Waldenström Macroglobulinemia: Clinical Presentation, Diagnosis, and Management

MIRIAM HOBBS, DNP, APRN, CNP, AMIE FONDER, PA-C, and YI L. HWA, DNP, APRN, CNP

From Mayo Clinic, Rochester, Minnesota

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Miriam Hobbs,DNP, CNP, APRN, 200 First Street SW, Rochester, MN 55905
E-mail: hobbs.miriam@mayo.edu

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Abstract

Waldenström macroglobulinemia is a rare hematologic malignancy characterized by an IgM-associated lymphoplasmacytic lymphoma. Often, it is associated with an indolent disease course, and many patients are candidates for careful monitoring. As many patients present with advanced age and nonspecific constitutional symptoms, careful consideration should be given to treatment decisions, including when and how to treat for maximized clinical benefit with minimal toxicity. This article provides an evidence-based practical approach to appropriate monitoring of the asymptomatic patient and management of symptomatic patients who require treatment for this rare malignancy.

CASE STUDY

Mr. P was initially incidentally noted to have an elevated total protein in 2001 on an annual physical exam. As he was asymptomatic, workup was delayed until May 2002 when he had a bone marrow biopsy that showed approximately 20% involvement with lymphoplasmacytic lymphoma. His IgM level at diagnosis was 3,470 mg/dL, with an M spike of 2.1 g/dL. He was subsequently followed on a quarterly basis without treatment. His immunoglobulin M level gradually rose between 4 and 5,000 mg/dL. He still remained asymptomatic and was observed off therapy.

Waldenström macroglobulinemia (WM) is a rare B-cell malignancy defined by the World Health Organization as infiltration of lymphoplasmacytic lymphoma in the bone marrow with associated hypersecretion of immunoglobulin M (IgM) monoclonal protein, belonging to the non-Hodgkin B lymphoma category (Swerdlow et al., 2016). Common clinical features that warrant treatment include anemia, thrombocytopenia, constitutional symptoms, symptomatic hepatosplenomegaly, bulky lymphadenopa-

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thy, and hyperviscosity in rare cases (Gertz, 2019). Waldenström macroglobulinemia is an indolent disease and may not result in signs and symptoms for many years. Although it remains incurable, survival is improving with the availability of additional therapies. This article provides an overview of the incidence, clinical features, and differential diagnosis, and highlights the diagnostic criteria and updates in treatment recommendations for WM. A case study is used to illustrate the approach of initial evaluation, latest diagnostic tests, and treatment guidelines that are applicable to the advanced practitioner in the clinical management of WM.

PREVALENCE/EPIDEMIOLOGY

Waldenström macroglobulinemia accounts for 1% to 2% of hematologic malignancies, with an annual age-adjusted incidence of 3.8 cases per million person-years. It is more common in advanced age, males, and Caucasians compared to younger age, females, and non-Caucasians (Kapoor, Paludo, Vallumsetla, & Greipp, 2015; Wang et al., 2012). A recent population-based study reported an age-adjusted incidence rate of 0.92 and 0.30 per 100,000 person-years for males and females, respectively, and with an age- and sex-adjusted incidence of 0.57 per 100,000 person-years (Kyle et al., 2018). The incidence of WM or IgM monoclonal gammopathy is higher among Caucasians than non-Caucasians. The median age at diagnosis is 63 for African Americans and 73 years for Caucasians (Kapoor et al., 2015). A genetic predisposition has also been suggested, as approximately 20% of patients with WM have a first-degree relative with a related hematologic disorder such as non-Hodgkin lymphoma (NHL), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), monoclonal gammopathy of undetermined significance (MGUS), acute lymphocytic leukemia (ALL), or Hodgkin lymphoma (HL; Kapoor et al., 2015).

