



WM GENOMICS AND TREATMENT OPTIONS

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The approval of ibrutinib as the first ever approved agent for use in symptomatic Waldenström's macroglobulinemia (WM) by the US Food & Drug Administration and many other international regulatory agencies ushered in a new era in the treatment of WM. A regulatory pathway was also chartered with the approval of ibrutinib for treatment of WM, attracting interest by pharmaceutical companies and providing a roadmap for the investigation and approval of other agents for WM.

With the approval of ibrutinib, debate has emerged on how WM is best managed and what priorities should be given for the development of medications like ibrutinib that require indefinite daily administration versus those that have a defined length of administration. While there is precedent for the use of daily medications to treat a multitude of disorders in everyday life, such as high blood pressure, cholesterol, or diabetes, the debate of "daily" versus "defined" has taken on more urgency as the high cost of drugs like ibrutinib is pitted against the efficacy and safety of other drugs traditionally used in the management of WM. However, such comparisons are not easy to undertake or justify because of many factors that need to be weighed beside actual drug costs. These other factors include the costs associated with treatment administration, supportive medications (such as Neulasta or Neupogen), blood transfusions, and treatment of short- and long-term side effects.

Treatment options for WM have traditionally relied on rituximab alone, or with alkylators (cyclophosphamide or bendamustine), nucleoside analogues (fludarabine or cladribine), immunomodulatory agents (thalidomide), or proteasome inhibitors (bortezomib or carfilzomib). While many lessons were learned from trials examining single agent and combination rituximab therapy, the most important ones have centered on how much disease eradication can occur (i.e. depth of response), how long such therapies can keep disease from progressing or coming back (i.e. durability of response), and the short- and long-term toxicities they can produce.

Rituximab was the first modern biological therapy used to treat indolent lymphomas such as WM. Rituximab binds to CD20 and attracts immune cells and immune system proteins such as complement that destroy CD20-expressing cells. The malignant clone in WM patients is made up of B-cells that exist in three morphologically distinct stages, including CD20-expressing mature B-cells, CD20-expressing lymphoplasmacytic cells, and non-CD20-expressing plasma cells. Most of the IgM made in WM patients comes from plasma cells, and for many patients the production of IgM produces symptoms such as hyperviscosity syndrome, IgM-related neuropathy, cryoglobulinemia, and cold agglutininemia that necessitate treatment.

Two schedules for single agent rituximab monotherapy were investigated in WM: a “standard” one with 4 weekly rituximab infusions and an “extended” one with 4 additional weekly infusions at weeks 12-16 following standard administration. With “standard” rituximab administration, the overall response rate (ORR) that includes minor responses (i.e. responses that reduce IgM by at least 25%) is 40%, while the major response rates (i.e. responses that reduce IgM by at least 50%) are 20-30%. With “extended” rituximab, the ORR is higher (50-60%), with major response rates of 40%. Deeper responses, such as very good partial responses (VGPR), where IgM is reduced by 90%, and complete responses (CR), where the IgM levels return to normal and no WM-related IgM is detected, are rare with rituximab, and the average time that these responses last is 13-29 months.

Responses to rituximab are slow, with time-to-best-response requiring up to 18 months. Since the malignant WM clone is also made up of plasma cells that do not have CD20, sparing of these cells usually occurs after rituximab alone. This, in turn, results in persistence of IgM-producing plasma cells that can trigger symptoms brought on by the production of IgM, as well as its accompanying light chain proteins (kidney failure, amyloidosis). A flare in serum IgM commonly occurs with rituximab and can induce hyperviscosity symptoms and/or aggravate symptoms attributed to IgM. With prolonged rituximab use, allergic reactions can occur in 10% of WM patients. Moreover, prolonged rituximab use can deplete good CD20-expressing B-cells and result in deficiencies of IgA and IgG that can lead to recurring sinus and bronchial infections necessitating antibiotics and, in more severe cases, requiring the use of intravenous gamma globulin (IVIG).

