EDITORIAL

The half-life of guidelines for Waldenström's macroglobulinaemia; short stickiness for a sticky disease?

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Waldenström's macroglobulinaemia (WM) is a B-cell lymphoproliferative disorder that has been challenging clinicians since it was first recognised by Dr. Waldenström in the mid-forties of the last century. Several reasons contribute to the difficulties that clinicians face with the management of patients with this disease. First, WM is a very rare entity. The overall age-adjusted incidence of WM is just 3.8 per million persons per year. As a comparison, the incidence of amyloidosis is 8 per million persons per year and the incidence of multiple myeloma is 40 per million persons per year.[1] Second, the wide clinical spectrum of the disease makes standardisation in when and how to treat complicated. The most common presenting symptom is fatigue, often related to a normochromic or normocytic anaemia. Organ-specific manifestations of the disorder are seen in less than a quarter of patients and include hepatomegaly, splenomegaly, and lymphadenopathy.[2] A unique characteristic of WM is the presence of monoclonal IgM protein. Due to its pentameric structure, antibody-binding specificity and protein-folding capacity, IgM paraproteinaemia can result in hyperviscosity syndrome, peripheral neuropathy, cold agglutinin haemolytic anaemia, type II mixed cryoglobulinaemia and immune complex vasculitis.[2] Although these syndromes can arise simultaneously, this is rarely the case and often, patients are referred to organ-specific specialists causing significant delay in diagnosis and treatment. Serum levels of IgM, however, have proven to be an unreliable marker for disease symptoms. Patients can present with markedly elevated IgM levels and infiltration of the bone marrow yet still not require therapy because they lack any symptoms. Conversely, patients with minimal clonal marrow infiltration and low levels of monoclonal IgM protein might require therapy for complications associated with IgM paraproteinemia.[3] In general, most patients who fulfil the criteria of WM do not require immediate therapy because many cases are detected before symptoms occur.
A third aspect which contributes to the absence of a clear standard of care for this disease is the fact that the large majority of clinical trials on WM are single-arm phase II studies. Many of such trials have been conducted in small series of patients and many include mixed patient populations including untreated, relapsed and refractory patients. Two smaller randomised trials have been published so far. One trial compared single-agent chlorambucil as continuous or pulse therapy. The other trial studied the addition of rituximab to the CHOP regimen in lymphoplasmacytic leukaemia of whom two thirds of the patients fulfilled the criteria of WM. Only very recently the results of a large phase III trial in 339 previously untreated patients with WM were published.[4] This study showed superiority of fludarabine as compared with chlorambucil as first-line treatment of WM. Although this study sets a benchmark for any future phase III trials its applicability to the current therapeutic options of patients with WM is limited since rituximab, now considered standard of care, was not part of the study regimen. Different phase II studies and the above-mentioned phase III study (CHOP vs R-CHOP) have shown that rituximab added to chemotherapy significantly enhances responses and progression-free survival without added major toxicity.

The above-described challenges in the clinical care of patients with WM are clearly reflected in a survey that has been carried out amongst Dutch Haemato-Oncologists, the results of which are published in this issue of the *Netherlands Journal of Medicine*.[5] The main results of this survey indicate that although diagnostic methods and

available treatment options for WM are generally well known, uncertainty exists on when to initiate treatment and how to deal with disease-specific and treatment-specific side effects such as hyperviscosity syndrome and the 'IgM flare syndrome'. Also, the survey clearly shows the lack of uniformity in the choice of treatment.

The lack of clinically applicable randomised trials and the overwhelming amount of novel agents highlights the need for guidance on the management of WM. A collaborative effort of the HOVON myeloma working party and the HOVON lymphoma working party resulted in the first Dutch guideline for the diagnosis and management of WM, which is also published in this issue of the *Netherlands Journal of Medicine*.[6] This practical guideline nicely integrates data from published trials with expert-based experiences and will improve standardisation of care for patients with WM in the Netherlands.

Although this guideline is currently up-to-date, its half-life is expected to be limited for two main reasons. First, treatment modalities for multiple myeloma and lymphoma are rapidly expanding and include novel agents with expected potency, also in WM, such as second-generation proteasome inhibitors and monoclonal antibodies, and third-generation immunomodulatory agents. Second, and probably more important, recent discoveries have unravelled the molecular mechanisms that are fundamental in the biology of the disease, paving the way for targeted therapies. Whole genome sequencing of lymphoma cells of patients with WM showed a recurring sequence variant resulting in the single nucleotide change L265P in the MYD88 gene in 90% of the WM samples. This activating mutation via the activation of IRAK kinases ultimately results in activation of NF-kB, a protein that is essential for the growth and survival of Waldenstrom's tumour cells.[7]

Activation of the IRAK-mediated NF-kB pathway by mutated MYD88 (L265P) depends on upstream activation of Bruton's tyrosine kinase (BTK).[8] Specific inhibitors of these kinases, including BTK inhibitors and IRAK inhibitors, have been and are being developed and clinically tested. Long-term effectiveness of these classes of drugs in WM is highly expected and clinical trials with the BTK-inhibitor ibrutinib have already been started. It is therefore anticipated that authors of this guideline need to reconvene in the near future in order to implement these promising new drugs in the management of patients with this still incurable disease.

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