Plasma Cell Dyscrasias

Treatment of Waldenstrom’s Macroglobulinemia

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Opinion statement

Waldenstrom’s macroglobulinemia is defined by bone marrow lymphoplasmacytic infiltration and by production of monoclonal IgM. Treatment is employed only to symptomatic patients. Alkylating agents (chlorambucil), nucleoside analogues and rituximab are reasonable choices for primary therapy. Combination therapy either with nucleoside analogues with alkylating agents and/or rituximab or rituximab with chemotherapy such as CHOP or cyclophosphamide are also reasonable frontline treatment options for WM patients. 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-morbidities, 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 candidate for autologous stem cell transplantation. For patients with refractory or relapsing disease, the use of an alternate first-line agent is reasonable. 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 and rituximab. For patients who develop resistance to all three classes of agents, alemtuzumab, thalidomide with or without dexamethasone or bortezomib could be tried.

Introduction

Waldenstrom’s macroglobulinemia (WM) is an uncommon B-cell lymphoproliferative disorder characterized by bone marrow infiltration with lymphoplasmacytic cells and by production of monoclonal immunoglobulin M (IgM). Supportive, but not necessary, criteria for the diagnosis of WM include and intertrabecular pattern of bone marrow infiltration and a characteristic immunophenotype: surface IgM+, CD5−, CD10−, CD19+, CD20+, CD23−, CD25+, CD27+, FMC7+, CD103−, CD138+. It should be noted that between 10% and 20% of patients may be positive for CD5, CD10 and CD23 and the presence of these antigens does not exclude the diagnosis of WM [1••].

Most patients with WM have clinical manifestations and laboratory abnormalities which are related to direct tumor infiltration and to the amount and specific properties of monoclonal IgM. Such patients require prompt initiation of treatment. However, some patients who fulfill the diagnostic criteria of WM...
are being diagnosed by chance without any symptoms or signs. Such patients with asymptomatic WM, should be followed without treatment until there is evidence of disease progression. Initiation of therapy is appropriate for patients who present or develop disease-related symptoms and signs such as fever, night sweats, weight loss, fatigue, hyperviscosity, symptomatic neuropathy, amyloidosis, symptomatic cryoglobulinemia, cold-agglutinin disease, or evidence of disease transformation. Furthermore, patients with hemoglobin <100 g/l, platelet count <100 × 10^9/l, bulky adenopathy or organomegaly should be considered for treatment [2]. Initiation of therapy should not be based on serum monoclonal protein levels per se, since these may not correlate with clinical manifestations of WM. However, a serum monoclonal protein level > 50 g/L places patients at higher risk for hyperviscosity and requires a thorough history, physical examination and funduscopic examination at regular intervals.

In some patients with WM, the predominant symptoms are related to elevated serum viscosity. Because 80% of IgM is intravascular, plasmapheresis performed by an automated blood separator leads to rapid reduction in circulating IgM. Relatively small reductions in serum IgM (i.e., 20–30%) can reduce viscosity by as much as 50–60% along with resolution of hyperviscosity-induced symptoms and signs. Symptomatic improvement may therefore occur with just one exchange, though several exchanges may be required for prolonged benefit. Because hyperviscosity is a direct result of immunoglobulin production by the tumor clone, plasmapheresis should be regarded as an interim measure and administration of symptomatic therapy should be initiated as soon as possible [3••].