To extend rituximab activity, rational combinations have been sought. Laboratory studies have provided logical justification for some, but not all, rituximab combinations. Many agents used with rituximab target non-CD20-expressing plasma cells and provide an important overlap to eradicate the entire WM clone. With most combination rituximab therapies, improvements in ORR and deeper responses have occurred. The ORR with rituximab and alkylators, nucleoside analogues, and proteasome inhibitors is 80-90%, with deeper VGPR/CR responses seen in 30-40% of WM patients. The use of maintenance rituximab has also contributed to deeper responses in WM. With deeper responses, improvements in the durations of response have been recognized. The attainment of VGPR or better has been observed to predict for longer response durations with many rituximab combinations. These findings were also recognized in a retrospective study that examined the outcome of 159 WM patients receiving rituximab-based therapy. CR or VGPR attainment was associated with average response durations that exceeded 90 and 75 months, respectively. For those that attained less deep responses, the average response durations were 43 and 31 months, respectively, and were 11 months in those without response or stable disease.

While depth and durability of response have increased with combination rituximab regimens, so has toxicity. Treatment-related adverse events following rituximab combinations have included myelodysplasia (damaged bone marrow stem cells), secondary malignancies such as acute leukemia, prolonged suppression of blood counts, immune system suppression, and neuropathy. Avoidance of nucleoside analogue drugs like fludarabine, limitations on alkylator drug exposure, adoption of weekly bortezomib regimens, and use of neuropathy-sparing proteasome inhibitors have impacted short- and long-term toxicity with rituximab combinations. Efforts to maintain and induce deeper responses with rituximab alone or in combination have shown promise and continue to be evaluated. Conversely, the use of stem cell transplant therapy following initial therapy has been avoided due to toxicity.

The discovery of highly recurrent MYD88 (95-97%) and CXCR4 (30-40%) mutations in WM patients has provided important new insights into the biology of WM and in the development of targeted therapies. Mutated MYD88 triggers the activation of Bruton's tyrosine kinase (BTK) in WM cells. Activated BTK turns on NF- κ B, a protein in WM cells that enhances the growth and survival machinery of WM cells. In addition, mutated MYD88 stimulates the production and activation of hematopoietic cell kinase (HCK), a protein that acts as a major switch for the activation of other WM cell growth-promoting pathways including AKT and ERK. The activity of BTK and HCK are both blocked by ibrutinib.

These basic science findings enabled a pivotal clinical trial of ibrutinib in symptomatic, previously treated WM patients and allowed the first ever "breakthrough" designation for an oncology drug, thereby enabling accelerated review. Sixty-three patients at the Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, and Stanford University Medical Center took part in the Phase II trial wherein patients received 420 mg a day of ibrutinib. Dose reduction was permitted for toxicities. The results of this study were originally published in the New England Journal of Medicine in 2015 and were just updated at the 2017 Annual Meeting of the American Society for Hematology (ASH). The findings showed an ORR of 90%, with 78% of patients attaining a major response, while 27% had a VGPR. Those patients with MYD88 mutations but no CXCR4 mutation showed the highest levels of ORR, major response, and even VGPR. Most of these patients show continued response beyond 5 years. Patients with both MYD88 and CXCR4 mutations had slower responses and lower ORR and major responses. Their responses lasted on average 4 years, which still favorably compares to other treatments used in previously treated patients. In contrast, those patients without a MYD88 mutation showed poor response activity and duration of response.

The high rates of response and durability of response with single agent ibrutinib were also observed in a study published in Lancet Oncology in 2017 wherein more heavily pre-treated, rituximab refractory patients received treatment. The impact of CXCR4 mutations was also observed in this study, in which WM patients with mutated CXCR4 had slower responses and slower improvements in their hemoglobin levels. A clinical trial of single agent ibrutinib in symptomatic patients with untreated WM was also reported at the 2017 ASH meeting. High levels of overall response (97%) and durable responses were also observed in this study, along with the impact of CXCR4 mutations on time-to-response and response rates. A randomized trial (iNNOVATE) comparing ibrutinib and rituximab versus rituximab in patients with symptomatic untreated and previously treated WM has been fully enrolled, and results are expected to be available in early 2018.

