ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Update on Waldenström's Macroglobulinemia

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H&O What is Waldenström's macroglobulinemia (WM)?

IG According to the World Health Organization (WHO), WM is classified as a lymphoplasmacytic lymphoma. It is defined by 2 criteria: the presence of lymphoplasmacytic cells in the bone marrow and demonstration of an immunoglobulin M (IgM) monoclonal gammopathy in the peripheral blood. Approximately 1,500 new cases are reported each year in the United States. This number is likely an underestimation of the true incidence, complicated by the poorly defined overlap between IgM-monoclonal gammopathy of undetermined significance (IgM-MGUS) and asymptomatic WM.

H&O What are some symptoms of WM, and what are they attributable to?

IG Patients typically present with symptoms attributable to tumor infiltration and/or monoclonal protein. Anemia, which reflects both marrow infiltration and the serum level of monoclonal protein, is the most common symptom. Symptoms and signs of hyperviscosity, cryoglobulinemia, protein-protein interactions, and Ab-mediated disorders, such as neuropathy and hemolytic anemia, may occur because of the high levels of the IgM monoclonal protein. Patients may experience headaches, blurring of vision, or nose bleeds. On occasion, patients can present with B symptoms like other lymphomas, such as night sweats, fevers, and weight loss. Rarely, clinical manifestations of the disease include those related to other sites, such as pulmonary or central nervous system infiltration (Bing-Neel syndrome).

H&O What is the diagnostic approach to confirm a suspected case of WM?

IG In order to confirm a diagnosis of WM, it is necessary to demonstrate an IgM monoclonal protein, along with histologic evidence of infiltration of the bone marrow by lymphoplasmacytic cells. The demonstration of an IgM monoclonal protein is not synonymous with the diagnosis of WM, however. This abnormality may be seen in several forms of B-cell lymphoproliferative disorders as well as in MGUS. Because the concentration of IgM varies widely in WM patients, there is no clearly defined concentration that reliably distinguishes WM from other lymphoproliferative disorders. Although IgM MGUS and smoldering WM fall within the definition of WM, these entities have a very indolent clinical course, and patients do not initially require treatment.

H&O What are the main treatment options, and which patients receive treatment?

IG Only patients with symptomatic disease will receive treatment. There are multiple treatment options now, and continuing improvements are helping to create a promising treatment landscape. Frontline treatment options for WM include oral alkylators (eg, chlorambucil), nucleoside analogs (cladribine or fludarabine), the monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec), as well as combinations of these agents. Cyclophosphamide is frequently administered in combination with rituximab. Newer agents, such as bendamustine (Treanda, Cephalon) and everolimus (Afinitor, Novartis), can also be considered in the treatment of WM.

Table 1. Treatment Regimens for Waldenström's Macroglobulinemia, Including Novel Compounds

Author (Publication, Year)	Number of Patients	Treatment	ORR	Median PFS (Months)
Treon (*J Clin Oncol,* 2009)	23	Bortezomib, dexamethasone, and rituximab	96%	30+
Ghobrial (*J Clin Oncol,* 2010)	37 (relapsed)	Bortezomib and rituximab	81%	19.5
Ghobrial (*Am J Hematol*, 2010)	26 (untreated)	Bortezomib and rituximab	100%	12+
Dimopoulos (*Semin Oncol,* 2003)	20 (10 untreated)	Thalidomide	85%	N/A
Treon (*Blood,* 2008)	25	Thalidomide and rituximab	72%	34.8
Ghobrial (*Clin Cancer Res*, 2012)	42	Enzastaurin	38%	10.9
Ghobrial (*Clin Cancer Res,* 2010)	37	Perifosine	35%	12.6
Ghobrial (*Blood*, 2013)	36	Panobinostat	47%	6.6

N/A=not available; ORR=overall response rate; PFS=progression-free survival.