**Systemic therapy**

**Alkylating agent-based chemotherapy**

- For many years the standard primary therapy for patients with WM has been the administration of oral alkylating agents such as chlorambucil, melphalan or cyclophosphamide. The agent most commonly used has been oral chlorambucil. Approximately 50% of patients achieve a partial response but complete responses are rare. After treatment with chlorambucil, the rate of fall of monoclonal protein level is slow and several months are required to determine the chemosensitivity of the disease [4]. A randomized trial reported by Kyle et al. indicated that chlorambucil administered either on a daily basis at low doses or intermittently at higher doses are equally effective schedules [5]. The addition of corticosteroids does not appear to increase response rate or survival, although they may be useful in patients who present or develop autoimmune hemolytic anemia or cryoglobulinemia. Most clinicians administer chlorambucil until there is a maximum reduction of monoclonal protein and then the treatment is discontinued. With this approach most patients will receive treatment for one to 2 years. There is no evidence that maintenance therapy prolongs the survival of patients but there are data to indicate that prolonged exposure to alkylating agents increases the likelihood of myelodysplasia and secondary leukemia [6]. For patients who have responded to chlorambucil and then relapse from an unmaintained response, readministration of chlorambucil may be effective.
- Combinations of alkylating agents with or without a vinca alkaloid or a nitrosourea or an anthracycline have been used as frontline treatment of WM. Although no prospective randomized trials have compared these regimens to single agent chlorambucil, there is no evidence of benefit from these combinations [6, 7].
Nucleoside analogues-based chemotherapy

- Several studies have evaluated the role of fludarabine and cladribine in WM, while the experience with pentostatin is more limited. The largest fludarabine trial was performed by SWOG and included 118 previously untreated, symptomatic patients. At least 50% reduction of serum monoclonal protein level was documented in 40% of patients including complete response in 3%. The median time to response was 2.8 months, the median event-free survival was 43 months and the median overall survival was 84 months [8]. Several phase II studies with a relatively small number of patients have evaluated the role of cladribine as primary treatment in WM. At least a partial response was documented in 64–90% of patients [9–11]. The number of cycles of cladribine administered in these trials varied considerably, but objective responses have been documented even with only two cycles of treatment. In one study the median time to response was 1.2 months and the median time to progression was 18 months [9]. The main toxicity of nucleoside analogues is hematological which can be severe and cumulative especially when multiple courses are administered. Furthermore the profound immunosuppression associated with these agents places the patients at risk for opportunistic infections. These agents may also damage marrow stem cells and impede stem cell collection.
- Both fludarabine and cladribine have been administered to patients failing primary therapy with alkylating agents. More experience has been accumulated with fludarabine and the activity of this agent has been confirmed in a randomized trial which compared salvage treatment with either fludarabine or with cyclophosphamide, doxorubicin and prednisone (CAP); 28% of fludarabine-treated patients versus 11% of CAP-treated patients responded \(P = 0.019\) and the median time to treatment failure was significantly longer in the fludarabine arm [12]. Cladribine has shown activity in 30–40% of previously treated patients with WM [13, 14]. The hematological and immunosuppressive complications of nucleoside analogues are more pronounced in pretreated patients.

High-dose therapy (HDT) – transplantation

- Recently, HDT supported by autologous or allogeneic stem cell transplantation has been performed in patients with WM. Several patients have received autologous stem cell transplantation during various phases of their disease and most were heavily pretreated. A variety of preparative regimens have been used such as high-dose melphalan or cyclophosphamide with or without total body irradiation. This modality was relatively well tolerated with a low rate of non-relapse mortality and with a high-response rate even in patients who were clearly refractory to several regimens of standard chemotherapy [15]. Furthermore, long-lasting complete responses have been observed in several patients [16, 17]. In a series of 10 patients with advanced WM who received HDT supported by autologous stem cell transplantation, there was a 60% probability of surviving without disease progression at 3 years post HDT [18].
- The experience with allogeneic stem cell transplantation is limited. A French study reported 10 patients with a median age of 46 years. All patients received a TBI-containing preparative regimens, 80% of patients
achieved an objective response including CR in six patients, but the treatment-related mortality was 40% [19]. In a series of 26 patients who received allogeneic transplantation with a variety of preparative regimens, there was 31% progression free survival at 3 years post transplant with a non-relapse mortality of 32% [18]. A non-myeloablative conditioning regimen has been administered to 12 heavily pretreated patients at a median 6.6 years after diagnosis. All patients received low dose TBI (2Gy) with \( n = 8 \) or without \( n = 4 \) fludarabine (30 mg/m\(^2\) X 3 days). Transplant related mortality was low (17%) and only one patient had grade 3 acute GVHD. Ten patients achieved at least PR (4 CR) having a 5 year progression free survival of 61% [20].