CLINICAL PRESENTATIONS

At diagnosis, approximately 19% to 28% of patients with WM are asymptomatic (Kyle et al., 2012; Pophali et al., 2019). These patients may remain asymptomatic for 5 to 10 years before developing symptoms that indicate to initiate therapy (Dhodapkar et al., 2009; Kyle et al., 2012). Typically, initial symptoms are nonspecific, including fatigue, malaise, weight loss, and fever. Over time, patients can develop signs related to cell infiltration and the IgM paraprotein. Bone marrow infiltration, seen in 100% of cases, can cause anemia, thrombocytopenia, and neutropenia. Extramedullary hematopoietic tissue infiltration, seen in 25% of cases, can cause lymphadenopathy, hepatomegaly, and splenomegaly (Kapoor et al., 2015). The most common clinical presentation at the time of symptomatic disease is anemia (Dimopoulos & Kastritis, 2019).

IgM paraprotein-mediated symptoms include hyperviscosity, IgM-related neuropathy, cryoglobulinemia, and cold agglutinin hemolytic anemia (Kapoor et al., 2015). Hyperviscosity is seen in 35% of cases and is evidenced by fatigue, dizziness, mucocutaneous bleeding, abnormal fundoscopy, retinal hemorrhage, blurred vision, high output cardiac failure, and rarely altered mental status or stroke (Kapoor et al., 2015; Leblond et al., 2016). Hyperviscosity symptoms are typically encountered when the viscosity level rises > 4 centipoise, although patients with a lower viscosity may require intervention. A funduscopic exam may reveal dilated and tortuous retinal veins, retinal hemorrhage, and papilledema as a result of retinal vein thrombosis. IgM neuropathy is seen in up to 40% of cases and is typically an indolently progressive, distal, symmetric, predominantly sensory peripheral neuropathy (Kapoor et al., 2015). Peripheral neuropathy related to WM is common in otherwise asymptomatic WM, and can be the only indication to start treatment. High titers of myelin-associated globulin antibodies (anti-MAGs) can be found in approximately 50% of these patients. This carries a different pathophysiology than amyloid-associated neuropathy, which should be ruled out (Dimopoulos & Kastritis, 2019). Cryoglobulinemia is symptomatic in < 5% of cases, asymptomatic in 20%, and is evidenced by Raynaud phenomenon/acrocyanosis, peripheral neuropathy, purpura, skin ulceration or necrosis, arthralgia, or glomerulonephritis related hematuria. Cold agglutinin autoimmune hemolytic anemia is seen in 10% of cases and typically presents with a hemoglobin > 7 g/dL. Significant hemolysis is quite rare—present in only 3% of cases (Kapoor et al., 2015).

Cell infiltration and IgM paraprotein effects on the kidney, gastrointestinal tract, and skin are rare, accounting for 4%, 4%, and 3% of cases, re-

spectively (Kapoor et al., 2015). Symptoms related to the underlying lymphoproliferative disorder are what distinguish MGUS and smoldering disease from active disease requiring therapy.

DIFFERENTIAL DIAGNOSIS

It is important to distinguish between IgM MGUS, smoldering WM, active WM requiring treatment, and related lymphoproliferative disorders. Key diagnostic criteria include the presence of a monoclonal IgM protein and at least 10% lymphoplasmacytic cells present in the bone marrow (Kapoor et al., 2017). However, clonal B cells with lymphoplasmacytic differentiation are not specific to WM and can be observed in patients with other B-cell disorders. Lymphoplasmacytic lymphoma without a monoclonal IgM protein is not WM, but the biology is not significantly different (Dimopoulos & Kastritis, 2019).

