blood advances

POINT Disease control should be the goal of therapy for WM patients

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This article has a companion Counterpoint by Treon and Castillo.

Waldenström's macroglobulinemia (WM) is a unique low-grade lymphoma in several aspects: the symptoms and complications of WM are not only related to the tumor burden, but also to the physicochemical and immunologic properties of the monoclonal immunoglobulin M (M-IgM) produced by the lymphoplasmacytic cells. Treatment is aimed at reducing lymphoplasmacytic infiltration and the subsequent decrease of M-IgM to ameliorate symptoms and complications associated with the expansion of the neoplastic cells and of the M-IgM. Setting the strategy of therapy for WM includes weighing the heterogeneity of clinical presentation, symptoms, and complications, whereas, because patients with WM are often of advanced age, treatment decisions may critically depend on patients' comorbid conditions, with toxicity risks often being the primary consideration.[1] The ultimate goal of cancer therapy is to cure; in contrast to high-grade lymphomas, acute leukemias, chronic myeloid leukemia, or myeloma, a complete eradication of the disease is probably not feasible with the current therapies for WM. The term "disease eradication" has not been defined in WM; a more accurate term is complete response (CR), in which no malignant cells or their products (M-IgM) are detected by conventional methods such as immunohistochemistry and immunofixation.[2] This is closer to a disease burden below the limit of detection rather than "disease eradication."

New approaches incorporating the presence and levels of MyD88 L265P as a marker of residual disease, similar to *bcr-abl* in chronic myeloid leukemia, are under investigation. Nonetheless, even conventional CR is uncommon with current treatments observed in $<$10% to 15% of patients treated with conventional regimens: for most patients with WM in remission, the disease is still detectable by monoclonal IgM and tumor cells in the bone marrow. Despite the low CR rates, WM usually follows a protracted course and the median survival of symptomatic patients is more than 7 to 10 years,[3] and it is common to see substantial symptom improvement even with minor responses, as detected by reduced IgM levels (as low as 25% to 50%) or with significant residual disease in the bone marrow.[4] When disease symptoms have improved and this symptom-free period lengthens, we can assume a condition of "disease control," which may last for several years.

Two of the most effective therapies for WM (monoclonal anti-CD20 antibodies and BTK inhibitors) cannot induce CR as single agents, but they have been associated with prolonged periods of disease control and long treatment-free intervals, but also with low short- and long-term toxicity. The depth of response has not been consistently associated with better outcomes and large-scale data regarding the impact of deeper responses in long-term survival are lacking. A short course of rituximab alone was associated with prolonged periods of disease control, with very limited toxicity[5,6] and no significant difference between patients who achieved major or minor responses, both in terms of progression-free survival (PFS) and of overall survival (OS).[6] Combination therapies, including immunotherapy (anti-CD20) tend to induce higher CR rates, but these are still low. With the dexamethasone, rituximab, and cyclophosphamide regimen, a relatively small subset of patients achieved a very good partial response (VGPR; defined as $\geq$90% reduction of monoclonal IgM) but still very few CR. These patients had prolonged PFS compared with patients who achieved a PR; however, there was no difference in the OS between patients with a partial response (PR) or VGPR/CR.[7] Only patients who failed to achieve at least a minor response during primary therapy with dexamethasone, rituximab, and cyclophosphamide (eg, patients in which therapy failed to control their disease) had worse outcomes in terms of both PFS and OS.

In another phase 2 study, among patients treated with rituximab, bortezomib, and dexamethasone, a small subset of patients achieved VGPR, very few achieved CR, and most achieved a PR; PFS was similar for patients who achieved PR or VGPR, longer than that of patients who achieved a minimal response but OS was not different for patients who achieved VGPR or PR or a minimal response.[8,9] A retrospective analysis in rituximab-treated patients indicated that CR or VGPR after rituximab-based

therapy was associated with longer PFS,[10] but the effect on OS could not be evaluated. Ibrutinib, as a single agent, is associated with very high response rates and long, maintained remissions in patients with relapsed or refractory WM. With PR rates >70% even in rituximab-refractory patients, but without CRs, symptoms resolve within few weeks and 18-month PFS is 70% to 86%[4,11]; median may exceed 3 to 4 years.

