How we treat Waldenström's macroglobulinemia

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Waldenström's macroglobulinemia (WM) is a lymphoplasmacytic lymphoma which produces monoclonal immunoglobulin M (IgM). Over the last decade, new treatment modalites have been developed for the management of this disorder. Our objective is to provide treatment recommendations for WM. A review of published reports was facilitated by a MEDLINE computer search and by a manual search of Index Medicus. Other sources included abstracts and conference proceedings. Most patients with WM who are diagnosed by chance without symptoms should not be treated. Initiation of treatment should not be based on level of serum monoclonal protein *per se*. The presence of cytopenia, significant adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy or cryoglobulinemia indicates the need for treatment. The main choices for primary treatment of symptomatic patients with WM include alkylating agents, the nucleoside analogs fludarabine or cladribine and the monoclonal antibody rituximab or combinations of these programs. There are no data from prospective randomized studies to recommend the use of one program over another. Nevertheless, the need for rapid disease control may favor the use of nucleoside analogs, whereas the presence of significant cytopenia may favor rituximab. High dose therapy with autologous stem cell transplantation may induce responses even in patients with resistance to all three class of agents. It may be prudent to avoid nucleoside analogs in patients who are candidates for high dose therapy. Despite the lack of randomized trials, a rational approach to the treatment of patients with WM is possible. Several factors, including the presence of cytopenias, need for rapid disease control, candidacy for autologous stem cell transplantation, age and co-morbid conditions, should be taken into consideration when choosing the most appropriate primary treatment.

Key words: Waldenström's macroglobulinemia, practice guidelines, rituximab, cladribine, fludarabine, chlorambucil.

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Waldenström's macroglobulinemia (WM) is a distinct clinicopathological entity confined to patients with lymphoplasmacytic lymphoma involving the bone marrow and with serum monoclonal immunoglobulin M (IgM).[1,2] This abnormality has also been described in some patients with lymph node patterns that are consistent with marginal zone lymphoma or mantle cell lymphoma, with phenotypic or cytogenetic features that overlap with those of WM. The rare occurrence of monoclonal IgM with large cell lymphoma probably reflects transformation of a low grade lymphoma.[2] Serum monoclonal IgM should be measured by serum protein electrophoresis because nephelometric quantification of immunoglobulins will overestimate the level of monoclonal protein with substantial variability between laboratories. The serum levels of IgM vary widely in WM and the diagnosis of this disorder should be made regardless of IgM concentration provided that there is demonstration of bone marrow infiltration by lymphoplasmacytic lymphoma as defined by the Revised European-American Lymphoma (REAL) classification and World Health Organization (WHO) criteria.[2] This is defined as a clonal proliferation of small lymphocytes showing evidence of plasmacytoid/plasma cell differentiation. The bone marrow smear shows a mixture of small lymphocytes, lymphoplasmacytoid cells and mature plasma cells. The percentage of these cellular populations may vary from patient to patient. There is frequently an increase in mast cells.[3,4] A bone marrow biopsy is considered necessary for the initial assessment of patients. The pattern of marrow infiltration may be interstitial or

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diffuse. Well-defined nodular infiltrates or a paratrabecular pattern are unusual.[2] In 90% of patients with this marrow morphology immunophenotypic analysis shows strong expression of surface IgM, of CD19 and CD20 but not CD10 or CD23. Cells showing plasmacytic differentiation express CD138 and monotypic cytoplasmic IgM. Clonal expression of CD5 and CD23 may be seen in 10% of patients and should not preclude the diagnosis of WM.[5]

Most patients with the diagnosis of WM have symptoms attributable to tumor infiltration and/or monoclonal IgM. These patients require treatment in order to control symptoms and reverse or prevent complications of the disease. Over the last years, however, an increasing number of patients who fulfill the diagnostic criteria of WM are diagnosed by chance. Despite the presence of lymphoplasmacytic infiltration of the bone marrow these patients have no symptoms or signs attributable to the underlying lymphoma or to the monoclonal IgM. These patients should be classified as having *asymptomatic Waldenström's macroglobulinemia*.[6]

The detection of monoclonal IgM in the serum is not synonymous with the diagnosis of WM. Several individuals are diagnosed with asymptomatic monoclonal IgM of less than 30g/L, a hemoglobin concentration exceeding 120g/L, no morphological evidence of marrow infiltration and absence of symptoms or signs attributable to tumor infiltration or to monoclonal IgM. This condition is classified as *IgM monoclonal gammopathy of undetermined significance (IgM-MGUS)*.[7]