**Rituximab**

- Rituximab is a chimeric human/mouse antibody with human constant regions and mouse variable regions isolated from a murine anti-CD20 antibody. Rituximab binds avidly to the CD20 antigen, which is expressed in 95% of B-cell lymphoma cells and on normal B-cells, but it is not present on precursor B-cells or stem cells. Since CD20 is almost always present on WM cell, rituximab because a rational treatment for this disease. The largest study reported so far was conducted by ECOG and included 34 untreated and 35 previously treated patients. Using standard dose rituximab therapy (i.e., 4 weekly infusions at 375 mg/m\(^2\)) at least a 50% reduction of serum monoclonal protein was observed in 35% of untreated and 20% of pretreated patients with WM. The median duration of response was 27 months [21]. Other studies have evaluated an extended rituximab dose regimen wherein patients received rituximab at 375 mg/m\(^2\)/week for 4 weeks which was repeated at week 12 [22, 23]. The response rates in these studies were higher (44, 48%) than those previously reported with standard dose rituximab. However, the impact on duration of response for extended over standard dose therapy remains to be clarified as does the role of rituximab maintenance in patients with WM.

- Time to response after rituximab is slow and exceeds 3 months on the average. In some studies an inferior response to rituximab was noted when the baseline serum monoclonal protein exceeded 40 g/l or the total IgM exceeded 6000 mg/dl [22, 23]. In many patients, a transient increase of serum IgM may occur immediately following initiation of rituximab. Such an increase does not herald treatment failure and in most patients will return to their baseline serum IgM level by 12 weeks [22, 24, 25]. However, patients with elevated baseline serum monoclonal protein may be particularly at risk for a hyperviscosity-related event and in such patients plasmapheresis should be considered in advance of rituximab administration with subsequent close monitoring of serum IgM and viscosity. Because of the decreased likelihood of response in patients with higher IgM levels, as well as the possibility that serum IgM and serum viscosity may be abruptly rise, rituximab monotherapy should not be used in such patients.

**Combination chemotherapy or chemoimmunotherapy**

- Since the main chemotherapeutic agents with activity in WM are alkylating agents and nucleoside analogues, the combination of these agents has been explored in this disease. Weber et al. administered two
cycles of oral cyclophosphamide along with subcutaneous cladribine to 37 patients with previously untreated WM. At least a partial response was observed in 84% of patients and the median duration of response was 36 months [26]. Dimopoulos et al. administered intravenous cyclophosphamide and fludarabine to previously treated patients with WM and observed partial responses in 55% [27]. The combination of fludarabine plus cyclophosphamide was evaluated in a recent study by Tamburini and et al., which included 49 patients, 35 of whom were previously treated. The response rate was 78% and the median time to progression was 27 months [28]. A recent report has indicated that fludarabine-based combinations may be associated with increased risk of myelodysplasia at a crude rate of approximately 10% [29].

- Because rituximab is non-myelosuppressive its combination with chemotherapy has been explored in previously treated and untreated patients with WM. Weber et al. administered rituximab along with cladribine and cyclophosphamide to 17 previously untreated patients with WM. At least a partial response was documented in 94% of patients including a complete response of 18%. With a median follow-up of 21 months no patient has relapsed (Weber Sem Oncol 2003). Treon et al. administered the combination of rituximab and fludarabine to 43 patients with WM, 32 of whom were previously untreated. The complete and partial response rates were 7 and 74% respectively. With a median follow-up of 17 months, 87% of patients who responded have not progressed [30]. Hensel et al. administered pentostatin, cyclophosphamide with (n = 13) or without (n = 4) rituximab to 17 patients with WM, nine of whom were untreated and they observed at least a partial response in 64% of all 17 patients and 76% of patients who received rituximab [31]. Recently Vargaftig et al. reported on the activity of the combination of fludarabine p.o., cyclophosphamide p.o. and rituximab i.v. in 21 patients with WM. Nineteen patients were previously treated with a median of two lines of therapy. The CR plus PR rate was 53% and the main toxicities were neutropenia and thrombocytopenia [32].