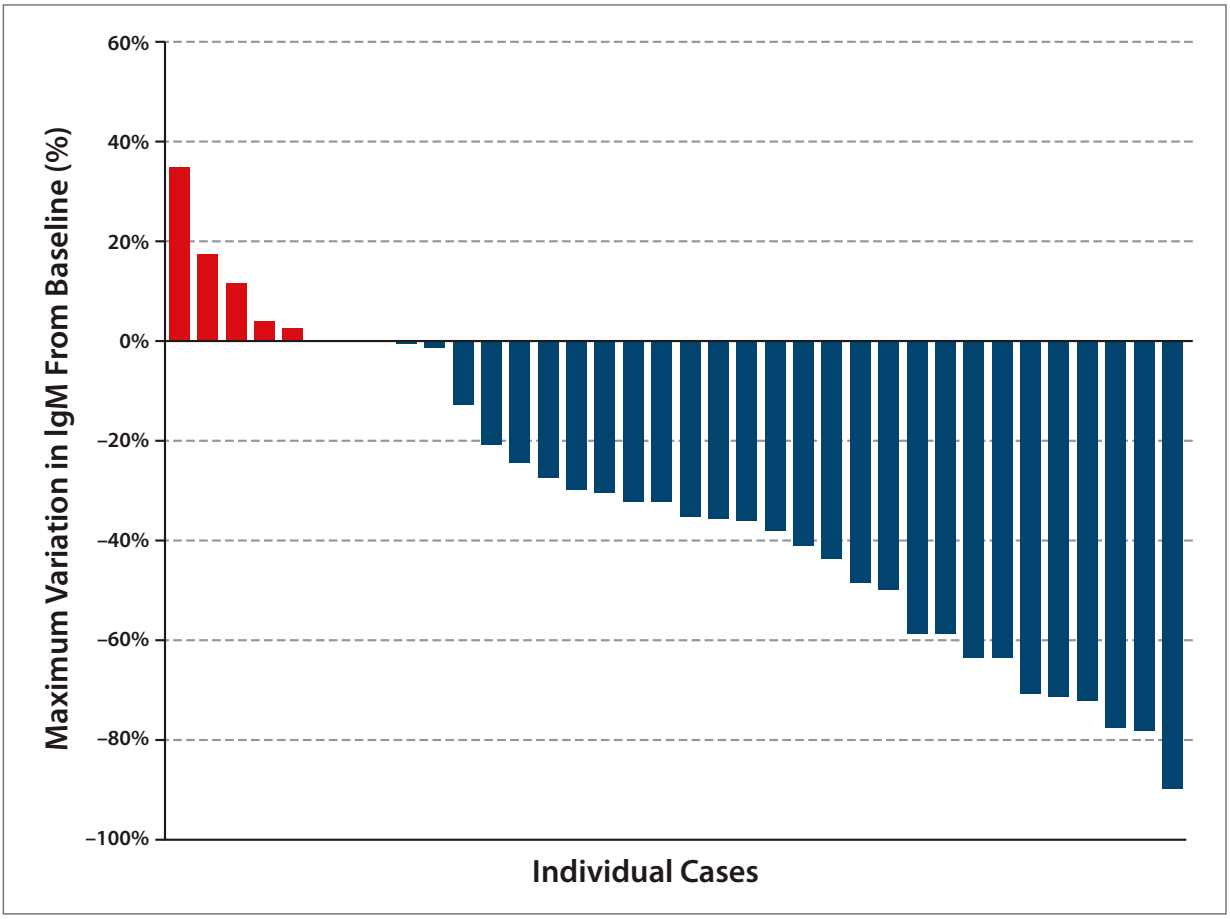

Figure 1. Waterfall of the maximum difference in immunoglobulin M (IgM) from baseline throughout the study (including follow-up; N=36).

This research was originally published in *Blood*. Ghobrial IM et al. Results of the phase II trial of single agent histone deacetylase inhibitor panobinostat in patients with relapsed/refractory Waldenstrom macroglobulinemia. *Blood.* 2013;121:1296-1303. © the American Society of Hematology.

H&O What other therapeutic options are under investigation?

IG A number of clinical trials are testing novel therapeutic agents, including second-generation proteasome inhibitors, immunomodulators, mammalian target of rapamycin (mTOR) inhibitors, histone deacetylase inhibitors, and Bruton's tyrosine kinase (BTK) inhibitors. Table 1 highlights treatment approaches, including regimens that involve novel compounds. We recently published data from a phase II clinical trial of panobinostat in patients with relapsed WM. Panobinostat was found to be an active therapeutic agent in this setting (Figure 1). These results warrant future investigation of histone deacetylase inhibitors as an active class of therapeutic agents in WM.

In February 2013, the US Food and Drug Administration (FDA) granted breakthrough therapy designation to the BTK inhibitor ibrutinib as a monotherapy for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL) and as a monotherapy for the treatment of patients with WM. A phase I open-label, dose-escalation trial by Advani and colleagues was presented at the 2012 American Society of Clinical Oncology (ASCO) meeting and subsequently published in the *Journal of Clinical Oncology*. The trial was designed to determine the dose, safety profile, pharmacokinetics, pharmacodynamics, and anti-tumor effects of ibrutinib. The response rates were very impressive overall, and 3 out of the 4 WM patients had a response to treatment. We are also looking forward to results of an ongoing clinical trial of ibrutinib in patients with relapsed and refractory WM disease, which has been submitted for reporting at the 2013 ASCO meeting.

H&O What gains have been made in the last decade regarding knowledge of the molecular basis of WM pathogenesis?

IG One of the biggest recent advances is the report by Treon and associates published in the *New England Journal of Medicine*, which concluded that *MYD88 L265P* is a commonly recurring mutation in patients with WM. Over 90% of patients with WM and 100% of patients with non–IgM-secreting lymphoplasmacytic lymphoma had *MYD88 L265P* expression. In contrast, *MYD88 L265P* was absent or rarely expressed in samples of patients with multiple myeloma, IgM-MGUS, or healthy subjects.

Further, other studies have suggested the importance of micro-RNA (miRNA) in supporting WM pathogenesis. Among deregulated miRNAs, miRNA-155 was shown to play a significant role in the biological characteristics of WM both in vitro and in vivo. Such results have provided the rationale for testing miRNA-based therapeutic approaches for the treatment of WM.

H&O What are the biggest remaining challenges?

IG Despite recent advances, there are no therapeutic agents for the specific treatment of WM that are approved by the FDA. WM remains a rare disease, and we still have a lot of preclinical work to do and more biology to understand. What are the driving mutations? What is the cause of clonal evolution in these patients? Why are some patients at higher risk than others? There is no good animal model for the disease. Furthermore, because WM patients are typically older, and approximately half die of causes unrelated to the disease, it is difficult to treat them homogeneously so that we have more information about their long-term follow-up.

Suggested Readings

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