

The real world of Waldenström's macroglobulinaemia



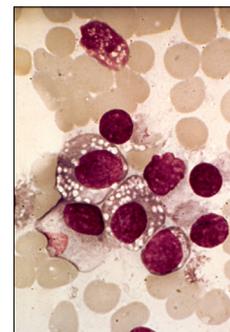
In *The Lancet Haematology*, Christian Buske and colleagues¹ report the results of their retrospective, medical record-based study to identify treatment and outcome patterns for patients with Waldenström's macroglobulinaemia. The authors invited academic and community physicians in ten European countries to complete retrospective chart reviews for patients they had treated over a period of 14 years (2000–14). The objective of the study was to obtain information about patient characteristics, reasons for treatment initiation, and type of treatments used, as well as the association between particular treatments and outcomes.

Buske and colleagues found that anaemia (72%), constitutional symptoms (58%), symptoms related to the IgM paraprotein (54%), and organomegaly (17%) were the most common reasons for treatment initiation, regardless of centre type (academic or community). These observations are in line with previous reports,² and point to anaemia as the most common reason for starting treatment in patients with Waldenström's macroglobulinaemia. Anaemia can be multifactorial in Waldenström's macroglobulinaemia: causes include accumulation of lymphoplasmacytic cells in the bone marrow, autoimmune haemolysis (including cold agglutinaemia), and iron deficiency due to hepcidin overproduction.³ Understanding the principal reasons physicians start treatment in clinical practice is important because endpoints in clinical trials are often limited to changes in IgM concentrations or markers of bone marrow disease burden. Incorporating meaningful endpoints that address important signs or symptoms of Waldenström's macroglobulinaemia, such as anaemia, is crucial for real-world practice because so many patients are affected by them. Moreover, not all available treatment options address the different aspects of Waldenström's macroglobulinaemia in the same way or to the same extent. For instance, whereas ibrutinib can lead to rapid improvements in haemoglobin concentrations, other drugs, such as alkylating agents or nucleoside analogues, show a lag-time in response, and some drugs, such as everolimus, might even potentiate anaemia.^{3,4}

The dearth of prospective, randomised clinical trials in patients with Waldenström's macroglobulinaemia is a major problem and most treatment guidelines

and individual treatment decisions in this disease are based on comparisons of phase 2 data. The absence of a standard of care for front-line treatment is reflected in the diversity of treatments offered, as shown in Buske and colleagues' review. When making decisions about treatment of Waldenström's macroglobulinaemia, physicians must weigh up tailoring treatment to a patient's symptoms, tolerance of medications, and avoidance of undue short-term and long-term toxic effects.^{3,4} However, Buske and colleagues' data suggest that decisions made in practice might also be affected by access to drugs, drug affordability, geographical preferences, and practice patterns, as reflected by the differences in practice between academic and community settings shown in this study. Monotherapy was the most frequently used regimen, predominantly chlorambucil in community-based care and rituximab in academic institutions. Patients treated in the academic setting were more likely to receive chemoimmunotherapy and combination therapy than were patients treated in the community. These differences in treatment preferences between specialist centres and community-based practice might have accounted for the difference in progression-free survival between the two settings in front-line treatment (hazard ratio 0.67, 95% CI 0.54–0.82; $p=0.0001$).

Use of monotherapy as the primary treatment approach is not unique to Europe. In a population-based study⁵ in 1458 Medicare beneficiaries in the USA who were diagnosed with Waldenström's macroglobulinaemia between 1994 and 2011, rituximab monotherapy was the primary therapy in 656 (45%) patients. Median progression-free survival with rituximab monotherapy is 18–24 months in treatment-naïve patients.^{6,7} Although combination therapies containing rituximab have resulted in deeper responses (lower IgM concentrations) and improved progression-free survival (48–72 months),^{8,9} rituximab monotherapy remains the mainstay of treatment for Waldenström's macroglobulinaemia in real-world settings. This important finding from two independent studies^{4,5} should be considered in trials aiming to change real-world practice. Indeed, the prospective, randomised INNOVATE study¹⁰ compared rituximab plus ibrutinib with rituximab alone in treatment-naïve or previously



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treated patients with symptomatic Waldenström's macroglobulinaemia. At a median follow-up of 26 months, ibrutinib plus rituximab resulted in higher overall (92% vs 47%) and major (72% vs 32%) response rates, as well as improved median progression-free survival (not reached vs 20 months), than did rituximab alone. Improvements were seen in both treatment-naïve and previously treated patients. Despite these findings, many questions regarding treatment of Waldenström's macroglobulinaemia remain, including the necessity of using rituximab along with ibrutinib, the effect of *MYD88* and *CXCR4* mutation status on long-term outcomes, and whether or not ibrutinib plus rituximab is preferable to other rituximab combinations. The study by Buske and colleagues provides important insights into the real-world treatment practices for Waldenström's macroglobulinaemia in Europe and a benchmark for advancement of novel treatments and approaches for this disease.

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