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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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