The somatic mutation of the myeloid differentiation primary response 88 (*MYD88*) is present in approximately 90% of patients with WM. This can be particularly helpful in cases of suspected but histopathologically difficult-to-interpret lymphoplasmacytic lymphoma (Kapoor et al., 2017). Splenic marginal zone lymphoma (SMZL), follicular lymphoma, and mantle cell lymphoma (MCL) can be distinguished from WM through immunophenotypic and molecular cytogenetic studies (Dimopoulos & Kastritis, 2019). Waldenström macroglobulinemia morphology has two types of clonal cells (B cells and plasma cells with varying degree of differentiation) that express typical immunophenotype (e.g., surface IgM+, CD20+, CD5+/–, CD22+, CD79+, CD25+, CD27+, FMC7+, CD10 +/–, CD23–, CD103– for B-cell population and CD138+, CD38+, CD45+, CD19+, CD56– for plasma cell population). In contrast to WM, morphology of clonal plasma cells is absent in SMZL, follicular lymphoma, and MCL. In MCL, the clonal cells are characteristically CD5+, CD23–, and most MCLs also have t(11;14)(q13;q32); a translocation is not seen in WM. Approximately 70% to 90% of follicular lymphomas have t(14;18), a translocation that results in the overexpression of B-cell leukemia/lymphoma 2 (BCL-2). *MYD88* is not expressed in follicular lymphoma or MCL. *MYD88* mutations can be seen in 10% of patients with SMZL. Deletion of chromosome 7 (del 7q) and trisomy 3 (+3q) and 5 (+5q) are common cytogenetic abnormalities in SMZL, while 30% to 50% of WM have deletion of chromosome 6 (Dimopoulos & Kastritis, 2019).

Asymptomatic patients with an IgM monoclonal protein < 3 g/dL, and < 10% clonal lymphoplasmacytic cells in the marrow are classified as having IgM MGUS. Asymptomatic patients with an IgM monoclonal protein and > 10% lymphoplasmacytic cells of the characteristic immunophenotype in the marrow are considered to have smoldering WM (Gertz, 2018). The risk of progression in patients with IgM MGUS to active disease is 1% per year (Go & Rajkumar, 2018).

Differentiation between MM and WM is fairly uncomplicated. Patients have IgM myeloma if they present with both an IgM protein and diagnostic findings of myeloma, which are CRAB features of hypercalcemia, renal insufficiency, anemia, bone lesions, and myeloma-defining events of 60% plasma cell involvement in the bone marrow, free light chain ratio of 100 or higher, and/or one or more focal lesion on MRI. In MM, bone marrow shows pure plasma cell morphology, whereas in WM, the bone marrow shows lymphoplasmacytic morphology (Dimopoulos & Kastritis, 2019).

DIAGNOSTIC APPROACH

The diagnostic evaluation should include CBC, complete metabolic panel, serum immunoglobulin levels, serum protein electrophoresis with immunofixation or isotype testing by mass spectrometry, 24-hour urine protein electrophoresis to evaluate for Bence-Jones proteinuria, beta-2 microglobulin for prognostic evaluation, bone marrow biopsy to determine morphology with cytogenetic studies and *MYD88* L265P testing, CT chest-abdomen-pelvis to evaluate for organomegaly and lymphadenopathy, as well as serum viscosity in cases of suspected hyperviscosity syndrome or IgM > 3,000 mg/dL (Dimopoulos & Kastritis, 2019). The commonly used diagnostic tests at initial evaluation are outlined in Table 1.

Once the presence of an IgM monoclonal protein with > 10% involvement of lymphoplasmacytic cells in the marrow is established, the next step is to distinguish smoldering from active disease. The determination of whether the approach should be watch and wait vs. therapeutic intervention depends on the severity of IgM-related constitutional symptoms such as fatigue, fever, weight loss, night

