Update in Waldenström's Macroglobulinemia

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Abstract

Everolimus, an mTOR inhibitor, perifosine, an AKT inhibitor, enzastaurin, a phosphatidylinositide3 kinase/AKT inhibitor, panobinostat, a histone deacetylase inhibitor, ofatumumab, a third-generation anti-CD20 monoclonal antibody, and ibrutinib, a Bruton tyrosine kinase inhibitor, and newer drugs from known active subclasses, such as pomalidomide (immunomodulatory) and carfilzomib (proteasome inhibitor) are promising drugs in various stages of study in WM. They may expand future treatment options.

Abbreviation: WM: Waldenström's Macroglobulinemia, LPC: Lymphoplasmacytic, MYD: Myeloid Differentiation Primary Response Gene, IgM: Immunoglobulin M, CNS: Central Nervous System, DLBCL: Diffuse Large B-Cell Lymphoma, ATM: Ataxia Telangiectasia-Mutated, BTK: Bruton's Tyrosine Kinase, IRAK1: Interleukin-1 Receptor-Associated Kinases, WHIM: Warts Hypogamma globulinemia Infections Myelokathexis, WT: Wild-Type, ERK: Extracellular Signal-Regulated Kinase, NF-κB: Nuclear Factor κB, LON: Late-Onset Neutropenia

Introduction

WM is defined by WHO as a lymphoplasmacytic lymphoma associated with a monoclonal IgM protein (regardless of its size) and bone marrow infiltration by clonal LPC cells [1]. Median age at diagnosis is70 years with male predominance. The incidence is lower in non-Caucasians [2]. It accounts for 1%-2% of hematological neoplasms [3]. There is personal or family history of autoimmune, inflammatory and infective disorders particularly Sjogren syndrome and autoimmune hemolytic anemia. There is increased risk of WM and other B-cell disorders amongst relatives of patients with WM [2].

IgM-MGUS is characterized by the presence of an IgM monoclonal protein, less than 10% clonal lymphoplasmacytic bone marrow cells, and no symptoms attributable to tumor mass or infiltrations [4]. It is a precursor state for WM. Approximately 2% of IgM MGUS patients evolve to a B-cell malignancy per year, with most of these individuals progressing to WM [5]. Smoldering WM is characterized by an IgM monoclonal protein, clonal lymphoplasmacytic bone marrow infiltration greater than 10%, no symptoms attributable to tumor mass or infiltration, and no IgM-mediated symptoms [4]. Clinical features are related to disease burden, such as cytopenias, organomegaly and constitutional symptoms, or to IgM paraprotein such as hyper viscosity syndrome, hemolytic anemia, immune complex vasculitis and amyloidosis or to autoantibody specificity such as peripheral neuropathy, cold hemagglutinin disease and acquired von Willebrand disease [2].

Bing Neel syndrome (rare) presents usually at WM relapse or at first diagnosis. Symptoms are diverse, non-specific and gradually progressive over weeks to months. They reflect LPC involvement of the CNS and rarely the peripheral nervous system. LPC may be detected in the cerebrospinal fluid, the meninges and/ or the cerebral parenchyma [6]. WM patients are at increased risk for second malignancies, including transformation to DLBCL (5-10%), myelodysplastic syndrome, acute myeloid leukemia and solid cancers [4]. Development of bulky rapidly enlarging lymph node masses, extranodal disease and marked elevation in serum lactate dehydrogenase are suggestive of transformation to DLBCL [2]. The genomic landscape of WM is characterized by highly recurring MYD88 (>90% of cases) resulting in a protein change from leucine to proline at amino acid position 265 [4].

In tumor cells, MYD88L265P triggers activation of NF-κB through BTK or IRAK (IRAK1 and IRAK4) pathways. MYD88L265P was present in 50% to 80% of IgM MGUS, suggesting an early oncogenic event for this mutation [5]. MYD88 mutation is not unique to WM. It distinguished WM from overlapping entities such as marginal zone lymphoma, chronic lymphocytic leukemia, and multiple myeloma, wherein MYD88L265P was either absent or infrequently observed (<10%) [4]. CXCR4 is mutated in 30% of WM patients. CXCR4 stimulation by its ligand CXCL12 activates AKT1 and mitogen-activated protein kinase family signaling, as well as facilitates cell migration and homing in WM cells [4]. The prolonged activation of CXCR4 signaling due to WHIM mutations

may exaggerate these effects. Polymorphisms of CXCR4 ligand and CXCL12 have been associated with poor post treatment clinical outcomes [7].