Finally some patients present with a complication caused by the monoclonal IgM, such as peripheral neuropathy, cold agglutinin disease, cryoglobulinemia or amyloidosis, but the concentration of monoclonal IgM is usually low, there is no evidence of lymphomatous tissue infiltration and the bone marrow is usually morphologically normal. When there is clinical suspicion of these diseases, immunofixation should be done to unmask a possible very low IgM peak that is undetectable by standard serum protein electrophoresis. Presumably, in such patients, specific properties of the monoclonal IgM caused symptoms even without evidence of overt WM. These conditions can be classified under the diagnosis of *IgM-related disorders*.[2]

The decision to treat or not

Individuals with IgM-MGUS should not receive any treatment but should be followed serially with physical examinations, blood counts, biochemichal surveys and electrophoretic studies. Recent data suggest that individuals with an IgM MGUS may have a higher risk of developing a malignant proliferative disorder than do individuals with IgG MGUS.[7] In a similar manner, patients with asymptomatic WM should be recognized at diagnosis and not treated because they may remain stable for several years. Relatively few studies have assessed the prognosis of such asymptomatic patients. It appears that the median time to progression is approximately 7 years. However the presence of both mild anemia and of relatively high serum monoclonal protein levels (>30g/L) predict the need to start treatment within one year from diagnosis.[8,9]

Criteria for defining disease progression in asymptomatic patients with WM have not been standardized. Disease progression may be defined by the earliest of either symptoms (fever, sweats, weight loss), an IgM-related complication (hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin anemia), bulky lymphadenopathy or splenomegaly, anemia (hemoglobin <100g/L), thrombocytopenia (platelet count<100×10^9/L) or evidence of disease transformation.[10] Initiation of therapy should not be based solely on serum monoclonal IgM levels, since these may not correlate with clinical manifestations of IgM. Nevertheless, a serum monoclonal protein level >50 g/L places patients at considerable risk of hyperviscosity and requires a thorough history, physical and fundoscopic examinations in order to diagnose early symptoms and signs of hyperviscosity promptly and thus initiate treatment. Table 1 shows clinical and laboratory parameters which may justify initiation of treatment in patients with WM. Finally patients with the diagnosis of an IgM-related disorder usually require treatment both

Table 1. Clinical and laboratory criteria for initiating therapy in Waldenström's macroglobulinemia.

Hemoglobin 10 g/dL
Platelet count <100×10^9/L
Immune hemolytic anemia
Immune thrombocytopenia
Bulky adenopathy
Significant organomegaly
Fever, night sweats, weight loss, fatigue
Symptoms and signs of hyperviscosity
Symptomatic peripheral neuropathy
Symptomatic nephrotic syndrome
Amyloidosis
Symptomatic cryoglobulinemia
Evidence of disease transformation

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to reduce the circulating and/or deposited IgM and to suppress the occult malignant clone which produces the macroglobulin.

Treatment

Plasmapheresis

Plasmapheresis, conducted with a continuous blood flow separator with albumin and saline replacement, is very effective in reducing the amount of circulating IgM rapidly in patients with hyperviscosity syndrome, because 80% of IgM is intravascular. Lowering the serum IgM concentration with plasmapheresis can significantly reduce serum viscosity and can lead to resolution of hyperviscosity-related symptoms. Reductions of IgM by an average of 35% decrease plasma viscosity from 5 to 2.1.[11,12] Concomitant administration of systemic treatment is required in all patients with symptomatic hyperviscosity in order to suppress the underlying malignant process, although the use of plasmapheresis alone may be justified in patients resistant to systemic treatment who suffer primarily from hyperviscosity. Intensive plasmapheresis has also been used successfully in some patients with an IgM-related disorder such as peripheral neuropathy, cryoglobulinemia and cold agglutinin disease. In such patients, serial plasmaphereses may reduce the monoclonal protein, allow symptomatic improvement and justify the subsequent administration of systemic therapy to achieve long-term control.

