therapies, phenotype-specific treatments, and curative strategies. Allogeneic hematopoietic stem cell transplantation and the recently approved gene therapies based on CRISPR-Cas9 (Exa-cel) and lentiviral vectors (Lovo-cel) have ushered in a new era, offering curative potential for eligible patients. The future therapeutic algorithm is anticipated to become even more personalized through the integration of these revolutionary treatments.

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Abstract 007

WALDENSTRÖM MACROGLOBULINEMIA

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Waldenström Macroglobulinemia (WM) is a rare disease. The median age at diagnosis is 70 years and approximately 60 percent of patients are male. The etiology of WM is not fully understood. Approximately 90-95% of WM patients have mutations in the MYD88 L265P gene and 40% have recurrent mutations in the CXCR4 gene. The clonal B cell population leads to abnormal monoclonal IgM production. The pentameric configuration of IgM molecules increases serum viscosity, slowing blood flow through capillaries. In patients with WM, clonal B cells can directly infiltrate hematopoietic tissues, causing cytopenias (e.g., anemia, thrombocytopenia, neutropenia), lymphadenopathy, hepatomegaly, and/or splenomegaly. Rarely, plasmacytoid lymphocytes may infiltrate the central nervous system or meninges. Most patients with WM present with nonspecific constitutional symptoms but up to a quarter of patients may be asymptomatic at diagnosis. Common symptoms include weakness, fatigue, weight loss, and nose and gum bleeding. Bone marrow aspiration and biopsy demonstrating lymphoplasmacytic lymphoma is an important component of the diagnosis of WM. The biopsy specimen is usually hypercellular and densely infiltrated with lymphoid and plasmacytoid cells. Intranuclear vacuoles containing IgM monoclonal protein (Dutcher bodies) are common in the malignant cells of WM. The following criteria must be met for a diagnosis of WM: • IgM monoclonal gammopathy (any level) must be present in the serum. • ≥10% of the bone marrow biopsy specimen must show infiltration by small lymphocytes with plasmacytoid or plasma cell differentiation (lymphoplasmacytic features or lymphoplasmacytic lymphoma) and an intertrabecular pattern. • The infiltrate should express a typical immunophenotype (e.g., surface IgM +, CD5-/+, CD10-, CD11c-, CD19+, CD20+, CD22+, CD23-, CD25 +, FMC7+, CD103-, CD138-). The plasmacytic component will be CD138+, CD38+, and CD45- or less prominent. The differential diagnosis includes chronic lymphocytic leukemia, marginal zone and mantle cell lymphoma. Not every VM patient requires treatment. For asymptomatic patients, follow-up without treatment every 3-6 months is recommended. Treatment is indicated for patients with symptomatic WM if any of the following are attributable to WM: • Systemic symptoms: B symptoms such as recurrent fever, severe night sweats, fatigue and/or unintentional weight loss • Cytopenias: Hemoglobin ≤10 g/dL or platelet count <100,000/microL; cold agglutinin anemia, immune hemolytic anemia, and/or thrombocytopenia • Symptomatic or large (≥5 cm) lymphadenopathy, symptomatic splenomegaly and/or tissue infiltration • End-organ damage: Hyperviscosity, peripheral neuropathy, immunoglobulin light chain (AL) amyloidosis with organ dysfunction, symptomatic cryoglobulinemia, pleural effusions or nephropathy due to WM Symptomatic hyperviscosity in a patient with an indication for treatment requires urgent plasmapheresis. Signs and symptoms associated with hyperviscosity include oronasal hemorrhage, blurred vision, headache, dizziness, paresthesia, retinal vein occlusion, papilledema, stupor, and coma. In patients with treatment indications but without symptoms of hyperviscosity, options include rituximab plus bendamustine or Bruton's tyrosine kinase inhibitors (such as ibrutinib, zanubrutinib, or acalabrutinib). Treatment of relapsed or refractory disease may include Bruton's tyrosine kinase inhibitors, bendamustine plus rituximab, nucleosome analog-based regimens, and venetoclax, if not previously used. High-dose chemotherapy and autologous or allogeneic hematopoietic cell transplantation (HCT) are rarely used in the treatment of WM.

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Abstract 008

REFRACTORY CHRONIC MYELOID LEUKEMIA: A REVIEW OF CURRENT THERAPEUTIC LANDSCAPE AND EMERGING CHALLENGES

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Chronic myeloid leukemia (CML) has become a paradigm of targeted therapy success; however, a proportion of patients develop refractory disease, marked by failure or intolerance to multiple TKIs. Optimal management requires integrating molecular, clinical, and patient-related factors into therapeutic decision-making [1,2]. **Mechanisms of Resistance and Genetic Complexity:** Resistance is commonly mediated by BCR::ABL1 kinase domain mutations. While second-generation TKIs (dasatinib, nilotinib, bosutinib) address many resistant clones, the T315I substitution remains uniquely sensitive to ponatinib [3,4]. Beyond kinase domain changes, clonal evolution with mutations in ASXL1, RUNX1, IKZF1, TP53, and DNMT3A has been increasingly recognized. These lesions, frequently encountered in advanced phases, are associated with poor response to TKIs, higher risk of progression, and inferior survival [5,6]. **Current Therapeutic Approaches:** Ponatinib remains the agent of choice for patients harboring T315I or compound mutations, with careful risk management to mitigate vascular events [4]. Asciminib, a first-in-class STAMP inhibitor targeting the myristoyl pocket of BCR::ABL1, has emerged as a major advance. By restoring kinase autoinhibition, asciminib demonstrated superior efficacy and tolerability over bosutinib in the ASCEMBL trial [3] and has shown promising results in real-world refractory populations. **TKI Selection Considerations:** In clinical practice, TKI selection is