MYD88 and CXCR4 mutation divide WM into three genomic groups (MYD88L265P CXCR4WT, MYD88L265P CXCR4WHIM, and MYD88WTCXCR4WT) on the basis of clinical manifestations and survival [7]. Other major pathway was the loss of chromatin remodeling proteins, ARID1A and ARID1B. ARID1A was the third most common single nucleotide variant target in WM, they are thought to exert their effects via p53 and CDKN1A regulation [4]. BCR-signaling-associated mutations occur less frequently (15% of WM cases), and are restricted to the CD79A and CD79B genes [8]. Epigenetic dysregulation, aberrations in the phosphatidylinositol 3-kinase/mTOR, NFκB, JAK/STAT signaling pathways, as well as bone marrow micro environmental interactions, may be other key factors involved in WM pathogenesis [4].

Diagnosis

Bone marrow aspirate and trephine biopsies should be obtained and supplemented by flow cytometric and immunohistochemistry studies [2]. The bone marrow pattern is predominantly intertrabecular [9]. The immuno-phenotype of WM consists of expression of pan-B-cell markers (CD19, CD20, CD22), cytoplasmic immunoglobulin (cIg), FMC7, CD38, and CD79a[10]and typically negative for CD3 and CD103 [9]. The plasma cells number is generally in the normal range, but they differ from normal and myeloma cells by being positive for CD38, and commonly express CD19, CD45, and CD20, but lack CD56 [10].

Workup

IgM levels by densitometry or total serum IgM quantitation by nephelometry must be determined. IgM values assessed by nephelometry are higher than M protein values determined by densitometry that is why sequential response assessments for individual patients must be carried with the same methodology [11]. Quantification of serum viscosity might be helpful [3]. Hyperviscosity syndrome is evident when IgM M-protein >40 g/l and/or [2] the serum viscosity exceeds 4 centipoise. Serum viscosity does not always correspond to the clinical severity of hyperviscosity. Venous engorgement 'sausaging' in the retinal veins by fundoscopy is an excellent indicator of clinically relevant hyperviscosity [3].

Evaluation of anti-myelin associated glycoprotein, antigangliosides M1 and anti-sulfatide IgM antibodies may support the diagnosis of IgM-related neuropathy. Also, the possibility of amyloid light-chain amyloidosis in association with peripheral neuropathy needs to be considered [3]. Screening for hepatitis B and C viruses is required prior to the introduction of rituximab-containing treatments [2]. An ultrasound or CT scan should be carried out to document organomegaly/

adenopathies. PET scanning is indicated when a large cell lymphoma transformation is suspected [3]. Testing for MYD88 is essential for patient's candidates for ibrutinib therapy [12]. Cytogenetic analysis is not required for the routine diagnostic assessment of WM [2]. Partial or whole 6q deletion is the most common recurrent chromosomal abnormality (approximately 50% of patients) and was associated with a complex karyotype, hypoalbuminemia, high β2-microglobulin levels [4] and an adverse prognosis [9].

Other cytogenetic aberrations, include trisomy 18 (15%) and 13q14 deletion (13%). Less than 10% of patients had trisomy 4, 17p13 (TP53) deletion, 11q22 (ATM) deletion, trisomy 12, or 14q32 (IGH) translocations. Deletion of 6q, 11q and trisomy 4 had adverse effects on survival. Recurrent deletions on 13q14 and 17p13 have been mostly seen in more advanced stages of the disease [4]. Although not unique to WM, inactivating mutations of TRAF3 (located on cytoband 14q32.32) lead to constitutive activation of NF-κB pathways and are recurrent findings in a small percentage (~5%) of WM patients [10].

