deteriorations in patient status are

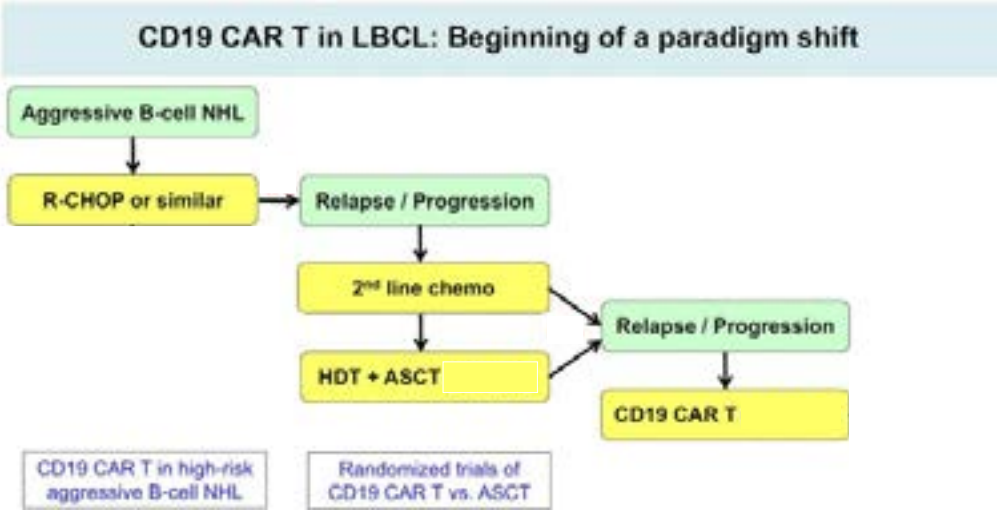

Figure 1, Treatment algorithm in LBCL; Adapted from S. Neelapu, WHU 2021 Presentation. https://careeducation.ca/dr-sattva-neelapu-cell-therapy-whu-2021/

Grade 1 CRS or ICANS
Manage on the floor as per grade specific guidelines

PERSISTENCE
continue monitoring and supportive care
consider tociluzumab for persistent CRS (>24-72 hr)

RESOLUTION
continue monitoring

DETERIORATION

Grade 2 CRS or ICANS
Consult and consider ICU admission (refer to admission criteria)

PERSISTENCE
1- CRS: repeat tocilizumab and consider steroids if refractory
2- ICANS: consider single dose steroids

IMPROVEMENT
if steroids were administered and symptoms improved: consider discontinuation or rapid taper

DETERIORATION

Grade 3 CRS or ICANS
Manage in ICU

PERSISTENCE
1- CRS: repeat tocilizumab (unless at maximum dose) and consider increasing dose of steroids if refractory
2- ICANS: consider high dose steroids

RESOLUTION
if steroids were administered and symptoms improved: consider rapid taper

DETERIORATION

Grade 4 CRS or ICANS
Manage in ICU

PERSISTENCE
High dose steroids or alternative third line therapies if refractory

IMPROVEMENT
if steroids were administered and symptoms improved: consider rapid taper

Figure 2 Indications for ICU admission and general ICANS management guidelines; courtesy of Mahmoud Elsawy, MD, MSc

quick and dramatic. Higher grade CRS is characterized by rapidly progressive capillary leak syndrome. Managing persistent hypotension with overt fluid management leads to inferior results versus early initiation of vasopressors.[26,27] Supportive care is the mainstay of ICANS management. Indications for ICU admission and general management guidelines are outlined in **Table 4** and **Figure 2**. Details of grading and specific management guidelines are discussed elsewhere.[25]

Summary

DLBCL is considered a curable disease with frontline therapy. Nevertheless, a significant proportion of patients will still experience disease relapses or are refractory to frontline treatment. The standard recommended therapy for this patient population is salvage therapy followed by ASCT. However, this treatment approach may still fail in achieving cures for a significant proportion of patients with R/R DLBCL. In addition, a subset of patients is ineligible for ASCT, not responsive to salvage chemotherapy, or will relapse post-ASCT. This patient group has a poor prognosis and requires effective treatment strategies. CAR-T cell therapy has revolutionized the treatment for those patients and provides a potential cure with long-term follow-up results supporting durable response with no new safety concerns. The arrival of this novel therapy has undoubtedly led to a positive change in the natural history of this disease with an otherwise grave prognosis. Furthermore, real-world data have confirmed pivotal trial results, adding another layer of evidence supporting the use of this treatment modality. The earlier application of CAR-T cell therapy during the treatment of patients with R/R DLBCL was investigated in trials and may potentially change the standard of care for those patients who relapse early or who are refractory to first-line therapy.

