Treatment options for relapsed Waldenström’s Macroglobulinemia

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Take home messages
- There are several treatment approaches available for relapsed WM patients.
- The choice of treatment for relapsed patients should be adapted to the fitness of the patient, previous therapy and the duration of response after last treatment.
- Rituximab-based regimens, Bortezomib containing regimens, and Ibrutinib are well tolerated and efficient treatment options in relapsed WM patients.
- The future goal is the development of chemotherapy-free approaches which are active independent from the genotype and are applied for a limited duration of time.

Introduction

Waldenström’s Macroglobulinemia (WM) belongs to the group of indolent B-Non-Hodgkin’s lymphomas, characterized by a mostly slowly progressing clinical course and recurrent relapses. There is no established treatment approach with curative potential so far and all patients with WM will ultimately relapse. Thus, salvage approaches are of key clinical relevance. Ideally, these salvage regimens should control disease without compromising quality of life. There are different treatment options in relapsed/refractory WM. The choice of treatment depends on many factors such as fitness of the patient, pretreatment and duration of response before the relapse. Treatment has to be tailored according to the individual patient’s situation. Fortunately, recent years have seen considerable progress in establishing new treatment concepts, first to name the introduction of the BTK inhibitor Ibrutinib.

When discussing the management of relapsed patients with WM, we have to be aware that there is no common standard approach. Therefore, these patients should be included in clinical trials, testing novel strategies and compounds, whenever possible (http://www.ccwm.eu/).

Current state of the art

When a patient relapses, a thorough diagnostic workup should be performed as described in detail in published guidelines. Relapsed patients should be only treated if they show criteria as defined by the Treatment recommendations from the Eighth International Workshop on Waldenström’s Macroglobulinemia such as lymphoma related symptoms, IgM values putting patients at risk to develop hyperviscosity (eg serum IgM > 60 g/l) or hematopoietic insufficiency. Thus, also in the relapsed situation, a watch and wait strategy is recommended.

If the patient is in need of treatment, the duration of response after the last treatment is critical for selecting the appropriate salvage treatment. Single-agent Ibrutinib is the treatment of choice for patients who have relapsed within 12 months from chemotherapy, including rituximab-refractory patients. Ibrutinib should be given until disease progression or non-tolerated toxicity. Around 20% of the patients develop a withdrawal syndrome, with an increased incidence in the relapsed setting. Furthermore, relapses are common after Ibrutinib discontinuation. For patients who relapse >2 to 3 years after receiving a rituximab-based regimen, an alternative rituximab-based combination may be considered. If DRC was used, rituximab with either bendamustine or bortezomib (with or without dexamethasone) may be used. Rituximab with nucleoside analogs is an active but also toxic combination and therefore should be used cautiously. Bortezomb in combination with rituximab is an effective regimen and allows SC application of both drugs. For patients who achieve a prolonged remission with their primary therapy (ie, >3–4 years), re-instituting the prior regimen may also be considered. For fit patients with a clinically aggressive course, high-dose therapy with autologous stem cell transplantation (ASCT) may be considered. However, taking long-term toxicities of ASCT into account other treatment options should be considered before and ASCT should be preferentially offered to high-risk, preferentially chemosensitive patients following ≥2 relapses. Furthermore,
Salvage Approaches in relapsed WM

Figure 1. Salvage approaches in patients with relapsed WM (adapted from (1)).

ASCT should not be used in patients responding to and tolerating Ibrutinib.

There are several clinical reports indicating that also allogeneic transplantation is feasible and effective in WM. A large series was reported by the EBMT7: The patients received allograft by either myeloablative (n = 37) or reduced-intensity (n = 49) conditioning. The patient population was highly selected with a median age of 49 years, and 47 patients had 3 or more previous lines of therapy. Fifty-nine patients (68.6%) had chemotherapy-sensitive disease at the time of allogetic SCT. The relapse rates at 3 years were 11% for myeloablative, and 25% for reduced-intensity conditioning recipients. The 5-year PFS and OS for WM patients who received a myeloablative allogetic SCT were 56% and 62%, and for patients who received reduced intensity conditioning 49% and 64%, respectively. However, to the end allogeneic transplantation is associated with a substantial risk for treatment related morbidity and mortality. Based on this allogeneic transplantation should not be considered in Ibrutinib-naïve patients, but could be considered in patients with relapsed/refractory WM to immunochemistry and Ibrutinib, preferably within clinical trials.