- In order to avoid the cumulative myelosuppression and immunosuppression induced by nucleoside analogues, the addition of rituximab to chemotherapeutic agents other than nucleosides has been also explored. Dimopoulos et al. administered the combination of dexamethasone, rituximab and cyclophosphamide to 60 previously untreated, symptomatic patients with WM. At least a partial response was observed in 70% with minimal myelosuppression. With a median follow-up of 24 months, 60% of the patients are still free of progression [33]. The German Low Grade Lymphoma Study Group has performed a randomized trial in previously untreated patients with lymphoplasmacytoid lymphoma, including WM in order to compare the regimen cyclophosphamide, doxorubicine, vincristine and prednisone (CHOP) with or without rituximab. There was a significant advantage in favor of R-CHOP versus CHOP with response rates of 94% versus 69% respectively [34].

**Investigational and novel agents**

- Thalidomide has been recently administered in several diseases, including plasma cell dyscrasias, due to its multiple actions including immunomodulation, anti-angiogenesis and altered expression of
adhesion molecules. In WM, small cohorts of patients, both pretreated and newly diagnosed, have been treated with thalidomide alone or in combination with dexamethasone and clarithromycin. At least a partial response has been documented in approximately 20% [35]. More recently thalidomide has been combined with rituximab in 25 patients, 70% of them achieved at least a PR but with a high rate (40%) of grade 3–4 neuropathy [36]. Lenalidomide, a more potent and less toxic immunomodulatory analogue has been also administered in combination with rituximab, to 12 patients with WM, 10 of them previously untreated. Three out of eight evaluable patients achieved a PR but there was high rate of treatment discontinuation mainly due to poor tolerance [37].

• Bortezomib is a selective proteasome inhibitor, which has shown significant activity in a variety of hematologic malignancies including multiple myeloma and mantle cell lymphoma. Based on these data, we treated 10 patients with refractory or relapsed WM with bortezomib administered at a dose of 1.3 mg/m² on days 1, 4, 8, and 11 in a 21 day cycle for a total of four cycles. Six patients achieved a partial response, which occurred at a median of 1 month. The median time to progression of responding patients was 11 months [38]. Preliminary results with the combination of bortezomib with rituximab and dexamethasone in 10 previously untreated WM patients were recently reported. There was a 100% PR rate, with responses occurring promptly after a median 1.1 month and without sensory or motor neuropathy [39].

• Alemtuzumab is a monoclonal antibody against CD52 antigen and is effective treatment for patients with chronic lymphocytic leukemia who have previously received a purine analogue. With the use of three-color flow cytometry Owen et al. showed that CD52 expression was demonstrable in all 20 patients with WM who have assessed. Preliminary clinical data on seven heavily pretreated patients who received treatment with alemtuzumab showed four partial and one complete response, with a median response duration of 13 months. Infectious complications were common and included CMV reactivation, herpes simplex reactivation, aspergillosis and tuberculosis [40]. More recently in a series of 25 WM patients treated with alemtuzumab, there was a 32% PR rate with similar infectious complications [41].

Conclusions

• Despite the lack of randomized trials, alkylating agents (chlorambucil), nucleoside analogues and rituximab are reasonable choices for the primary therapy of symptomatic patients with WM. Furthermore, a recent consensus report indicated that combination therapy either with nucleoside analogues with alkylating agents and/or rituximab, or rituximab with chemotherapy such as CHOP or cyclophosphamide are also reasonable frontline treatment options for WM patients. The activity of these combinations appear at least at good as if not better than single agent therapy with either alkylating agents or nucleoside analogues or rituximab [42].