Risk stratification

In International Prognostic Scoring System for WM I (IPSSWM), 5 covariates (age > 65 years, hemoglobin ≤11.5 g/dL, platelet counts ≤100x10⁹/L, β2-microglobulin>3mg/L, serum monoclonal protein >70 g/L) defined 3 risk groups (low, intermediate and high risk respectively) [13]. The risk category is designated as low (zero or 1 risk factor, except age), intermediate (age older than 65 years or 2 risk factors), or high (>2 risk factors) [4]. These three risk categories are associated with 5-year survival rates of 87%, 68% and 36% respectively [2]. Lactate dehydrogenase level may have a role in separating the high-risk patients into two distinct categories [9]. IPSSWM risk category is used for risk stratification in randomized clinical trials [13].

Close observation is recommended for patients who do not fulfill the criteria for WM, and for whom laboratory evidence is the only indicator of disease progression (eg, a minor decrease in hemoglobin level with asymptomatic anemia or mild increases in IgM) or mild increase of lymphadenopathy or splenomegaly without patient discomfort [12]. They can be safely observed at 3-6 monthly intervals. The risk of progression to symptomatic disease is 59% at 5 years [2]. Criteria for initiation of therapy is IgM-related complications and/or symptoms related to direct BM involvement by tumor cells such as cytopenias, constitutional symptoms and bulky extramedullary disease [12].

Urgent therapy is needed in symptomatic hyperviscosity, moderate to severe hemolytic anemia and symptomatic cryoglobulinemia [12]. Plasma exchange may be warranted in asymptomatic individuals, such as those with multiple vascular co-morbidities and in patients with a high plasma viscosity >4cP prior to red cells transfusion [2].

Management of symptomatic, untreated WM patients

Rituximab alone is considered in peripheral neuropathy related to the IgM anti-myelin-associated glycoprotein activity [9] or in frail patients who are less likely to tolerate chemoimmunotherapy [12].

Chemoimmunotherapy combinations

The combination of rituximab with chemotherapy is the first option in medically fit patients particularly, when rapid response is needed [3] because rituximab is an active non myelosuppressive agent [12]. Response rate of 70-90% have been reported in rituximab based combination [14]. The choice of chemotherapy depends on comorbidities, how fast disease control is required, and the manifestations of the disease [12]. R-CHOP is no longer considered a first-line choice [13], Dexamethasone, rituximab, and cyclophosphamide (DRC) is a primary choice in frail patients requiring combination therapy. Toxicities were mild, with only 9% of patients having grade 3 to 4 neutropenia [12].

Bendamustine-rituximab (BR) is effective in patients with high tumor bulk [12]. Bortezomib-rituximab combination may be considered in patients with specific high-risk features (i.e., high IgM levels, symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia, amyloidosis and renal impairment) or in younger patients to avoid use of alkylator or nucleoside analog therapy [13]. Bortezomib should ideally be given once per week and possibly by a subcutaneous route. For urgent reduction of the IgM level, bortezomib can be started at twice-per-week doses for 1 or 2 cycles and then be changed to once-per-week dosing to reduce risk of neurotoxicity [12]. Bortezomib is not toxic to stem cells [13]. Rituximab plus carfilzomib are mainly used as an emerging neuropathy-sparing option. No grade ≥3 neuropathy was observed [12]. Single agent chlorambucil may still be suitable therapy for very frail patients in whom combination therapy is considered inappropriate [2].

Response criteria

a) CR: Absence of serum monoclonal IgM protein by immunofixation, normal serum IgM level, complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline, morphologically normal bone marrow aspirate and trephine biopsy.

b) VGPR: Monoclonal IgM protein is detectable, ≥90% reduction in serum IgM level from baseline, complete resolution of extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline, no new signs or symptoms of active disease.

c) Partial response: monoclonal IgM protein is detectable ≥50% but <90% reduction in serum IgM level from baseline, reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline, No new signs or symptoms of active disease.

d) Minor response: monoclonal IgM protein is detectable ≥25% but <50% reduction in serum IgM level from baseline, no new signs or symptoms of active disease.

e) Stable disease: monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline, no progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly, no new signs or symptoms of active disease.

f) Progressive disease: ≥25% increase in serum IgM level (an absolute increase of 5 g/L (0.5 g/dL) from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease [13].