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WITH GREAT POWER COMES GREAT RESPONSIBILITY: MANAGING SIDE EFFECTS OF NOVEL TREATMENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

The treatment paradigm shift in CLL has uprooted many clinicians' standard practices. Previously, treatment largely depended on age, organ function and "fitness" based on clinical trials which used CIRS (cumulative illness rating scale) scores[1]. Today, as a hematologist who mainly treats patients with CLL, treatment strategies are more complex and multi-factorial. Treatments are based on molecular profiling, which aids in the identification of lower-risk patients for time-limited treatment[2] options versus higher-risk patients (IGVH unmutated[3], del 17p or TP534) who benefit from continuous therapies[5,6]. The highest-risk patients can be identified using a staging system for CLL known as the CLL-International Prognostic Index (CLL-IPI)[7-10]. However, increased CIRS scores are prognostic for poor outcomes independent of the CLL-IPI[11]. As a result, selecting the right treatment for the right individual has never been more important, especially in the era of novel therapeutics. This treatment selection decision pathway includes understanding both patient factors and medical factors that may influence patient outcomes.

Novel time-limited treatment options in Canada at this time include venetoclax and obinutuzumab[2] combination therapy for patients who are deemed "unfit" for FCR (fludarabine, cyclophosphamide, rituximab) in the frontline setting and venetoclax and rituximab[12] in the relapsed setting. Venetoclax can also be used as monotherapy[13] in the relapsed setting **(Figure 1)**.

In the front-line setting obinutuzumab is the monoclonal antibody in the VenO regimen. It can cause TLS, infusion related reactions, neutropenia, and febrile neutropenic events[2,14-18]. Venetoclax, is an oral agent delivered following obinutuzumab administration on Cycle 1 Day 22 continuing through Cycle 2 Day 28[18]. One of the major challenges in the treatment of CLL with venetoclax involves the assessment of tumour lysis syndrome (TLS) risk **(Figure 2).**

Venetoclax is initiated at a starting dose of 20 mg once daily for 7 days and then titrated to a weekly ramp-up schedule of 400 mg over a period of 5 weeks. The TLS monitoring requirements recommend bloodwork 3 days a week to ensure no evidence of TLS after each dose escalation[18]. Blood chemistry monitoring should be performed for all patients at 6 to 8 hours post-dose, and 24 hours post-dose for the first dose of 20 and 50 mg, and pre-dose at subsequent ramp-up doses. The next dose should not be administered until 24-hour blood chemistry results have been evaluated.

Since the risk of developing TLS is highest when treatment is initiated and the overall tumor mass is highest, debulking may be warranted. Our center will often pre-treat patients with a dose of 10 mg for a week to help reduce the risk of TLS and extend the ramp-up schedule to 6 weeks. The use of pharmacological agents as part of a debulking strategy should be considered in certain scenarios to improve