Thus, although these therapies cannot eradicate, they can effectively control the disease and provide long remissions with low toxicity, during which patients with WM live with their disease in a symbiotic fashion: malignant cells and/or their products (M-IgM) are present, but there are no symptoms of the disease (B-symptoms such as fatigue, anemia, hyperviscosity, thrombocytopenia) after therapy. The "symbiosis" of WM and the patient is not only evident in patients who have received therapy, but starts much earlier: during the asymptomatic WM stage, patients do not have symptoms related to their disease despite bone marrow infiltration and IgM production.[12] Such individuals may live for several years without developing symptoms and may not progress to symptomatic WM for decades.[13,14] Thus, a "controlled disease" state is common before additional events causes symptomatic WM. Based on this evidence, therapies aiming at long, maintained disease control, with minimal or low toxicity, provide a long survival and are reasonable primary strategies for most patients.

Nonetheless, is CR and disease eradication achievable in WM? We are limited by available treatments, but also, although disease eradication is a goal for every malignancy, toxicities and other costs should be balanced by the expected benefits. Is additional toxicity associated with combinations of effective drugs and extended duration of therapy justified? Retrospective data indicate that maintenance with rituximab in WM may increase the probability of CR and prolong PFS, but at the expense of prolonged therapy, financial cost, and additional toxicity without clear evidence of survival benefit.[15] Consolidation may also increase CR rates: high-dose therapy supported with autologous stem cell transplantation is a toxic therapy but it induced CR in patients with chemosensitive relapse.[16] However, CR (defined by immunofixation negativity) was associated with marginally prolonged PFS, without any difference in the OS,[16] which was similar to the expected PFS and OS achieved today by orally available BTK inhibitors, even in rituximab-refractory patients.[4,11] Are there other options to achieve prolonged CR and disease eradication? Data regarding the use of allogeneic hematopoietic stem cell transplant are limited, coming from retrospective case series and including selected patients mostly with refractory disease, but a graft-versus-lymphoma effect seems to exist[17-21] and, in some patients, may lead to real eradication of the disease, with survival curves leveling a few years posttransplant.[17-19] The complications of this approach are still high, however, and transplant-related mortality is still significant.[17-19]

Many of the patients with symptomatic WM are elderly, and age and other frailty-related conditions limit life expectancy. For such patients, the benefits brought by new and effective treatments may never be evident; rapid symptom relief and control of the disease with low toxicity are the reasonable goals of therapy. For young patients with WM, however, a different strategy may be justified. In such patients, several different lines of therapies will probably be required over the years to control their disease, with the risk of developing resistance to therapy, disease transformation, or complications associated with the long exposure to various therapies. Another group of patients for which disease control may not suffice are those in which the toxicity of the M-IgM protein is significant (for example, in patients with IgM-related amyloidosis), and even low residual amounts of the M-IgM can be very toxic. In such patients, a strategy incorporating a "decisive hit" in the disease may be more appropriate.

New treatment options, still under investigation, may change our approach. Combinations targeting different aspects of the disease biology (eg, anti-CD20 with BTK inhibitors, proteasome inhibitors) could become a "total therapy" approach able to induce deep responses and perhaps disease eradication, but, such data are not available and toxicities are unknown. Anti-bcl2 therapy with venetoclax induces deep responses in chronic lymphocytic leukemia resistant to current therapies; data in WM are still to be presented but may be a new option[22] and part of a future "disease eradication strategy." Immunotherapy targeting immune synapse or anti-CD38 targeting the plasma cell component of the disease may also become part of future treatments.

Until we have safe "disease-eradicating" therapies, for most patients with symptomatic WM, aiming at long maintained disease control prolongs survival and provides a good quality of life, with minimum short- and long-term toxicities. For patients with aggressive disease, those who are very young, and those for which disease control may not be enough, we definitely need alternative strategies aiming at disease eradication, and we should continue our efforts to develop more effective and safer therapies for the ultimate goal: to reach to a cure.

Authorship

Contribution: E.K. and M.A.D. reviewed the literature and wrote the manuscript.

Conflict-of-interest disclosure: E.K. reports funding from Genesis Parma, Takeda, Janssen Amgen, and Prothena. M.A.D. reports funding from Novartis, Janssen, Celgene, Takeda, BMS, Genesis Pharma, and Amgen.

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DOI 10.1182/bloodadvances.2017005645