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Waldenstrom Macroglobulinemia ☆

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Abstract

In the past years, new developments have occurred both in the understanding of the biology of Waldenstrom Macroglobulinemia (WM) and in therapeutic options for WM. WM is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy. Despite advances in therapy, WM remains incurable, with 5–6 years median overall survival of patients in symptomatic WM. Therapy is postponed for asymptomatic patients, and progressive anemia is the most common indication for initiation of treatment. The main therapeutic options include alkylating agents, nucleoside analogues, and rituximab. Studies involving combination chemotherapy are ongoing, and preliminary results are encouraging. No specific agent or regimen has been shown to be superior to another for treatment of WM. As such, novel therapeutic agents are needed for the treatment of WM. In ongoing efforts, we and others have sought to exploit advances made in the understanding of the biology of WM so as to better target therapeutics for this malignancy. These efforts have led to the development of several novel agents including the proteasome inhibitor bortezomib, and several Akt/mTor inhibitors, perifosine and Rad001, and immunomodulatory agents such as thalidomide and lenalidomide. Studies with monoclonal antibodies are ongoing and promising including the use of alemtuzumab, SGN-70, and the APRIL/BLYS blocking protein TACI-Ig atacicept. Other agents currently being tested in clinical trials include the PKC inhibitor enzastaurin, the natural product resveratrol, as well as the statin simvastatin. This report provides an update of the current preclinical studies and clinical efforts for the development of novel agents in the treatment of WM.

Keywords: Waldenstrom Macroglobulinemia; Novel therapy; Transplantation

1. Introduction

Waldenstrom Macroglobulinemia (WM) is a distinct low-grade B-cell lymphoma characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of a serum IgM monoclonal gammopathy [1], first

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described by Dr. Jan Gosta Waldenstrom in 1944. WM has an overall incidence of approximately 3 per million persons per year, accounting for approximately 1–2% of hematological cancers, and approximately 1500 new cases diagnosed per year in USA [2,3]. This incidence might be underestimated because many patients are misdiagnosed or not diagnosed early due to lack of symptoms at early stages of the disease. The median age varies between 63 and 68 years, with 55–70% men [4]. The incidence of WM is higher among whites, with blacks representing only 5% of all patients [5].

WM is believed to be predominantly a sporadic disease; however, studies have demonstrated a high familial incidence of this disease, with 18.7% of the patients having at least a first degree relative with a B-cell neoplasm [6,7]. Moreover, patients with a familial history of WM or a plasma cell disorder received the diagnosis at a younger age and with greater bone marrow involvement. The main risk factor for the development of WM is preexisting IgM-monoclonal gammopathy of undetermined significance (MGUS), which confers 46 times higher relative risk than for the general population) [8]. Morra et al. [9] showed a progressive increase in the risk of transformation from asymptomatic IgM-MGUS to symptomatic WM, with increasing IgM levels. A possible association between hepatitis C virus and WM had been suggested [10], but this has been negated recently by Leleu et al. [11]. Reports of links between human herpes virus-8 and WM are unconfirmed.

The origin of the malignant clone is thought to be a B-cell arrested after somatic hypermutation in the germinal center, before terminal differentiation to plasma cells [12,13]. The malignant cells have undergone VH gene somatic mutation, but not isotype class switching. Deletions in 6q21-22.1 were confirmed in most WM patients regardless of family history [14]. Analysis of 14q32 indicates the absence of Ig heavy chain (IgH) rearrangements in WM [15]. Many genes are thought to be dysregulated in WM, but further studies to define the role of these genes in the pathogenesis of WM are underway [16]. WM is characterized by upregulation of cytokines and chemokines that induce proliferation and survival of the malignant clone. These include B-lymphocyte stimulator (BLyS), IL-6, CD40 ligand, BAFF, APRIL, and stromal derived factor (SDF-1) [16–20].

2. Diagnostic criteria

WM is currently classified by the Revised European American Lymphoma (REAL) and World Health Organization (WHO) systems as a lymphoplasmacytic lymphoma [1,21]. The median age varies between 63 and 68 years, with 55–70% men [4]. WM cells express pan B-cell markers including CD19, CD20, and CD22, but lack CD10, CD23, CD38, FMC7, and cytoplasmic Ig [22]. CD5 and CD23 are expressed in 5–20% and 35% of the cases, respectively [23].

3. Signs and symptoms

WM is a heterogenous disease and patients can present with a broad spectrum of symptoms and signs [24,25]. Most patients with the diagnosis of WM have symptoms attributable to tumor infiltration, to circulating IgM, to tissue deposition of IgM, and to autoantibody activity of IgM. The most common clinical presentations are related to cytopenias, specifically anemia related to replacement of the bone marrow with tumor cells. Fatigue is a very common presentation of WM that is multifactorial, due at least in part to the underlying degree of cytopenia. Patients may also present with symptoms of hyperviscosity related to elevate IgM levels including headache, blurring of vision, and epistaxis. Hepatosplenomegaly and lymphadenopathy occur in 20% of the patients, and some patients may present with B symptoms including night sweats, fever, and weight loss. Other presentation features include peripheral neuropathy, cryoglobulinemia, skin rash (Shnitzler's syndrome is the term for IgM monoclonal gammopathy associated with urticarial skin lesions, fever, and arthralgia), cold-agglutinin hemolytic anemia, and amyloidosis. Anti-myelin-associated glycoprotein (MAG) antibody has been implicated in the demyelinating neuropathy found in WM [26].

4. Differential diagnostic

The presence of clonal B cells with lymphoplasmacytic differentiation in the bone marrow or a serum monoclonal IgM protein are not pathognomonic for WM and may be seen in other B-cell lymphoproliferative disorders including splenic marginal zone lymphoma (SMZL) [27,28]. SMZL can be distinguished from WM on the basis of immunophenotypic and molecular cytogenetic stud-