Systemic treatments

Alkylating agent-based treatment

The standard first-line treatment for patients with WM has long been based on alkylating agents such as chlorambucil, melphalan or cyclophosphamide. Single agent chlorambucil either on a daily basis at low doses or intermittently at higher doses has been the drug tested in most series of patients with WM. Approximately 50% of patients achieve a partial response (defined as a reduction of at least 50% of the serum monoclonal protein) and complete responses are rare. A recently reported randomized study which compared chlorambucil 0.1 mg/kg daily continuously with chlorambucil 0.3 mg/kg for one week every 6 weeks indicated similar response rates and similar median survivals at 5.4 years.[13] There is no evidence that the addition of corticosteroids to chlorambucil improves survival. However corticosteroids may be added in patients who present or develop autoimmune cytopenias.[6] Several phase II trials have attempted to improve response rates and survival by administering combinations of alkylating agents with or without a vinca alkaloid, a nitrosurea or an anthracycline. Although no prospective randomized trials have compared these more complicated regimens to single agent chlorambucil, the reported response rates and survival times do not indicate an obvious benefit from the combinations.[6] After treatment with alkylating agent-based therapies, the rate of IgM reduction is slow and several months are required to determine the chemosensitivity of the disease. In most studies alkylating agents have been administered for one to two years and have exposed the patients to the risk of myelodysplasia or secondary leukemia.

Table 2. Primary treatment of WM with cladribine.

Series	*Number of patients*	*Response n. (%)*
Dimopoulos[16]	26	22 (85)
Delannoy[17]	11	8 (73)
Fridik[18]	10	9 (90)
Lewandowski[19]	11	7(64)
Hampshire[20]	14	9 (64)
Total	72	55 (76)

Nucleoside analog-based treatments

Over the last 15 years the nucleoside analogs fludarabine and cladribine have been used for the primary treatment of several lymphoproliferative disorders including WM. A small European multicenter study included 20 previously untreated patients who received intravenous fludarabine at a dose of 25 mg/m^2 daily for 5 consecutive days every 4 weeks for up to 6 courses. Partial response or better occurred in 79% of patients and the median time to progression was 40 months.[14] The largest fludarabine trial was performed by the South West Oncology Group and included 118 previously untreated symptomatic patients. A reduction of monoclonal IgM was observed in 40% of patients including a complete response in 3%. The median time to response was 2.8 months. The median event-free and overall survivals were 3.5 years and 7 years, respectively.[15]

Cladribine has also been administered to previously untreated patients either at a dose of 0.1 mg/kg/day as a 7-day continuous intravenous infusion or at a dose of 0.12 mg/kg/day in 2-hour intravenous infusion for 5 consecutive days at monthly intervals. Objective responses were seen in 64% to 90% of patients[16-20] (Table 2). The number of cycles administered in these studies varied considerably but

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Table 3. Salvage treatment of WM with fludarabine or cladribine.

Series	Number of patients	Response n. (%)
Fludarabine		
Dimopoulos[22]	26	8 (31)
Zinzani[23]	12	5 (42)
Leblond[24]	71	21 (30)
Dhodapkar[15]	64	22 (34)
Total	173	56 (32)
Cladribine		
Dimopoulos[26]	46	20 (45)
Betticher[27]	24	9 (38)
Delannoy[17]	16	8 (50)
Lewandowski[19]	14	9 (64)
Hampshire[20]	19	12 (63)
Total	119	58 (49)

**These trials combined varying percentages of patients with primary resistant disease, patients who had relapsed off therapy and patients in resistant relapse.*

Table 4. Treatment of WM with rituximab.

Series	Number of patients	Response n. (%)
Byrd[28]	7	3 (43)
Foran[29]	7	2 (29)
Treon[30]	30	8 (27)
Dimopoulos[31]	52	23 (44)
Gertz[33]	69	19 (28)
Treon[34]	29	14 (48)
Total	194	69 (36)

significant tumor reduction has been documented with as few as two cycles of cladribine. The median time to response has ranged from 1.2 months to 5.8 months in the various studies. At the MD Anderson Cancer Center, oral cyclophosphamide was added to subcutaneous cladribine and 2 courses of this combination was administered to 37 previously untreated patients. At least a partial response was documented in 84% of patients and the median duration of unmaintained responses was 36 months. In 80% of relapsing patients the disease could be controlled again by resumption of therapy.[21]

There have been no randomized trials comparing a nucleoside analog versus an alkylating agent as primary treatment for WM. However a report from the MD Anderson Cancer Center indicated that the response rate of patients treated with cladribine-based regimens was higher than that obtained after treatment with alkylating agents. Furthermore, the cause-specific median survival after treatment with cladribine is longer than that noted previously.[21]

Both fludarabine and cladribine have been administered to patients in whom primary treatment with an alkylating agent had failed. Several phase 2 studies have shown that fludarabine is active in approximately 30% of patient with pretreated WM[22,23,24,15] (Table 3). The activity of this agent was confirmed in a randomized trial which compared fludarabine to cyclophosphamide, doxorubicin and prednisone (CAP). At least a partial response was documented in 28% of fludarabine-treated patients and in 11% of CAP-treated patients (p=0.019). Furthermore, the median time to treatment failure was significantly longer in patients treated with fludarabine.[26] Cladribine has been administered to more than one hundred patients with pretreated WM. The rate of objective responses ranged from 38% to 63% in the different studies[26,27,17,19,20] (Table 3). The response rate is higher and the duration of the response is longer with either nucleoside analog when the analog is given to patients with primary refractory disease or to patients relapsing off therapy rather than to patients with disease in resistant relapse.

