

Update on Treatment Recommendations From the Fourth International Workshop on Waldenström's Macroglobulinemia

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ABSTRACT

Waldenström macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized by lymphoplasmacytic bone marrow infiltration along with an immunoglobulin M (IgM) monoclonal gammopathy. Patients with disease-related cytopenias, bulky adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation should be considered for immediate therapy. Initiation of therapy should not be based on serum IgM levels alone, and asymptomatic patients should be observed. Individual patient considerations should be considered when deciding on a first-line agent including the presence of cytopenias, need for rapid disease control, age, and candidacy for autologous transplantation. Therapeutic outcomes should be evaluated using updated criteria. As part of the Fourth International Workshop on Waldenström's Macroglobulinemia, a consensus panel updated its recommendations on both first-line and salvage therapy in view of recently published and ongoing clinical trials. The panel considered encouraging results from recent studies of first-line combinations such as rituximab with nucleoside analogs with or without alkylating agents or with cyclophosphamide-based therapies (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone or cyclophosphamide and dexamethasone) or the combination of rituximab with thalidomide. Such therapeutic approaches are likely to yield responses at least as good as, if not better than, monotherapy with any of the alkylating agents, nucleoside analogs, or rituximab. In the salvage setting, reuse of a first-line regimen or use of a different regimen should be considered along with bortezomib, alemtuzumab, autologous transplantation, and, in selected circumstances, allogeneic transplantation. Finally, the panel reaffirmed its encouragement of the active enrollment of patients with WM onto innovative clinical trials whenever possible.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an immunoglobulin M (IgM) monoclonal gammopathy. This condition is considered to be a lymphoplasmacytic lymphoma as defined by the Revised European-American Lymphoma and WHO classification systems.¹ Patients with a disease-related hemoglobin level of less than 100 g/L, platelet count of less than $100 \times 10^9/L$, bulky adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation should be considered for immediate therapy.² Initiation of therapy should not be based on serum monoclonal protein levels alone, and asymptomatic patients should be ob-

served.² Asymptomatic patients with a low β_2 -microglobulin and a hemoglobin level ≥ 12 g/dL may have an indolent course with a long-lasting period of not requiring therapy even when their monoclonal protein exceeds 30 g/L. Therapeutic outcomes should be evaluated using updated consensus panel criteria (Appendix Table A1, online only).³ As part of the Fourth International Workshop on Waldenström's Macroglobulinemia, which was held from June 29 to 30, 2007 in Kos, Greece, a consensus panel charged with providing treatment recommendations for WM updated its recommendations on both first-line and salvage therapy options in view of recently published and ongoing clinical trial results (Table 1). In the recommendations that were formulated at the Third International Workshop on Waldenström's Macroglobulinemia, the panel considered encouraging results from studies addressing the use of extended-dose rituximab as well as combination

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Table 1. Updated Consensus Panel Recommendations for First-Line and Salvage Therapy From the Fourth International Workshop on Waldenström's Macroglobulinemia

| Recommendations |
|-----------------------------------------------------|
| First-line therapy |
| Combination therapy (as outlined in Table 2)* |
| Monoclonal antibody (ie, rituximab) |
| Nucleoside analogs (ie, fludarabine or cladribine)* |
| Alkylators (ie, chlorambucil)* |
| Salvage therapy |
| Reuse or alternative use of a first-line agent* |
| Combination therapy (as outlined in Table 4)* |
| Bortezomib-based therapy |
| Thalidomide ± corticosteroids |
| Monoclonal antibody (alemtuzumab) |
| Autologous transplantation |

*The use of alkylator agents such as chlorambucil and nucleoside analogs should be limited in patients who are eligible for autologous stem-cell transplantation. Cyclophosphamide, although an alkylating agent, is not toxic to stem cells and may be incorporated in regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone or dexamethasone, rituximab, and cyclophosphamide.