Table 1. Diagnostic Workup of Waldenström Macroglobulinemia

Step	Test	Indications
Clinical assessment	Vital signs	Signs/symptoms suspecting diagnosis of Waldenström macroglobulinemia
	Weight	
	History and physical exam	
	Retinal exam	If IgM ≥ 3000 mg/dL, or suspected hyperviscosity
Laboratory tests	CBC differential	Assessing presence of IgM-monoclonal gammopathy
	Comprehensive metabolic panel	
	Serum quantitative immunoglobulins A, M, G, free light chain assay, SPEP and SIFE or M-protein isotype	
	24 hours urine collection of UPEP and UIFE or M-protein isotype	
	Serum beta-2 microglobulin, LDH	Prognostic evaluation
	Serum viscosity	Suspected hyperviscosity
Radiology test	Chest/abdominal/pelvic CT with contrast if possible	Evaluate for organomegaly and lymphadenopathy
Pathologic evaluation	Bone marrow aspirate and biopsy with immunohistochemistry and/or flow cytometry	Assessing bone marrow morphology with monoclonal lymphoplasmacytic infiltration
	Cytogenetics and FISH	Detecting *MYD88* mutation
Additional evaluation	Abdominal fat aspirate (Congo red staining on fat and bone marrow)	Rule out amyloidosis if presence of peripheral neuropathy
	Nerve conduction study/electromyogram	
	Cryoglobulin, cold agglutinin, anti-MAG antibodies	
	Neurology consult	

Note. CBC = complete blood cell count; SPEP = serum protein electrophoresis; SIFE = serum immunofixation electrophoresis; UPEP = urine protein electrophoresis; UIFE = urine immunofixation electrophoresis; FISH = fluorescence in situ hybridization; MAG = myelin-associated glycoprotein.

sweats, coexisting amyloidosis with organ dysfunction, or hyperviscosity (Kapoor et al., 2017).

PROGNOSIS

5-year survival for all age groups has improved over time, from 57% in 1980 to 78% in 2005, although advanced age is a poor prognostic factor (Kristinsson et al., 2013). The median overall survival was reported as 8 years from 2001 to 2010, increased from 6 years from 1991 to 2000 based on a report of a large database of 5,784 patients with WM (Castillo et al., 2015). The latest report of 10-year survival rate of WM is 66% (Castillo, Olszewski, Cronin, Hunter, & Treon, 2014).

Risk stratification using the International Prognostic Scoring System (IPSS) was developed through an analysis of symptomatic treatment-naive patient data (Kapoor et al., 2017). Patient outcomes vary widely, and the IPSS provides meaningful prognostic information. Key risk factors prior to initiation of therapy identified include age > 65, hemoglobin ≤ 11.5 g/dL, platelet count ≤ 110, serum beta-2 microglobulin > 3 mg/L, and serum monoclonal protein > 70 g/L. Zero or one risk factor (except older age) is associated with low-risk disease and median survival of 142 months. Any two risk factors or older age alone are associated with intermediate-risk disease and median survival of 99 months. Three or more risk factors are associated with high-risk disease and a median survival of 43 months (Morel et al., 2009).

CURRENT GUIDELINES FOR RECOMMENDED TREATMENT

Many patients are candidates for observation with close monitoring, typically every 3 to 6 months. It

is important to carefully evaluate the patient to determine if there is a need for treatment. If there is any doubt, one should consider reevaluating the patient in 1 to 2 months to determine if there is evidence of disease progression (Gertz, 2018). The goal of therapy in WM is to gain symptom relief and minimize further organ dysfunction while preserving quality of life (Kapoor et al., 2017).

There is a lack of comparative trial data, making it difficult to provide treatment recommendations based on high-quality evidence. However, the East German Lymphoma Study Group conducted a randomized trial of rituximab (Rituxan)/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) vs. bendamustine/rituximab (BR) in a cohort of patients with low-grade lymphomas. A subset analysis was conducted, showing that 41 patients had WM; 22 received BR, while 19 received R-CHOP. The response rate was 95% in both groups, but the PFS was 36 months in R-CHOP and not reached in BR. There was also less toxicity in the BR group. This trial led to the recommendation of BR as standard frontline therapy in WM. The treatment doses recommended in the study were bendamustine at 90 mg/m^2/day on days 1 and 2 and rituximab at 375 mg/m^2/day on day 1. Cycles repeat every 28 days, with a goal of 6 cycles (Rummel et al., 2013).

The two widely used guidelines are based on the recommendations by the National Comprehensive Cancer Network (NCCN) and the Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART). The National Comprehensive Cancer Network lists the following as preferred regimens for WM: BR; bortezomib (Velcade)/dexamethasone/rituximab (BDR); ibrutinib (Imbruvica) +/– rituximab; and dexamethasone/rituximab/cyclophosphamide (DRC; NCCN, 2019).

