Best Practice & Research Clinical Haematology 29 (2016) 194–205

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

Current therapy guidelines for Waldenstrom's macroglobulinaemia

Efstathios Kastritis, Meletios A. Dimopoulos*

Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Keywords:
Rituximab
Ibrutinib
Bortezomib
Carfilzomib
Fludarabine

A B S T R A C T

Waldenstrom's macroglobulinaemia (WM) is a B-cell neoplasm in which bone marrow is infiltrated by lymphoplasmacytic cells that secrete monoclonal immunoglobulin M (IgM). More than a decade ago, specific criteria were agreed to define diagnosis and symptomatic disease requiring therapy; however, treatment recommendations change as new options emerge. Treatment decisions consider specific disease characteristics (burden of disease, IgM levels, presence of cytopenias) and patient characteristics (age, comorbidities, toxicity). Recently, the impact of specific mutations (in *MYD88* and *CXCR4*) in response to specific therapies has been reported, and this may affect treatment decisions in the future. Chemo-immunotherapy combinations based on rituximab with cyclophosphamide/dexamethasone, bendamustine or bortezomib/dexamethasone are indicated for most patients. The BTK inhibitor ibrutinib was recently approved for patients with WM, and is a new option for selected newly diagnosed or relapsing patients. New B-cell receptor inhibitors, second-generation proteasome inhibitors and mammalian target of rapamycin inhibitors are promising; however, more data are needed from high-quality clinical trials.

Introduction

Waldenstrom's macroglobulinaemia (WM) is a lymphoplasmacytic lymphoma characterized by infiltration of the bone marrow by clonal lymphoplasmacytic cells which produce immunoglobulin M

* Corresponding author. Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, 80 Vas. Sofias Avenue, Athens 11528, Greece. Fax: +30 213 216 2511.
E-mail address: mdimop@med.uoa.gr (M.A. Dimopoulos).

http://dx.doi.org/10.1016/j.beha.2016.08.023
1521-6926/

(IgM) [1]. WM is diagnosed based on clinical and pathological criteria that were proposed at the Second International Workshop on WM (IWWM-2), together with criteria defining symptomatic WM that requires therapy [2,3]. These criteria have been followed to guide treatment decisions, but treatment options for patients with WM have changed. WM workshops [4–6], the National Comprehensive Cancer Network and other societies have published recommendations and guidelines [7–10] for the management of patients with WM in order to follow the development of new therapies. These guidelines and recommendations reflect changes in the availability of new therapies and their combinations; since the era of alkylators and nucleoside analogues, treatment options have expanded to include monoclonal antibodies, proteasome inhibitors (PIs) and BTK inhibitors.

Indications for treatment

The most important decision regarding therapy for a patient with WM is when to start. Not all patients with a diagnosis of WM need immediate therapy, and only patients fulfilling the criteria of symptomatic disease [3] should be treated; otherwise, patients should be followed without therapy. The criteria for the initiation of therapy include the presence of IgM-related complications, cytopenias, constitutional symptoms or bulky disease. For patients who do not fulfil the criteria but in whom laboratory evidence may indicate a possible development of progressive disease (e.g. a minor decrease in haemoglobin level with asymptomatic anaemia, mild increase in IgM, mild increase in lymphadenopathy, or splenomegaly without discomfort for the patient), it is better to observe them closely and discuss the possibility that therapy may be required [3]. The treating physician should be aware that reasons other than WM may cause symptoms such as anaemia, and that an investigation should be performed for the cause of anaemia, especially if this the only feature of symptomatic disease.

Evaluation of response to therapy

Evaluation of the response to therapy is important for treatment decisions, prognosis and comparison between different therapies. The consensus-based uniform response criteria for WM are based mainly on the degree of reduction in M proteins [4,5,11], with >50% reduction of IgM constituting a major response (i.e at least a partial response). However, IgM levels should be evaluated with caution, especially early in the course of rituximab-based therapy (or other anti-CD20 monoclonal antibodies), because of the common IgM flare phenomenon [12–14] which does not necessarily imply disease progression. IgM flare will resolve in most cases, but additional tests may be required to discriminate from disease progression. Extramedullary disease (lymph nodes, spleen) should also be evaluated carefully, and may resolve later in the course of the disease. In patients treated with agents such as bortezomib, everolimus or even ibrutinib, tumour reduction in the bone marrow may not be proportional to the suppression of IgM levels [15–19]. Thus, IgM kinetics may vary depending on therapy, and this should be taken into account. In discordant cases (i.e. progressive disease vs IgM flare), additional investigations (computed tomography, bone marrow evaluation) should be considered.

Treatments for WM

Treatment options are increasing at a pace that is discordant to the number of patients enrolled in clinical trials. Quality data from prospective phase 3 studies are lacking. Thus, most data on WM treatment are from small phase 2 studies. Several agents have shown modest-to-moderate single-agent activity, but combinations of different agents are very effective.

Plasmapheresis

The most rapid therapy to manage complications of very high circulating IgM, as in patients with IgM-related hyperviscosity, is plasmapheresis. As such, plasmapheresis should always be used immediately for patients with symptomatic hyperviscosity, and it should be considered in order to prevent IgM flare in patients with high IgM levels prior to rituximab administration. Plasmapheresis alone is not effective for long-term control of disease, and must be followed by a rapidly acting cytoreductive treatment targeting the IgM-producing lymphoplasmacytic cells [6,20,21].