therapy with nucleoside analogs, nucleoside analogs plus alkylating agents, or rituximab with combination chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide and dexamethasone, as reasonable options for the treatment of WM and determined that such therapeutic approaches were likely to yield responses that were at least as good as, if not better than, those previously obtained with the recommended use of single-agent alkylator, nucleoside analog, or standard-dose rituximab therapy. Such approaches were considered reasonable options for the treatment of WM patients in both the up-front and salvage settings. However, randomized studies addressing the efficacy and toxicity of such novel approaches over previously established standard of care options were recommended to discern the extent of the benefits. The panel emphasized that individual patient considerations, such as the presence of cytopenias, need for rapid disease control, age, and candidacy for autologous transplant therapy, should be weighed in making the choice of a first-line treatment and that, for patients who may be eligible for autologous transplantation, exposure to alkylator agents and nucleoside analogs should be discouraged in view of reports suggesting damage of stem cells by these agents.⁴ The panel also considered options for the treatment of relapsed disease and provided recommendations on the use of alternate first-line agents, reuse of a first-line agent, use of combination myelotoxic chemotherapy, and use of thalidomide as a single agent or in combination therapy. Furthermore, the panel affirmed, for eligible patients, a role for high-dose chemotherapy with autologous peripheral-blood stem-cell transplantation in primary refractory or relapsed disease while stressing that allogeneic or nonmyeloablative allogeneic transplantation procedures should be cautiously approached in view of the associated high mortality and/or morbidity risks and should be undertaken in the context of a clinical trial.

Since the recommendations of the Third International Workshop on Waldenström's Macroglobulinemia, which were made 2

years ago,^{5,6} a new International Prognostic Staging System for WM (IPSSWM) has been defined,⁷ and several clinical trials exploring the combination of rituximab and chemotherapy have been reported. Thus, the panel believed that updated recommendations were needed.

The formulation of IPSSWM was a multicenter collaborative project resulting from the analysis of a large number of previously untreated, symptomatic patients who required treatment. According to the IPSSWM, five adverse features (age > 65 years, hemoglobin ≤ 11.5 g/dL, platelet count ≤ 100 × 10⁹/L, β₂-microglobulin > 3 mg/L, and serum monoclonal protein concentration > 70 g/L) define three risk groups. Low risk is defined by the presence of ≤ one adverse characteristic and age ≤ 65 years; high risk is defined by the presence of more than 2 adverse characteristics; and intermediate risk is defined by the presence of two adverse characteristics or age more than 65 years. The 5-year survival rates were 87%, 68%, and 36% for the low-, intermediate-, and high-risk groups, respectively. Although 96% of the patients included in this analysis had received first-line treatment with alkylating agents, nucleoside analogs, or combinations of these agents, the IPSSWM has been recently validated in an independent series of patients treated with rituximab alone or in combination with dexamethasone and cyclophosphamide as first-line therapy.⁸

RITUXIMAB IN COMBINATION WITH NUCLEOSIDE ANALOGS

Thomas et al⁹ updated The University of Texas M. D. Anderson Cancer Center experience with two consecutive 6-week courses of cladribine, cyclophosphamide, and rituximab in 18 previously untreated patients. The overall response rate (complete response [CR] plus partial response [PR]) was 94%, including CR in 17% of patients. Median time to response was 2.4 months, and median duration of response was 58.6 months. Laszlo et al¹⁰ treated 29 patients (including 16 previously untreated patients) with four monthly courses of rituximab at a dose of 375 mg/m² on day 1 and subcutaneous cladribine at a dose of 0.1 mg/kg for 5 days. CR plus PR was demonstrated in 59% of patients, and a minor response (MR) was demonstrated in 24% of patients. A pharmacogenomic analysis showed a statistically significant lower expression of the human equilibrative nucleoside transporter gene in patients who achieved MR or stable disease (SD) compared with patients who achieved CR or PR (*P* = .014). Tedeschi et al¹¹ administered rituximab 375 mg/m² on day 1, fludarabine 25 mg/m² intravenous (IV) on days 2 through 4, and cyclophosphamide 250 mg/m² IV on days 2 through 4 (RFC) every 4 weeks for six courses to 19 patients (five previously untreated) with WM. Nine patients developed an IgM flare; 79% achieved at least a PR. Ten patients showed a delayed response with a progressive reduction of the monoclonal protein after a median of 10 months. The RFC regimen, but with oral fludarabine and cyclophosphamide, was administered to 25 mainly pretreated patients in seven French centers. A PR was observed in 69%, and an MR was observed in 9%. The median duration of response was 8 months. The main toxicity was hematologic.¹² These trials confirm the significant activity of combinations that include rituximab and nucleoside analogs. Such regimens may be particularly useful when rapid disease control is required because of hyperviscosity, bulky lymphadenopathy or splenomegaly, symptomatic cryoglobulinemia, and so on. The hematologic and immunosuppressive complications of nucleoside analogs are well established.¹³ However, two recent reports have suggested an increased incidence of Richter's

transformation and development of myelodysplastic syndromes/secondary acute myelogenous leukemia in WM patients treated with nucleoside analog–containing therapy.^{14,15} These data favor limiting exposure of WM patients to nucleoside analogs, particularly in younger patients.