Maintenance rituximab is recommended by NCCN for patients in CR for initial therapy or asymptomatic patients achieved very good, partial or minor response [14]. Maintenance rituximab increased incidence of grades 1 and 2 sinobronchial infections along with reduction of uninvolved immunoglobulins (IgA and IgG). It appeared to extend PFS and OS in comparison with observation [12].

Management of symptomatic previously treated WM patients.

Re-treatment with prior regimen used for symptomatic, untreated patients may be considered if a response was achieved for 2 or more years with the prior regimen [12]. Repeat bone marrow aspirate and trephine assessment and CT scanning prior to the reintroduction of treatment [2].

BR is well tolerated in relapsed/refractory disease. Prolonged myelosuppression occurred in patients who had received prior nucleoside analog therapy [12]. Ofatumumab is a fully human monoclonal antibody (IgG1) that targets a CD20 region at a different epitope than that of rituximab. It may represent a potential therapeutic option in rituximab in tolerant patients. A therapeutic test dose with appropriate prophylaxis should be considered before ofatumumab administration. There is a risk of IgM flare as with rituximab [14]. Rituximab with purine analogs (rituximab and fludarabine / rituximab, fludarabine, and cyclophosphamide) remain an option for patients with high-risk of relapsing disease and adequate performance status. They have a median PFS exceeding 50 months. In patients who may be candidates for single agent oral therapy, oral fludarabine (if available) is recommended over chlorambucil [13].

Novel agents

Immunomodulatory agents: Given the potential adverse events of lenalidomide and pomalidomide, their use should be considered in the context of a clinical trial [12]. Ibrutinib is an orally administered, irreversible inhibitor of BTK. It represents a novel and effective treatment option for both treatment naive and relapsing patients not candidates for chemoimmunotherapy [12]. Extramedullary disease was affected by ibrutinib therapy [15]. It prevents binding of MYD88 to BTK in L256P cells [14].

Ibrutinib showed rapid response kinetics, with a median time to response of 4 weeks [15]. The response was highest among patients with MYD88L265P and those with absent CXCR4 mutation [14].

The incidence of ibrutinib-triggered peripheral lymphocytosis was higher among patients with MYD88L265PCXCR4WT than among patients with MYD88L265PCXCR4WHIM [15]. Overall treatment with ibrutinib is well tolerated in WM patients [15]. Patients who progressed on first-line ibrutinib should not be retreated with ibrutinib [12]. A potential off-target effect is atrial fibrillation (5%) in patients with history of arrhythmia [15]. Ibrutinib produces a mild decrease in QT interval of unknown underlying mechanism and safety relevance [12]. **The mammalian target of rapamycin (mTOR) inhibitor (everolimus)** owing to the toxicities (hematologic, mouth sores and pulmonary pneumonitis) associated with everolimus, this agent is best considered in patients who are unresponsive or progressed after multiple lines of other better-tolerated therapies [12]. Discordance between serum IgM level and bone marrow disease response is common and complicates response assessment [12].

CXCR4 antagonist (plerixafor): The feasibility of long-term use of plerixafor for has been reported in patients with WHIM syndrome. It sensitizes engineered WM cells to express CXCR4WHIM receptors to undergo apoptosis in response to ibrutinib. Clinical trials of other CXCR4 inhibitors are ongoing [15]. The Akt inhibitor perifosine has shown a response rate of 35% but is associated with high levels of gastrointestinal toxicity. Histone deacetylase inhibitor panobinostat as a single agent has resulted in a minimal response or better in 47%. The median progression-free survival was 6.6 months [9]. MYD88 peptide inhibitor, MYD88L265P-directed immune activation and CD19 directed chimeric antigen receptor T cell therapy are 3 highly innovative WM specific therapies [16].