Mayo Clinic created a treatment algorithm for WM to synthesize the literature into practical treatment recommendations, known as mSMART (Kapoor et al., 2017). The mSMART algorithm outlines a recommendation for BR (4–6 cycles) in newly diagnosed patients who have bulky disease (extensive lymphadenopathy/extramedullary disease), profound cytopenias (hemoglobin ≤ 10 d/dL, platelets < 100), constitutional symptoms, or hyperviscosity symptoms. Plasmapheresis is recommended prior to BR in patients presenting with hyperviscosity symptoms. DRC is an alternative therapy for those patients having low disease burden, i.e., the absence of extensive lymphadenopathy. Stem cell collection after 4 to 6 cycles is recommended for all transplant-eligible patients. Single-agent rituximab can be considered for hemoglobin < 11 g/dL or symptomatic anemia, platelets < 120, IgM neuropathy, WM-associated hemolytic anemia, or symptomatic cryoglobulinemia. Asymptomatic smoldering patients are candidates for observation (Kapoor et al., 2017). In the setting of salvage therapy, mSMART guidelines recommend to repeat the original therapy if greater than 3-year time to next therapy (TTNT) was achieved. If not, options include ibrutinib monotherapy, BDR, BR, or DRC. Autologous stem cell transplantation could be considered in select patients, primarily younger patients with multiple relapses or primary refractory disease (Kapoor et al., 2015; Leblond et al., 2016).

The role of rituximab maintenance therapy is controversial. It was addressed in two retrospective series of rituximab-naive WM patients who received and responded to rituximab-containing treatments. Maintenance rituximab appeared to improve PFS and OS compared to observation off therapy (Treon et al., 2011; Zanwar, 2019). Maintenance rituximab was investigated in a prospective clinical trial, randomizing 2 years of maintenance rituximab vs. observation after induction with BR. After a median 5.9 years of observation, the study failed to demonstrate improvement in PFS or OS in the maintenance rituximab group (Rummel et al., 2019). As only retrospective data support the use of maintenance rituximab in WM, and a prospective trial failed to demonstrate benefit, a risk-benefit discussion with the patient would be important for practitioners considering maintenance therapy.

RETURN TO CASE STUDY

In July 2013, 12 years after the initial identification of a monoclonal protein, Mr. P's IgM level started to rise precipitously, reaching approximately 8,400 mg/dL. He also experienced constitutional symptoms, including fatigue with anemia. He was then started on BR, with the first cycle consisting only of bendamustine to prevent IgM flare due to his high IgM. He had an excellent response, with a near 90% reduction of IgM after completing a

total of 5 cycles of treatment. He has been off chemotherapy since November 2013.

OVERVIEW OF THERAPIES

Common therapeutic agents with activity against WM include alkylating agents (bendamustine), monoclonal antibodies (rituximab), Bruton tyrosine kinase (BTK) inhibitors (ibrutinib), and proteasome inhibitors (bortezomib). Other classes of drugs with activity in WM include nucleoside analogs, immunomodulatory drugs, mammalian target of rapamycin (mTOR) inhibitors, histone deacetylase (HDAC) inhibitors, AKT inhibitor, P13 kinase delta inhibitor, and serine/threonine kinase inhibitors (Kapoor et al., 2015). Common treatment regimens, along with PFS and overall response rates, are listed in Table 2.

Bendamustine is an alkylating agent with characteristics of a purine nucleoside analog and is given intravenously. A primary potential toxicity of bendamustine is long-term myelosuppression. Dose reductions for myelosuppression are appropriate (Gertz, 2018). Cytopenias are a common but manageable toxicity, and they are less severe than the myelosuppression noted in R-CHOP (Buske, 2018).