RITUXIMAB IN COMBINATION WITH AGENTS OTHER THAN NUCLEOSIDE ANALOGS

Rituximab has been combined with chemotherapeutic agents other than nucleoside analogs. Dimopoulos et al¹⁶ reported the final analysis of a regimen consisting of dexamethasone 20 mg followed by rituximab 375 mg/m² IV on day 1 and cyclophosphamide 100 mg/m² orally bid on days 1 to 5 (DRC) that was administered to 72 previously untreated patients with symptomatic WM. An objective response was documented in 83% of patients, including 7% with CR, 67% with PR, and 9% with MR. The median time to response was 4.1 months. The 2-year progression-free survival rate was 90%. Only 9% of patients experienced grade 3 or 4 hematologic toxicity. Abonour et al¹⁷ reported the outcome of 16 previously untreated patients who were treated with the combination of rituximab and CHOP (R-CHOP) administered every 3 weeks at standard doses. This Eastern Cooperative Oncology Group trial (which was closed prematurely because of poor accrual) showed that the R-CHOP combination achieved a PR in 91% of patients with a rapid median time to response of 1.6 months; with a median follow-up time of 18.3 months, median duration of response has not yet been reached. Myelosuppression was the main toxicity. These studies indicate that combinations of rituximab with chemotherapeutic agents other than nucleoside analogs are highly active, non–stem-cell toxic, first-line treatments that are suitable for patients in whom stem-cell collection is considered.

On the basis of *in vitro* data that suggested a synergistic effect of rituximab with the immunomodulatory agents thalidomide and lenalidomide, the Waldenström's Macroglobulinemia Clinical Trials Group (WMCTG) conducted two phase II clinical trials in symptomatic patients with WM combining thalidomide or lenalidomide with rituximab.^{18,19} Intended therapy for patients on the phase II study of thalidomide plus rituximab (RT) consisted of thalidomide administered at 200 mg daily for 2 weeks, followed by 400 mg daily thereafter for 1 year. Patients received four weekly infusions of rituximab 375 mg/m² beginning 1 week after initiation of thalidomide, followed by four additional weekly infusions of rituximab 375 mg/m² beginning at week 13. Eighty percent of patients were previously untreated, and 23 of 25 patients were assessable. Responses included one CR, 15 PRs, two MRs, and one SD, for overall and major response rates of 78% and 70%, respectively. With a median follow-up time of 42+ months, the median time to progression was 35 months for assessable patients and 38+ months for responders. Responses were unaffected by FcγRIIIA-158 polymorphism status (81% v 71% for VV/FV v FF, respectively), IgM levels (78% v 80% for < 6,000 v ≥ 6,000 mg/dL, respectively), and serum β₂-microglobulin (71% v 89% for < 3 v ≥ 3 g/dL, respectively). Dose reduction of thalidomide was required in all patients and led to discontinuation in 11 patients. Among the 11 patients experiencing ≥ grade 2 neuropathy, 10 demonstrated resolution to grade 1 (n = 3) or complete resolution (n = 7) at a median of 6.7 months (range, 0.4 to 22.5 months).¹⁸

In a phase II study of lenalidomide and rituximab in WM,¹⁹ patients were initiated on lenalidomide 25 mg daily on a syncoated

schedule wherein therapy was administered for 3 weeks followed by a 1-week pause for an intended duration of 48 weeks. Patients received 1 week of therapy with lenalidomide, after which rituximab (375 mg/m²) was administered weekly on weeks 2 to 5 and then weeks 13 to 16. Twelve of 16 patients were assessable, and responses included four PRs, four MRs, and three SDs, for overall and major response rates of 67% and 33%, respectively; the median time to progression was 15.6 months. Acute decreases in hematocrit were observed during the first 2 weeks of lenalidomide therapy in 13 (81%) of 16 patients, with a median hematocrit decrease of 4.4% (range, 1.7% to 7.2%). Despite reduction of initial doses to 5 mg daily, anemia continued to be problematic without evidence of hemolysis or more general myelosuppression. Therefore, the mechanism for pronounced anemia in WM patients receiving lenalidomide remains to be determined, and the use of this agent among WM patients remains investigational.