Monoclonal antibody therapy

Rituximab is a chimeric human/mouse antibody that binds avidly to the CD20 antigen which is almost invariably expressed on WM cells. Several studies have indicated that when rituximab is administered at a dose of 375 mg/m^2/week intravenously for 4 weeks 30% to 40% of patients achieve at least a partial response[28-34] (Table 4). Furthermore additional patients with a lesser reduction of monoclonal protein levels appear to benefit from rituximab with improvement of cytopenia and reductions in organomegaly and lympadenopathy. This agent appears to be equally effective in previously untreated and pretreated patients.

Rituximab is well tolerated although mild infusion-related symptoms such as fever, chills and headaches are seen in approximately one-quarter of patients. Treatment with rituximab is not associated with myelosuspression and is not toxic to stem cells. Thus, this agent is an appropriate treatment for patients who present or develop cytopenias and for those who are candidates for high-dose therapy. The time to respond to rituximab is slow and exceeds 3 months on the average. Furthermore, the time to best response may require up to 18 months. In approximately 30% of patients an increase of serum IgM may be noted shortly after the initiation of rituximab.[31,35] This *IgM flare* may be sustained for up to 4

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Table 5. Treatment of WM with high-dose therapy and autologous stem cell transplantation.

Series number	Number of patients	Complete response n. (%)
Desikan[37]	8	100 (13)
Anagnostopoulos[38]	4	75 (0)
Tournilhac[39]	18	95 (11)
Munshi[40]	6	83 (0)
Seyfarth[41]	10	100 (20)

months and it is important to note that it is not associated with treatment failure since in most patients, serum IgM will return to its baseline value and will decrease. In some studies an inferior response to rituximab has been noted when the baseline serum monoclonal protein exceeds 40 g/L or the total IgM exceeds 6000 mg/dL.[31,34] However, a large American study did not show a correlation between baseline serum monoclonal protein level and the probability of response to rituximab.[33] Until this issue is clarified, we recommend that single agent rituximab should be used with caution in patients at risk of hyperviscosity syndrome.[32] Rituximab has shown promise in the symptomatic improvement of peripheral neuropathy associated with WM or in the context of an IgM-related disorder.

The combination of rituximab with chemotherapy is being actively investigated. Weber *et al*. added rituximab to the cladribine and cyclophosphamide combination and administered this regimen to 17 previously untreated patients with WM. They observed a partial response in 94% of patients including a complete response in 18%. With a median follow-up of 21 months, no patient has relapsed.[21] A similar experience has been reported with the combination of fludarabine and rituximab.[36]

High-dose therapy and transplantation

There is limited experience with the use of high-dose therapy supported by autologous stem cell transplantation (ASCT) in the management of WM[37-41] (Table 5). This limited experience is partly a consequence of the high frequency of patients aged >70 years, the high response rate and prolonged remissions with current therapies, coupled with the 20-25% fatality from unrelated diseases. In most series, patients were treated during a late phase of their disease after refractoriness to conventional chemotherapy had developed. High-dose therapy has consisted of chemotherapy alone such as melphalan or BEAM or a combination of chemotherapy with total body irradiation. This modality induced objective responses in the majority of patients including several patients who had been resistant to several regimens of standard chemotherapy. In view of the small number of patients included in each series and because patients were treated at various phases of their disease, it is difficult to assess the duration of response after ASCT. Stem cells should be collected before exposure (or after limited exposure) to nucleoside analogs in potential candidates for ASCT. Until more data become available, patients who should be considered for high dose therapy are those under the age of 70 with progressively shorter remissions or with resistant disease whose prior therapy has been limited to permit autologous blood stem cell collection. Prospective randomized trials are needed in order to assess the potential benefit of high dose therapy as first line treatment in patients with WM.