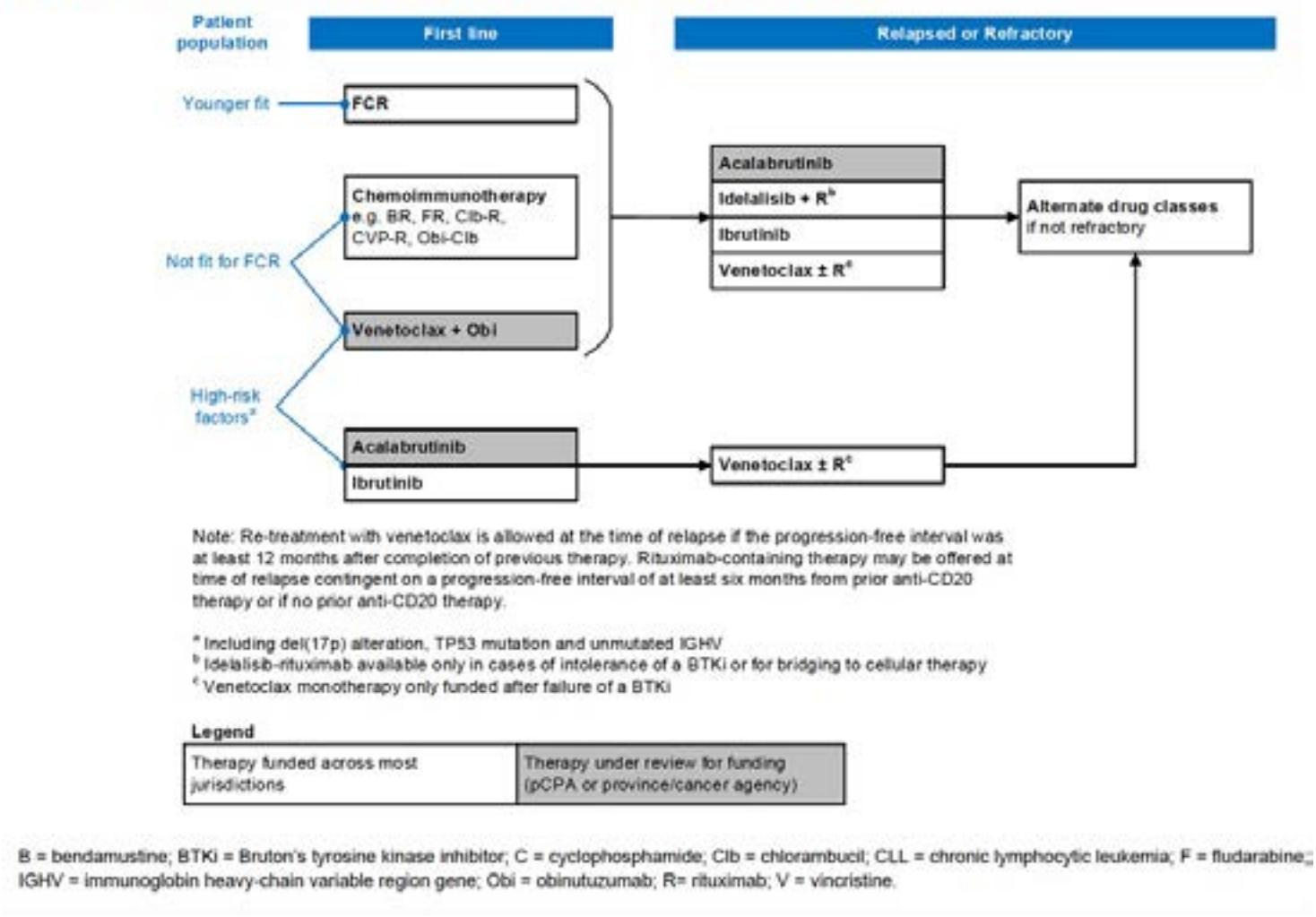

Figure 1. Treatment algorithm for CLL; CADTH Reimbursement Review Provisional Funding Algorithm; May 2021

the tolerability and safety of first treatment cycles with chemoimmunotherapy. Some data shows that obinutuzumab reduces the TLS risk from high risk to moderate risk when a debulking strategy is initiated[18]. The ramp-up can also be shortened in the inpatient setting if required especially in a second line setting when patients are rapidly progressing off a Bruton's Tyrosine Kinase Inhibitor (BTKi)[19] to gain control rapidly.

A similar approach applies in the relapsed setting. In relapse, rituximab is administered after the venetoclax, in cycle 2 and thus minimal debulking pre-ramp-up occurs. The total duration of rituximab therapy in combination with venetoclax is 6 months, a similar duration with obinutuzumab in the frontline setting. However, the treatment duration of venetoclax is 24 months in relapse setting instead of 12 months as administered with obinutuzumab front line. Other side effects commonly experienced (≥ 20% of any Grade) with the use of venetoclax as monotherapy are neutropenia, diarrhea, nausea, anemia, thrombocytopenia, fatigue, upper respiratory tract infection and cough. The most common (≥ 20%) adverse reactions of any grade reported in patients receiving venetoclax in combination with obinutuzumab were neutropenia, and diarrhea. The most common (≥ 5%) Grade 3/4 reactions in the venetoclax + obinutuzumab patients were neutropenia, anemia, and febrile neutropenia.

There are a number of simple interventions available to manage adverse events related to venetoclax. The use of granulocyte colony-stimulating factor (G-CSF) in the setting of combination monoclonal anti-CD20 agent + venetoclax has been shown to be helpful especially in the frontline, when depth of response for optimal remission in a short period is the goal. In the past, the concern was that G-CSF use could mask marrow toxicity in combination with chemoimmunotherapy, thereby increasing the risk of MDS or secondary AML [20,21]. Another approach to managing adverse reactions includes holding the venetoclax and dose reductions as shown in trials [2,12]. Holding of the monoclonal antibody is not recommended unless there is a clinically significant event such as febrile neutropenia. These time-limited novel options benefit patients by providing them time off therapy[2,12]. There are