Rituximab is an anti-CD20 monoclonal antibody antineoplastic agent. When rituximab adheres to CD20, an antigen expressed on the surface of B cells, it leads to cell lysis of B lymphocytes (Salles et al., 2017). Rituximab has a safe toxicity profile without long-term treatment-related toxicity or an impact on stem cell mobilization and collection (Gertz, 2019).

An important potential toxicity is infusion-related reactions that commonly occur during the initial infusion and include transient dyspnea, hypertension, cough, bronchospasm, angioedema, chills, rash, and nausea and vomiting (Patel & Khan, 2017). Hepatitis B reactivation can occur; therefore, patients should be screened for hepatitis B infection prior to treatment initiation (Gertz, 2019). Use of rituximab as a single agent may increase the risks for "IgM flare," a phenomenon in which a transient rise of IgM occurs after initiation of rituximab, resulting in hyperviscosity-related complications and in severe cases that urgent plasmapheresis is necessary (Ghobrial et al., 2004). The IgM flare phenomenon is less frequently observed when rituximab is administered in combination with cytotoxic chemotherapy (Gertz, 2019). Therefore, rituximab monotherapy is not recommended for patients with a high IgM level (Dimopoulos et al., 2014). If pursuing rituximab monotherapy, plasmapheresis can prevent IgM flare in patients with high IgM levels (Leblond et al., 2016). The 2016 guidelines of the American Society for Apheresis and the 2016 consensus treatment recommendations proposed by the International Workshops on WM (IWWM-8) state that to reduce the risk of IgM flare in patients with IgM > 4,000 mg/dL, plasmapheresis is advised as initial therapy (Leblond et al., 2016). IgM flare is an expected potential event and should not be confused as treatment failure.

Rituximab alone provides inferior treatment response compared to combined regimens with

Table 2. Common Treatments for Waldenström Macroglobulinemia

Regimen	Phase	ORR	PFS
Bendamustine and rituximab	3 subanalyses	95%	69 m
Rituximab	3	48%	20.3 m
Dexamethasone, rituximab, and cyclophosphamide	2	83%	35 m
Bortezomib, dexamethasone, and rituximab	2	85%	43 m
	2	96%	57% at 5 years
Ibrutinib	2	90.5%	60% at 5 years
	3	90%	86% at 18 m
	2	100%	92% at 18m
Ibrutinib and rituximab	3	92%	82% at 30 m

Note. ORR = overall response rate; PFS = progression-free survival. Information from Dimopoulos & Kastritis (2019).

other anti-WM agents (Santos-Lozano et al., 2016). A recent meta-analysis of 22 studies confirmed that rituximab-based combined therapy with an alkylator, purine analog, or proteasome inhibitor is highly effective and well tolerated for patients with WM (Zheng et al., 2019).

Ibrutinib, an oral agent, is a BTK inhibitor typically used as monotherapy. The oral route offers convenience, and clinical trials have shown effectiveness with ORR 91% and estimated 2-year PFS of 69% (Treon et al., 2015). However, diarrhea, bleeding, and atrial fibrillation (10.7%) are important nonhematologic toxicities. Another concern is that it should be given indefinitely, as rapid IgM increases have been reported on its cessation. Therefore, once starting the drug, the patient typically needs to be on indefinite therapy until disease progression or unacceptable toxicity (Gertz, 2019). The *CXCR* mutation can impact response to ibrutinib, with improved responses to *MYD88* L265P/CXCR4WT compared to *MYD88* L265P/CXCRWHM genotype (Dimopoulos & Kastritis, 2019).

Bortezomib, used in BDR, is a proteasome inhibitor given subcutaneously. It is commonly used in combination with rituximab and dexamethasone and is an effective novel agent in WM treatment. Bortezomib blocks the enzyme function of the proteasome to break down proteins and accumulation of proteins results in activation of cancer cell apoptosis. Peripheral neuropathy is one of the most common and challenging toxicities associated with bortezomib therapy, but this risk is mitigated through subcutaneous rather than intravenous administration without causing a significant impact on response (Moreau et al., 2011). Risk of herpes zoster reactivation is increased, and antiviral prophylaxis is required for patients receiving treatment with proteasome inhibitors. Bortezomib-containing therapy is recommended in patients with high IgM level, renal impairment, cryoglobulinemia, or cold agglutinemia (Kastritis & Dimopoulos, 2018).