The experience with allogeneic transplantation is even more limited. Complete responses are more frequent than with ASCT but the treatment-related mortality is around 40%. This procedure should be restricted to young patients with available siblings and with WM that is progressing despite treatment with all the previously described treatment modalities.[42,43]

Biological agents

Thalidomide

In view of the activity of thalidomide in multiple myeloma, this agent has been administered to patients with WM. Single-agent thalidomide was associated with an objective response in 25% of patients. However, several side effects such as constipation, weakness and peripheral neuropathy were noted in most patients. The combination of clarithromycin, low-dose thalidomide and dexamethasone was active in about 30% of patients.[44] However, without randomized trials it is hard to interpret whether the addition of clarithromycin has any added benefit over thalidomide and dexamethasone. This treatment may be administered to patients in whom other more active and less toxic agents have failed.

Bortezomib

The proteasome inhibitor bortezomib has significant activity in refractory and relapsed myeloma. Clinically relevant doses of bortezomib induced cell death of the WM-WSU cell line model and primary tumor cells freshly isolated from WM patients including patients refractory to nucleoside analogs and rituximab.[45] Furhtermore, this drug has been administered to a few patients with WM and preliminary evidence suggests that is clinically effective *in vivo*.[46]

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Table 6. Primary treatment of WM: advantages and disadvantages of the three main agents used.

	Response	*Time to Response (months)*	*Duration of treatment (months)*	*Cost*	*Myelosuppression*	*Opportunistic infections*	*Stem cell toxicity*	*Miscellaneous*
Chlorambucil	50%	> 6	12-24	low	moderate	no	yes	secondary leukemia
Nucleoside analogs	70-80%*	1.5-5	2-6	average	significant*	yes**	yes	
Rituximab	40%	3-5	1	high	none	no	no	IgM flare, less active when peaks are high

**The SWOG trial observed a 40% response rate with fludarabine; **when only 2 courses of cladribine are used, myelosuppression is moderate and opportunistic infections are rare.*

Splenectomy

Case reports and small series of patients, in most of whom conventional chemotherapy had failed, indicate that removing a significantly enlarged spleen can result in a marked decrease of serum monoclonal protein. Some of these remissions lasted for many years.[47,48] The removal of a major source of IgM-producing cells and elimination of hypersplenism may, in part, explain the beneficial effect of splenectomy in some patients with WM. However, massive splenomegaly is rare in WM and with currently available data it is not possible to predict how often splenectomy may be helpful.

Treatment strategies

The three main agents for systemic primary treatment of patients with WM are alkylating agents (chlorambucil), nucleoside analogs (fludarabine, cladribine) and the monoclonal anti-CD20 antibody, rituximab. There are no data from prospective randomized trials to support the use of one agent over another.[49] These agents have advantages and disadvantages which are shown in Table 6. Outside a clinical trial several factors should be taken into account when choosing the most appropriate primary treatment. These factors include the age of the patient and possible co-morbid diseases, the presence of cytopenias and especially thrombocytopenia, the presence of symptoms and signs indicative of hyperviscosity, the need for rapid disease control due to severe symptoms, significant splenomegaly or lymphadenopathy, symptomatic peripheral neuropathy and whether the patient is a candidate for autologous stem cell transplantation (Figure 1). It should be clarified that it is not currently possible to recommend upfront high-dose therapy with ASCT for a particular subset of patients with WM. Until more data are available, it may be reasonable to consider this option for a younger patient who presents with high serum β2-microglobulin and severe anemia. Despite the lack of randomized trials, some suggestions can be made: (i) for patients who present with symptoms and signs of hyperviscosity, plasma exchange should precede any systemic treatment; (ii) patients who are not and will not be candidates for high-dose therapy, any one of the three main primary treatments could be used. However, when rapid disease control is needed, cladribine or fludarabine may be preferable. For the