BORTEZOMIB

On the basis of laboratory data and preliminary clinical data, bortezomib, a reversible proteasome inhibitor, has been evaluated in the context of two prospective phase II studies. In a multicenter study of the WMCTG,²⁰ 27 patients received up to eight cycles of bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 repeated every 21 days. All but one patient had relapsed or refractory disease. The overall response rate was 85%, with 10 and 13 patients achieving an MR (< 25% decrease in IgM) and a major response (< 50% decrease in IgM), respectively. Responses were prompt and occurred at a median of 1.4 months. The median time to progression for all responding patients in this study was 7.9 months (range, 3 to 21.4+ months), and the most common grade 3 or 4 toxicities occurring in ≥ 5% of patients were sensory neuropathies (22.2%), leukopenia (18.5%), neutropenia (14.8%), dizziness (11.1%), and thrombocytopenia (7.4%). Importantly, sensory neuropathies resolved or improved in nearly all patients after cessation of therapy. As part of a National Cancer Institute of Canada study, Chen et al²¹ treated 27 patients with either untreated or previously treated disease. Patients in this study received bortezomib using the standard schedule until they either demonstrated progressive disease or were two cycles beyond best response. The overall response rate in this study was 78%, with major responses observed in 44% of patients. Sensory neuropathy occurred in 20 patients (five with grade ≥ 3) and occurred after two to four cycles of therapy. Among the 20 patients who developed a neuropathy, it resolved in 14 patients and improved by one grade in one patient at 2 to 13 months.

The addition of rituximab and corticosteroids to bortezomib has been the subject of both preclinical and clinical investigation in various B-cell malignancies. In an ongoing trial by the WMCTG, bortezomib has been combined with dexamethasone and rituximab for the primary therapy of patients with WM.^{22,23} As part of this study, patients are receiving IV bortezomib 1.3 mg/m² and dexamethasone 40 mg on days 1, 4, 8, and 11, along with rituximab (375 mg/m²) on day 11 for four consecutive cycles followed by four maintenance cycles begun 3 months after induction therapy and then administered every 3 months. Among the 23 treated patients, the overall and major response rates were 96% and 78%, including four patients (17%) who achieved a CR. Median time to response was rapid at 1.1 month.

However, the development of grade 3 peripheral neuropathy continues to be concerning using this schedule and may occur in up to one third of patients. Similar results have been also reported from Agathocleous et al.²⁴

An interesting observation with the use of bortezomib in a subset of WM patients has been the discordance observed between serum IgM levels and bone marrow responses, suggesting that, for some patients, bortezomib may be inhibiting IgM secretion independent of direct tumor cell killing.^{20,25} Why discordance between serum IgM levels and disease burden occurs in a subset of patients receiving bortezomib remains to be clarified. However, from a clinical perspective, clinicians need to be aware of possible discordance of serum IgM levels and clinical response to bortezomib, and a bone marrow biopsy (and/or computed tomography scans in the event the patient has baseline adenopathy/splenomegaly) should be considered to clarify response in circumstances where the patients underlying clinical status remains to be clarified. These data indicate that bortezomib and bortezomib-based combinations are active in WM and should be strongly considered for patients who have experienced treatment failure with alkylating agents, nucleoside analogs, and rituximab.

ANTI-CD52 MONOCLONAL ANTIBODY

Alemtuzumab is a humanized monoclonal antibody that targets CD52, an antigen widely expressed in bone marrow lymphoplasmacytic cells in WM patients, as well as in mast cells, which are increased in the bone marrow of patients with WM and provide growth and survival signals to WM lymphoplasmacytic cells. As part of a WMCTG effort,²⁶ 28 patients with the Revised European-American Lymphoma/WHO clinicopathologic diagnosis of lymphoplasmacytoid lymphoma, including 27 patients with IgM (WM) and one with immunoglobulin A monoclonal gammopathy, were enrolled onto a prospective, multicenter study. Five patients were untreated, and 23 patients were previously treated, all of whom had previously received rituximab. Three daily test doses (3, 10, and 30 mg IV) were followed by alemtuzumab 30 mg IV three times a week for up to 12 weeks. All patients received acyclovir and sulfamethoxazole-trimethoprim or equivalent prophylaxis. A median of 33 infusions (range, 10 to 36 infusions) after test dosing were administered. Among 25 patients assessable for response, the overall response rate was 76%, including eight PRs (32%) and 11 MRs (44%). Hematologic toxicities were common among previously treated (but not untreated) patients and included grade 3 or 4 neutropenia (39%), thrombocytopenia (18%), and anemia (7%). Grade 3 or 4 nonhematologic toxicities for all patients included dermatitis (11%), fatigue (7%), and infection (7%). Cytomegalovirus reactivation and infection were commonly seen among previously treated patients and may have been responsible for one death on study. Two other patients also experienced treatment-related death. With a median follow-up time of 8.5+ months, 11 of 19 responding patients remain free of progression. An up-front study by the WMCTG examining the role of alemtuzumab in combination with rituximab is planned given the results of this study and data suggesting benefit with combined antibody therapy in related indolent B-cell malignancies.²⁷⁻²⁹

HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM-CELL TRANSPLANTATION

Over the last 2 years, several studies evaluating the role of high-dose therapy in WM have been reported. Kyriakou et al³⁰ performed a retrospective analysis of 201 patients from the European Bone Marrow Transplant Registry (EBMT) who underwent autologous stem-cell transplantation (ASCT). At transplantation, 86% of patients had chemotherapy-sensitive disease, and 14% had relapsed or refractory disease. The treatment-related mortality rate was 8%. The 5-year progression-free and overall survival rates were 33% and 61%, respectively. Similar results have been reported by Dhedin et al,³¹ who updated the French experience with 32 patients who underwent ASCT. The median event-free survival time was 37 months (range, 2 to 119 months), and the 5-year overall survival rate was 58%. These data support the concept of a dose-response effect in WM and confirm that ASCT may induce long-term response even in heavily pretreated patients.

ALLOGENEIC STEM-CELL TRANSPLANTATION

The role of allogeneic stem-cell transplantation (alloSCT) has been also clarified further over the last 2 years. Kyriakou et al³² reported the experience of the European Bone Marrow Transplant Registry with 106 patients with WM who underwent alloSCT. Seventy percent of patients had chemotherapy-sensitive disease and 30% had chemotherapy-refractory disease at the time of transplantation. Conventional conditioning was administered to 41% of patients, and reduced-intensity conditioning was administered to 59%. The 1-year nonrelapse mortality rate was 27%. The 5-year progression-free and overall survival rates were 48% and 63%, respectively. This analysis indicated that alloSCT is feasible in patients with WM but with a substantial treatment-related mortality.³² The French group reported on 22 patients who had received either myeloablative alloSCT (n = 11) or reduced-intensity alloSCT (n = 11). In the myeloablative and reduced-intensity alloSCT patients, the transplantation-related mortality rates were 36% and 27%, respectively, and the median event-free survival times were 36 months and not reached, respectively. The relapse rate was 36% for myeloablative alloSCT and 0% for reduced-intensity alloSCT.³¹ Anderson et al³³ updated the Seattle experience with reduced-intensity conditioning alloSCT in 12 patients who were conditioned with 2 Gy of total-body irradiation with or without fludarabine at a median time of 6.6 years from the initial diagnosis of WM. The treatment-related mortality rate was 17%; 10 of 11 assessable patients responded after transplantation (four CRs and six PRs). The 5-year progression-free survival rate was 61%. The median time to CR was 12 months, supporting the notion of a graft-versus-tumor effect.³³

RECOMMENDATIONS FROM THE FOURTH INTERNATIONAL WORKSHOP ON WALDENSTROM'S MACROGLOBULINEMIA

In view of the body of data outlined in this article, the consensus panel on therapeutics provided further recommendations for the first-line and salvage treatment of WM (Tables 1 to 4; Appendix Tables A2 and A3, online only). Rituximab-based therapies may be the preferred initial treatment for most patients with WM. When rapid disease

Updated Treatment Recommendations on Waldenström Macroglobulinemia

Table 2. First-Line Therapeutic Options for Waldenström Macroglobulinemia: Updated From the Consensus Panel Recommendations of the Third International Workshop on Waldenström's Macroglobulinemia

| Therapeutic Class and Agents | Evidence for Efficacy | Level of Recommendation |
|---------------------------------------------------------------------|-----------------------|-------------------------|
| Nucleoside analogs plus alkylators* | | |
| Cladribine or fludarabine plus cyclophosphamide | IIa | B |
| Nucleoside analogs plus rituximab* | | |
| Fludarabine plus rituximab; cladribine plus rituximab ¹⁰ | IIa | B |
| Nucleoside analogs plus alkylators and rituximab* | | |
| Cladribine, cyclophosphamide, and rituximab ⁹ | IIa | B |
| Fludarabine, cyclophosphamide, and rituximab ^{11,12} | III | C |
| Pentostatin, cyclophosphamide, and rituximab | III | C |
| Cyclophosphamide-based combination therapy plus rituximab | | |
| CHOP and rituximab ¹⁷ | IIa | B |
| Cyclophosphamide, dexamethasone, and rituximab ¹⁶ | IIa | B |
| Immunomodulatory drugs plus rituximab | | |
| Thalidomide and rituximab ¹⁸ | IIa | B |
| Monoclonal antibody | | |
| Rituximab (standard or extended schedule) | IIa | B |
| Nucleoside analogs* | | |
| Cladribine or fludarabine | IIa | B |
| Alkylator agents* | | |
| Chlorambucil | IIa | B |