Caution

i. Avoid continuous oral alkylator cyclophosphamide, chlorambucil and bendamustine or nucleoside analogue (cladribine and fludarabine) therapy if SCT is considered [14].

ii. Patients receiving purine analogues, alemtuzumab and bendamustine should receive irradiated blood products for Life [2].

iii. Serum IgM can spike (IgM flare) during rituximab-based therapy (or other anti-CD20 monoclonal antibodies) for several weeks or months independent of tumor cell killing. This does not imply disease progression, in most cases; it will resolve [13]. On the other hand, bortezomib or everolimus can suppress IgM level [14].

iv. Rituximab should be avoided or withheld during the first 1 or 2 courses of systemic therapy until IgM levels decrease to a safer level, or plasmapheresis should be performed before giving rituximab to patients with high IgM levels (typically >4000 mg/dL) [12] because IgM flare could prompt symptomatic hyperviscosity.

v. LON has been described with rituximab, mostly when it is combined with chemotherapy. An association between a specific polymorphism in the IgG Fc receptor (FcgRIIIa-V158F) and LON has been described [12].

vi. Best response to alkylators [2], purine analogue and monoclonal antibody therapy, may not be achieved until 6 months after treatment. These agents selectively deplete CD20+ B-cell component with sparing of the CD138+ plasma cell component of the disease. There is significant B-cell depletion in the marrow but suboptimal IgM responses [11]. Satisfactory IgM responses may be achieved after many months into treatment. Bone marrow assessment is recommended to assess response. Conversely, bortezomib-containing regimens may demonstrate excellent IgM responses but suboptimal bone marrow responses [2].

vii. Prophylaxis against herpes zoster is strongly recommended for WM patients receiving proteasome inhibitors [14].

viii. Vaccinations should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy [2].

ix. Transient increases in serum IgM levels commonly occur when ibrutinib was withheld because of toxic effects or procedures. These levels decreased with reinstitution of therapy [15].

x. An off-target effect of ibrutinib on platelet aggregation has been described in CLL trials. Care should be taken if anticoagulant therapy or drugs that inhibit platelet function is used. Test for von Willebrand activity in patients with a history of bleeding diathesis. In case of surgery, ibrutinib should be held at least 3 to 7 days pre- and post surgery, depending upon the type of surgery and the risk of bleeding [12].

Treatment-associated morbidity: Prolonged risk of secondary infections with monoclonal antibodies and purine analogues, risk of long-lasting cytopenias, myelodysplasia and secondary malignancies from fludarabine, and worsening of peripheral neuropathy related to bortezomib [4]. Grade 2 or greater neutropenia and thrombocytopenia may occur with ibrutinib in heavily pretreated patients [12].

Stem cell transplantation

Stem cell collection should be performed pre-emptively after patients achieve first remission. ASCT is an effective treatment option for eligible patients up to 75 years. It is recommended

in high risk WM with elevated lactate dehydrogenase indicating a high tumor burden. It should ideally be offered at early relapses [17]. Chemosensitivity at the time of transplant is the most important predictor of response [2]. ASCT is not as beneficial for patients exposed to more than 3 lines of therapy or with chemotherapy refractory disease. Allogeneic SCT, when appropriate, should preferably be considered investigational due to high non relapse mortality [12].

Follow-up should include history, physical examination, blood count, routine chemistry and quantification of IgM every 3 months for 2 years, every 4-6 months for an additional 3 years, and subsequently once a year with special attention to transformation and secondary malignancies, including secondary leukemia. Radiological or ultrasound examinations every 6 months for 2 years are recommended, and annually thereafter only in cases of initial splenomegaly or lymph node enlargement. Regular CT scans are not necessary outside clinical trials [3].

Future options

Trials with ibrutinib and other BCR inhibitors are needed to assess their efficacy and tolerability in treatment-naive patients. BCR inhibitors combined with proteasome inhibitors in relapsed/refractory setting would be of interest to overcome resistance by interfering with the 2 key pathways that are affected by MYD88. Combination of CXCR4 antagonists with ibrutinib in patients with CXCR4WHIM mutation as well as Obinutuzumab, as a combination partner in WM are of interest [12].

Conclusion

The long survival and advanced age of presentation in WM must be considered when selecting the most appropriate treatment.

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