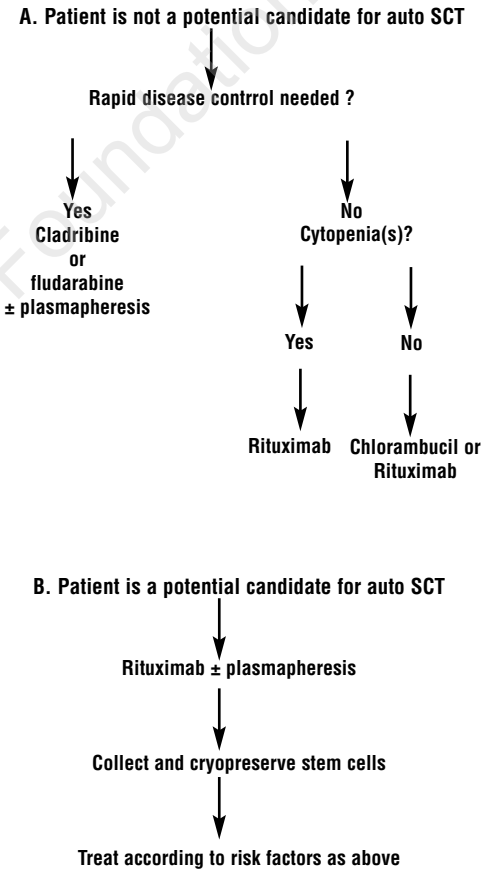

Figure 1. Primary treatment of WM.

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Table 7. Salvage treatment of WM.

Primary treatment	*Salvage treatment*
Chlorambucil	Chlorambucil if long unmaintained remission Rituximab if cytopenia and candidate for auto-SCT Fludarabine/cladribrine if rapid disease control is needed
Fludarabine/cladribine	Fludarabine/cladribine if long unmaintained remission Rituximab Chlorambucil (no data are available)
Rituximab	Rituximab if long unmaintained remission Fludarabine/cladribrine if rapid disease control is needed Chlorambucil

patient whose primary reason for treatment is cytopenia, rituximab may be indicated. In contrast, single agent rituximab should be avoided when serum IgM is significantly elevated; (iii) for patients who are candidates for high-dose therapy (or may be candidates at some point of their disease), every effort should be made to avoid exposure to nucleoside analogs prior to stem cell collection and cryopreservation. Outside the setting of a clinical trial, the administration of high dose therapy should be reserved only for patients refractory to alkylating agents, purine nucleoside analogs and rituximab. Prospective trials should assess the role of combination therapy with a nucleoside analog and rituximab with or without alkylating agents as primary treatment for WM. Preliminary data from Weber *et al.* indicate that the combination of cladribine, cyclophosphamide and rituximab produces prolonged unmaintained remissions.[21]

For patients with refractory or relapsing disease, the use of an alternate first-line agent is reasonable (Table 7). For patients who are resistant to alkylating agents either a nucleoside analog or rituximab will be effective in 30-40% of cases. If these patients are considered for high-dose therapy and transplantation, rituximab would be preferable unless stem cells have already been collected. For patients relapsing from unmaintained remission, there is a high likelihood that the same agent that induced the remission will be effective again if readministered.

For patients who develop resistance to all three class of agents, there are few valid options. Every effort should be made to collect blood stem cells and to proceed to high-dose therapy and transplantation, but this is usually not possible. Such patients are best served by being treated within the context of a phase II trial. Outside a study, thalidomide with or without dexamethasone could be tried.

Conclusions and future directions

Over the last fifteen years, significant advances have been made in the treatment of WM. Not only alkylating agents but also nucleoside analogs, monoclonal antibodies and high-dose therapy are now availbale. The judicious and sequential application of these treatments can induce disease control for long periods of time in most patients with WM. Improvements in cell and molecular biology will enhance our understanding of the pathogenesis of this disease and are likely to help us to develop targeted therapies. Meanwhile several questions remain to be answered. Macroglobulinemia has a relatively protracted course with the median survival of patients ranging from 7 to 10 years in most series. There is evidence that the transformation of WM to diffuse large cell lymphoma is occurring more frequently as the survival of patients lengthens. This transformation represents an important but treatable complication of disease evolution. Such transformation, along with deaths from unrelated diseases, may be a common cause of death.[6,21] However, several patients die from complications of WM within a few years of diagnosis. So far there is no consensus on what features at diagnosis predict short survival. There is preliminary evidence that β_2-microglobulin at diagnosis may identify patients with a poorer prognosis. Such patients would be appropriate candidates for trials that incorporate high-dose therapy with ASCT early in the course of the disease. On the other hand there is preliminary evidence that the combination of chemotherapy (nucleoside analogs in particular) with rituximab is associated with improved response rates and a relevant number of patients may achieve a complete response. Studies of large series of patients for long periods are needed to assess the impact of these combinations on the duration of unmaintained disease control and on survival related to WM, in view of the increasing frequency of death due to other causes.

All the authors participated in the design and interpretation of the literature regarding the treatment of WM. Furthermore, all have had numerous original articles published on this disease.

MAD wrote the first draft. GM, VL, AA and RA revised the manuscript critically. Finally all the authors approved the final version which was submitted. The authors declares no potential conflict of interest. There is no potentially redundant publication.

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