In comparison with other therapies used to treat WM, use of ibrutinib results in rapid responses, with a time to at least a minor response of 4 weeks. In 10% of patients, atrial fibrillation can occur but does not limit ibrutinib continuance in most patients. Risk of bleeding with procedures and concurrent use of blood thinning medications remain a concern, as do decreased blood counts in heavily pre-treated patients. Unlike rituximab-based therapies, IgA and IgG levels remain unchanged with ibrutinib, and infectious complications are uncommon. Persistent low-grade musculoskeletal, skin, and gastrointestinal toxicities can occur with ibrutinib and result in dose reduction and treatment cessation in some WM patients. Withholding ibrutinib for procedures or adverse events can lead to rapid increases in serum IgM, constitutional (fevers, chills, sweats) complaints, and decreased hemoglobin, signifying that residual tumor cells have the potential to rapidly propagate disease. For these reasons, ibrutinib therapy should not be stopped unless medically indicated. These findings contrast with what is typically observed following rituximab-based therapy, wherein the typical post-treatment course is disease latency, followed by slow disease recurrence over time.

The lack of CR observed in WM patients on ibrutinib, regardless of MYD88 or CXCR4 mutation status, also indicates an “intrinsic” resistance. Signaling studies of surviving WM cells in patients on prolonged ibrutinib therapy (>6 months) showed that while BTK activity was suppressed, an alternative pathway by the IRAK1/IRAK4 proteins was not effected by ibrutinib and contributed to WM cell survival. “Acquired” ibrutinib resistance (i.e. resistance after the patient responds) is also an emerging problem in WM patients. Mutations that prevent ibrutinib from binding to BTK were identified in half of a handful of WM patients who progressed after responding to ibrutinib. Nearly all these patients had mutated CXCR4. MYD88 mutated WM cells engineered to express one of these BTK mutations showed ibrutinib resistance, reflecting the importance of these mutations as contributors of “acquired” resistance.

While in most WM patients deep responses and long-term disease control can be attained with prolonged ibrutinib therapy, those without MYD88 mutations and those with mutated MYD88 and CXCR4 may be at higher risk of either non-responsive disease, suboptimal responses, or “acquired” resistance in the latter. “Intrinsic” resistance in patients with mutated MYD88 and no CXCR4 mutations can also lead to rapid disease progression if ibrutinib is stopped. For these reasons, a strategy dependent on disease control with ibrutinib alone should not be viewed as optimal for WM. Many insights into WM cancer biology, as well as mutated MYD88 and CXCR4 signaling, have provided important clues for rational drug development aimed at eradicating the malignant clone in WM.

As previously mentioned, one of the important limitations of rituximab is sparing of IgM-producing plasma cells that do not express CD20. These cells make up 10-15% of the WM clone. Daratumumab targets CD38, highly expressed on WM plasma cells. Strategies using daratumumab and rituximab, as either dual therapy or with other therapeutics, are of interest and offer a means to target the entire WM malignant clone. A Phase II study of daratumumab in previously treated WM has been initiated (www.clinicaltrials.gov NCT03187262) and will offer critical insights into targeting the plasma cell compartment, along with the potential to combine rituximab with other agents aimed at expunging the entire WM clone.

As mentioned before, a randomized study (iNNOVATE) is also examining the combination of ibrutinib with rituximab (www.clinicaltrials.gov NCT02165397). Since activating CXCR4 mutations promote ibrutinib resistance, a clinical trial combining the CXCR4-blocking antibody ulocuplumab with ibrutinib has also been initiated at our institution in WM patients with CXCR4 mutations (www.clinicaltrials.gov NCT03225716).

Compounds that inhibit IRAK1/IRAK4 are also under intense pre-clinical investigation and are aimed at overcoming intrinsic ibrutinib resistance in MYD88 mutated diseases. A research project to develop IRAK inhibitors is being supported by the IWMMF and has produced highly selective and potent IRAK inhibitors that show synergistic WM cell killing when combined with ibrutinib.

BCL-2 is a protein that is overexpressed in WM cells and blocks the killing effects of ibrutinib. The BCL-2 inhibitor, venetoclax, showed major response activity in 4 WM patients treated in a Phase I study. A clinical trial examining venetoclax in previously treated WM patients is near complete enrollment (www.clinicaltrials.gov NCT02677324) and will inform a planned successor study of venetoclax with ibrutinib.

Lastly, other BTK inhibitors are currently under investigation (e.g. BGB-3111, acalabrutinib, GS-4059) in WM, and a study comparing the efficacy and safety of BGB-3111 directly to ibrutinib is currently enrolling subjects (www.clinicaltrials.gov NCT03053440). The activity and safety of these other BTK inhibitors will provide important insights on the use of this class of agents and help to better determine their positioning relative to other therapeutics used to treat WM.

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