WM is a disease of the elderly and many patients suffer from co-morbidities, excluding the application of dose intense treatments. Thus, in particular, in the elderly patient, Ibrutinib is an excellent choice also in patients with longer remission duration. Ibrutinib as single agent has less activity in patients with mutated MYD88 and also particularly in patients with longer remission duration. Ibrutinib improves outcome in these genotypes compared to wild-type. A recent study has shown that addition of Rituximab to Ibrutinib ± Rituximab and also particularly in patients with MYD88 mutations WM falls into three genotypes: the genotypes MYD88WT/CXCR4WT, MYD88WT/CXCR4MT, and the genotype MYD88MT/CXCR4WT. Importantly, Ibrutinib showed substantial less activity in MYD88WT/CXCR4MT, but also in MYD88WT/CXCR4MT genotypes, demonstrating that there is the need to develop concepts to improve Ibrutinib activity in the CXCR4 mutated and MYD88WT/CXCR4WT patients. In a recently published prospective phase III clinical trial patients with treatment naïve or relapsed WM were randomized between Ibrutinib/Rituximab vs Placebo/Rituximab. The primary end-point PFS was significantly improved in the Ibrutinib arm with a risk reduction for progression of 80%. The combination of Rituximab/Ibrutinib was also well tolerated and no new toxicity signals were discovered. Of note, the Rituximab/Ibrutinib combination was able to induce responses largely independent of the genotype and also the PFS was comparable between the different genotypes. Patient numbers were limited in these subgroups, follow-up is still short for this indolent disease and the duration of treatment was imbalanced with a short 2 times 4-weekly application in the Placebo/Rituximab arm vs infinite treatment in the Ibrutinib arm. However, these data indicate that it is possible to develop chemotherapy-free concepts also for WM patients with unfavorable genotype.8 Another potential approach is the combination of proteasome inhibitors with Ibrutinib as a phase II trial with carfilzomib demonstrated genotype independent activity in WM.11 Prospective studies will prove this concept in the near future. Another approach is the BCL2-inhibitor Venetoclax: in a phase II study in relapsed/refractory WM patients, this compound was well tolerated and demonstrated high activity with OR of 87% and a major response of 80%. However, activity of Venetoclax was lower in patients with the MYD88MT/CXCR4MT genotype and also in patients previously treated with Ibrutinib.12 One of the major challenges will be to develop concepts for WM patients after Ibrutinib failure. Venetoclax is one attractive candidate and as mentioned before had activity in patients previously treated with Ibrutinib achieving 80% overall response and 60% major response. Follow-up is still short and patient number was limited in this trial, so that the role of Venetoclax has still to be defined in this therapeutic situation.12 Currently tested therapies include targeting of the CD38 antibody expressed on plasmacytic WM cells with Daratumumab or impairing CXCR4 activity by anti-CXCR4 antibodies. So far it is unclear, whether these approaches are effective and whether their efficacy is compromised by previous Ibrutinib treatment.

In summary, there are several effective and well tolerated treatment options for relapsed WM patients available today. Treatment should be selected according to the duration of response to the previous treatment, the nature of the previous treatment(s) and the fitness of the patient. The goal is to develop chemotherapy-free approaches, which act in all genotypes and do not need permanent application. Ibrutinib is a major step in this
direction and has grossly changed the treatment landscape in WM. Ongoing and future trials aim at establishing Ibrutinib-based approaches, which act independently from the genotype and only need timely limited application.

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