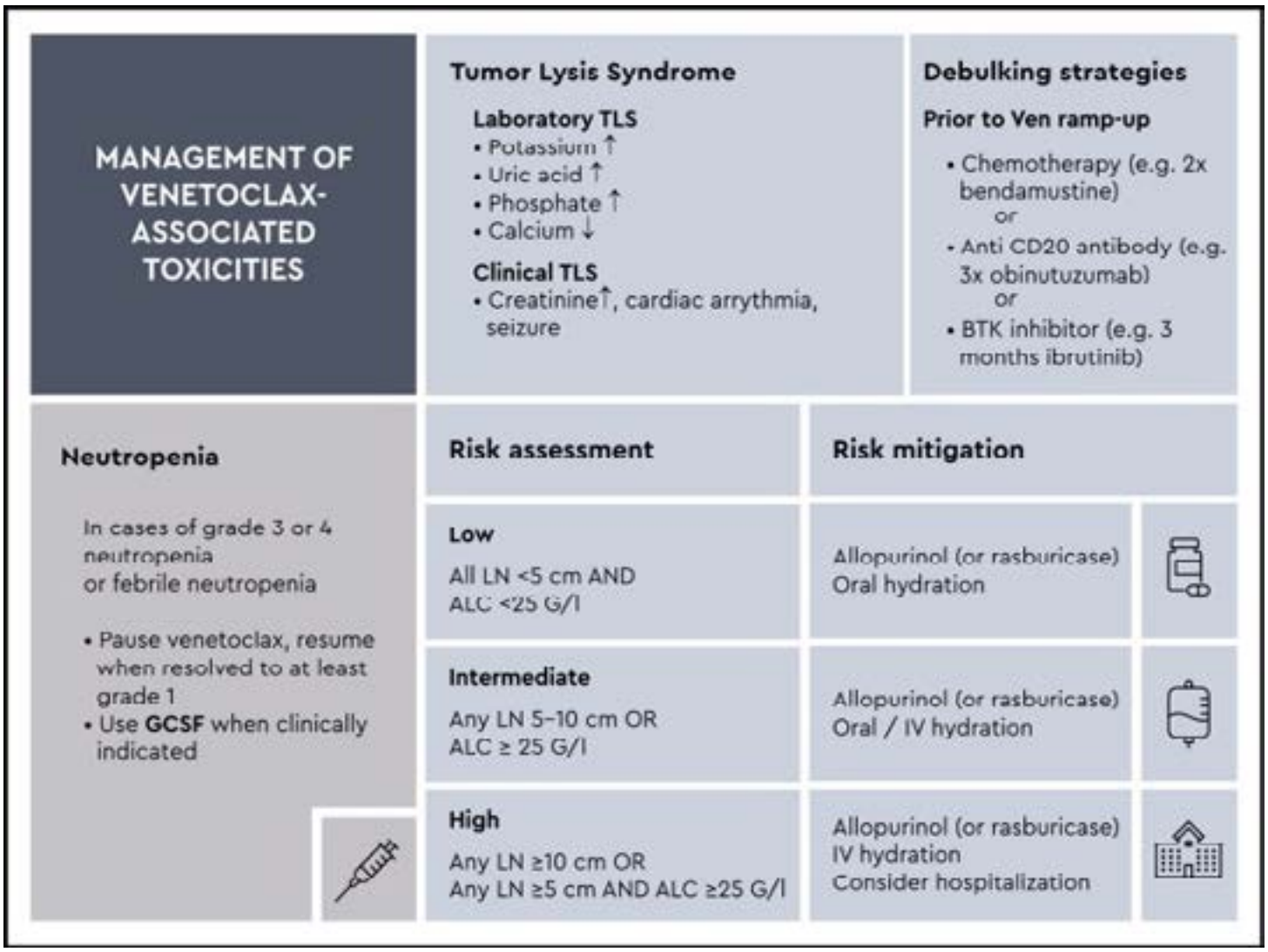

Figure 2. Preventing and monitoring for tumor lysis syndrome and other toxicities of venetoclax during treatment of chronic lymphocytic leukemia; adapted from Fischer et al

fewer side effects related to cardiac and skin toxicities but diarrhea and or constipation may occur.