• 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-morbidities, 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 candidate for autologous stem cell transplantation. It should be clarified that it is not currently possible to recommend upfront HDT 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 HDT, any one of the three main primary treatments could be used. However, when rapid disease control is needed, combination chemotherapy or chemoimmunotherapy may be preferable. For the 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 HDT (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 HDT should be reserved only for patients refractory to alkylating agents, purine nucleoside and rituximab.

• For patients with refractory or relapsing disease, the use of an alternate first-line agent is reasonable. 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 HDT 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 classes of agents, there are few valid options. Every effort should be made to collect blood stem cells and to proceed to HDT 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, alemtuzumab, thalidomide with or without dexamethasone or bortezomib could be tried. Some patients may benefit from treatment with combination chemoimmunotherapy.

Future directions

• Over the last 10 years, the treatment options for patients with WM have increased. Furthermore, recent advances in the pathogenesis and biology of WM may result in the development of novel, specific treatments for WM. Until then, several questions regarding the treatment of these patients should be addressed. Because WM is a low-grade lymphoproliferative disorder affecting primarily elderly individuals, a significant number of patients die from unrelated diseases. Disease-specific survival, rather than overall survival, should be a more accurate end point of prospective trials involving patients with WM.

• Studies that address the mechanisms of resistance to rituximab may help us select patients who are more likely to benefit and may provide an opportunity to circumvent primary or secondary resistance. Furthermore, it is unclear whether standard administration or rituximab, extended rituximab, or even maintenance rituximab is the best way to administer this agent.
Besides rituximab, other monoclonal antibodies are worthy of study in WM. Initial studies in profiling tumor cells from patients with WM for serotherapy target antigens show that there is considerable intrapatient clonal variation in antigen expression and that combined monoclonal antibody therapy may permit targeting of all members of the tumor clone. Screening patients may also permit customized combination monoclonal antibody therapy.

There is evidence from phase II studies that the combination of chemotherapy with rituximab is associated with improved response rates. Furthermore, with these combinations, a sizeable number of patients may achieve a complete response. However, the optimal duration of such regimens has not been defined. This is an important issue in view of the cumulative myelosuppression and immunosuppression that these combinations may induce especially when a nucleoside analogue is included. Prospective studies are needed to assess whether rituximab should be combined with nucleoside analogs, alkylating agents, or both classes of agents. End points of such studies should include not only response rates but also response duration, feasibility of stem-cell collection, incidence and severity of infections, and overall survival.

Macroglobulinemia has a relatively protracted course, with a median survival ranging from 7 to 10 years in most series. However, several patients die as result of complications of WM within a few years after diagnosis. Such patients, when $\leq 70$ years of age, could be appropriate candidates for trials that incorporate HDT with ASCT early in the course of the disease. Preliminary evidence suggests that the presence of both anemia and elevated serum $\beta_2$-microglobulin may identify at diagnosis patients with impaired prognosis.

Development in cell and molecular biology are likely to help us develop targeted therapies for WM. Comparative studies of gene expression profiling and proteomic analysis of WM versus multiple myeloma reveal significant overlap but also distinct differences. These differences may be associated with differential features in the biologic behavior and drug sensitivity of these diseases.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance


Important consensus panel report which provided a clear clinical and pathological definition of WM


Consensus panel recommendations on the treatment options of previously untreated and pretreated patients with WM


7. Annibali O, Petrucci MT, Martini V, et al.: Treatment of 72 newly diagnosed Waldenstrom macroglobu-
time to treatment failure in first line treatment of patients with lymphoplasmacytoid/ic immunocytoma (LP-IC) – results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *ASH Annu Meet Abstracts* 2004, 104:162.