Cyclophosphamide, used in DRC, is another alkylating agent, typically given orally. This regimen is associated with moderate myelotoxicity but high activity and a generally favorable toxicity profile (Buske, 2018).

In the setting of salvage therapy, the Mayo consensus is to repeat the original therapy if greater than 3-year TTNT was achieved. If not, options include ibrutinib monotherapy, BDR, BR, or DRC. Autologous stem cell transplantation could be considered in select patients, primarily younger patients with multiple relapses or primary refractory disease (Kapoor et al., 2015; Leblond et al., 2016).

When considering a more tailored approach to therapy, the following considerations may prove helpful. Patients with high tumor bulk benefit from rapid-acting regimens such as BR or ibrutinib/rituximab. If cytopenias are present, regimens with less myelotoxicity include BDR or ibrutinib/rituximab compared to BR. If a patient is at risk for hyperviscosity, significant cryoglobulinemia, or cold agglutinin disease, plasmapheresis should be considered. If rapid IgM reduction is needed, BR or BDR are preferable. If cardiac amyloidosis is co-occurring, avoiding ibrutinib due to atrial fibrillation risk is recommended (Dimopoulos & Kastritis, 2019).

EVALUATION OF TREATMENT RESPONSE

Response assessment in WM is evaluated using criteria from the Sixth International Workshop on WM. Sequential assessment of response following the completion of therapy is important, because there are many cases of delayed response (Owen et al., 2013).

- A complete response (CR) is defined as the absence of serum IgM protein by immunofixation/isotype, normal serum IgM level, complete resolution of baseline extramedullary disease, and morphologically normal bone marrow aspirate.
- Very good partial response (VGPR) is ≥ 90% reduction of the serum IgM from baseline with complete resolution of extramedullary disease and no sign of progression.
- Partial response (PR) is ≥ 50% but < 90% reduction of IgM with reduction of any baseline extramedullary disease and no new evidence of active disease.
- Minor response (MR) is ≥ 25% but < 50% reduction in IgM and no progression of extramedullary disease.
- Stable disease (SD) is IgM stability within 25% above/below baseline.

- Progressive disease (PD) is ≥ 25% increase in IgM from nadir and/or clinical progression attributable to WM (Owen et al., 2013).

The time to initial response in many regimens is 4 to 8 weeks (Gertz, 2019). In a retrospective review of BR vs. DRC, the time to best response was similar for both at 7 weeks (Paludo et al., 2018).

RETURN TO CASE STUDY

Mr. P has been off chemotherapy since November 2013. Since then, his IgM has been coming down, and as of April 2019 there was a continued downward trend, with a nadir of 1,100 mg/dL and an M spike of 0.8 g/dL. Five years later, he had nearly achieved VGPR with continued deepening of response. He continues to be monitored on a quarterly basis with office visits to evaluate for patient-reported symptoms, and labs including complete blood count and monoclonal protein studies.

CONCLUSION

Waldenström macroglobulinemia is a rare, indolent IgM-associated lymphoplasmacytic lymphoma. Many patients are candidates for careful monitoring. When treatment is warranted, the goal is to control symptoms and manage tumor burden. Therefore, it is important to treat the patient, not the numbers; treatment is only warranted when the monoclonal protein is causing symptoms. When treatment is warranted, practitioners should consider bendamustine/rituximab for frontline therapy due to the excellent response rates, ease of use with a limited the duration of 4 to 6 cycles, and moderate toxicity profile. When initiating therapy, patients may experience an IgM flare with the first dose of rituximab. If there is concern for hyperviscosity syndrome, providers should consider giving the first cycle without rituximab. IgM flare should not be confused for disease progression. ●

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