Venetoclax administered as monotherapy may also be considered when high risk patients progress on continuous therapy with BTKi or when patients do not tolerate BTKi due to their toxicity profile[13]. It is important to note that in both the CLL [14] trial and in retrospective reviews of real-world clinical practice, only 80-85% of patients achieved dose escalation to the maximum recommended dose of 400 mg daily[22]. In some studies, rates of neutropenia with venetoclax monotherapy in the relapsed setting were 47% [22] and in the CLL[14] setting it was 53%[2]. Thrombocytopenia was observed in greater than one-third of cases in both real world evidence and trial settings[2, 22]. These toxicities were managed by either dose holds or dose reductions[2]. Febrile neutropenic episodes (FNE) occurred in 10-12% of patients, and may be managed with the use of G-CSF[2, 22].

BTK inhibitors have changed the treatment landscape for patients with high-risk CLL. They have been used in salvaging patients in relapse who were initially treated with chemotherapy[23]. In addition, their widespread uptake in the frontline has spared many patients from treatments that are not efficacious [24-26]. Published toxicities [27] associated with BTKi use include off target effects such skin rashes, folliculitis, panniculitis, paronychia due to the on target endothelial growth factor receptor effects, gastrointestinal effects commonly associated with interleukin-2–inducible T-cell kinase (ITKs), and non-thrombocytopenia-associated bleeding due to inhibition of platelet aggregation [28,29]. Arthralgias have also been reported in studies and in the real world [23,29,30]. It is important for clinicians to be aware that significant variation may exist between rates of adverse effects documented in the initial pivotal studies using BTKi and in a real-world settings. Real-world data has shown differing rates of dose reductions or discontinuation (increased) in the frontline and relapsed

settings. Over time cardiac events, including atrial fibrillation, hypertension, ventricular arrythmias and sudden death have been associated with the use of BTKi [29,31] and may be due to off-target effects. A 140 mg dose of ibrutinib (1/3 of the prescribed dose) has been shown to enable 90% BTK inhibition. Although, it is hypothesized that some of the off-target effects of the drug in both blood and lymph nodes contribute to deep and lasting remission. That said, dose reductions or dose holds may also be used to offset these toxicities especially in low risk individuals[32,33]. RWE studies corroborated this[28,34], and clinical trials also reported drug discontinuation as an option for the management of adverse reactions as demonstrated in the ECOG 1912 study [25]. However, the risk of sudden death still remained [25,31]. The rates of atrial fibrillation for ibrutinib have been reported to be in 10-20% range in both the real world [25,28] and trial settings [24-26]. The next generation of BTKi are proving safer than ibrutinib. Where head-to-head data are available, decreased rates of atrial fibrillation and hypertension are observed for acalabrutnib[35,36] (rates of 3-4% for all grades for both) and decreased rates of atrial fibrillation (1-3%) and similar rates of hypertension (10-13%) with zanubrutinib [37]. Zanubrutinib has been associated with higher rates of neutropenia than ibrutinib, however due to the short period of follow up in clinical trial reporting (12 months), this toxicity profile needs further assessment [37].

Acalabrutinib is most often used in our center due to a decreased side effect profile and minimal risk of sudden death. Our center has rarely reported atrial fibrillation in our acalabrutinib patients however we may also be better at selecting patients for BTKi use. The discontinuation of a BTKi (due the atrial fibrillation) is not recommended in high-risk patients unless medical management of the atrial fibrillation is of concern. If a patient has been initiated on ibrutinib, clinicians may consider challenging the patient with a second-generation BTKi[38] before discontinuing this line of therapy. In lower risk individuals whose atrial fibrillation does not resolve and who require therapy, a switch to a BCL-2 inhibitor-based fixed-duration therapy is a viable treatment option. If the patient is low risk and has been on therapy for at least 22 months with ibrutinib, there is also the possibility of stopping treatment until disease relapses requiring re-initiation of treatment[25].

Patients on BTKi are at higher risk for developing hypertension. This may occur early or later in the course of therapy. Patients with undiagnosed hypertension should be assessed and co-managed with their primary care physicians. In those patients on established therapy, whose disease is well-controlled and who develop hypertension, dose reduction and engagement with primary care is warranted. Care coordination with cardio-oncology may also be a good resource if available. Second generation BTKi have also been associated with a lower incidence of arthralgias [30] and bleeding but may produce drug-specific side effects such as headaches with acalabrutinib [6,35], which typically present within the first 12 weeks of initiation of therapy[29].

As we look to the future of novel therapies for the treatment and management of CLL, emerging agents such as pirtobrutinib portend a toxicity profile that is similar to current second generation BTKi in both BTKi-naïve and sensitive patients [39,40]. Additional studies involving newer BTKi such as nemtabrutinib have the potential for even lower rates of cardiac events which may provide clinicians with further tools in their therapeutic armamentarium to optimize safety and efficacy outcomes for CLL patients.

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