Abbreviation: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*The choice of appropriate therapy should take into account the candidacy of a patient for high-dose chemotherapy because prolonged use of both alkylating agents and nucleoside analogs can deplete hematopoietic stem cells.

control is needed, the use of cyclophosphamide-based therapy such as R-CHOP or DRC could be an appropriate choice. Cyclophosphamide can be used in patients who are transplantation candidates because it is not toxic to stem cells. Early reports for the combination of bortezomib, dexamethasone, and rituximab are encouraging and may represent an ideal choice for patients with hyperviscosity in whom rapid reduction of the paraprotein is needed. For patients who are, or may be in the future, candidates for ASCT, appropriate primary therapies include R-CHOP, DRC, and RT. For patients whose main indication for treatment is cytopenias (and especially thrombocytopenia), DRC or RT, in view of their lower myelotoxicity, may be preferable, even for patients who are not candidates for stem-cell collection. A combination of rituximab with a nucleoside analog with

or without cyclophosphamide may also be appropriate, especially if the patient has features of advanced disease. Finally, some selected patients with low-risk disease may be appropriate candidates for single-agent rituximab or for chlorambucil because of associated comorbidities. Presence of cytopenias and low levels of monoclonal protein may favor rituximab, whereas slow progression and older age may favor chlorambucil. However, in the absence of randomized trials, it remains to be determined which first-line therapy is optimal and whether the higher response rate associated with combination chemoimmunotherapy will ultimately translate into improved patient survival.

The choice of salvage therapy depends on the specific first-line treatment used, the quality of response, the duration of response, and other variables such as patient age, tolerance of initial therapy, candidacy for stem-cell transplantation, and so on. For relatively long unmaintained responses, the initially effective treatment should be seriously considered if initially well tolerated. Reuse of a first-line single agent or combination is reasonable if a patient achieved an unmaintained response that lasted for at least 12 months; otherwise, use of an alternate single agent or combination is recommended. For patients who have short remissions or resistance to a first-line regimen, second-line treatment may include agents of a different class either alone or in combination. In that setting, the RFC regimen may be appropriate, although it should be avoided in younger patients and patients who are eligible for ASCT in whom stem cells have not previously been collected and stored. Bortezomib-based therapy may also be an appropriate second-line choice. In view of recent data on the activity of alemtuzumab in pretreated patients, this agent may represent a reasonable third-line therapy. The place of high-dose therapy with ASCT or alloSCT requires further evaluation in the context of prospective trials, which should focus primarily on patients with high-risk disease or on an individual basis in selected young patients with aggressive, high-risk disease.

Table 3. Recommendations From the Fourth International Workshop on Waldenström's Macroglobulinemia for the Management of Newly Diagnosed Symptomatic Waldenström Macroglobulinemia Patients According to Specific Conditions

| Clinical Condition | Recommended Treatment |
|--------------------------------|-----------------------------------------------------------------------------------|
| Transplantation candidate | |
| Cytopenias | DRC; rituximab + thalidomide |
| High M-protein | R-CHOP; DRC |
| Non-transplantation candidate | |
| Cytopenias | DRC; rituximab + thalidomide |
| High M-protein | Nucleoside analogs + rituximab; nucleoside analogs + rituximab + cyclophosphamide |
| Comorbidities | |
| Low M-protein and cytopenias | Rituximab |
| Older age and slow progression | Chlorambucil |

Abbreviations: DRC, dexamethasone, rituximab, and cyclophosphamide; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 4. Salvage Therapeutic Options for Waldenström Macroglobulinemia: Updated From the Consensus Panel Recommendations of the Third International Workshop on Waldenström's Macroglobulinemia

| Therapeutic Class and Agents | Evidence for Efficacy | Level of Recommendation |
|-------------------------------------------------------------------------------|-----------------------|-------------------------|
| Alkylator agents*† | | |
| Chlorambucil | IIa | B |
| Nucleoside analogs*† | | |
| Cladribine or fludarabine | Ib | A |
| Monoclonal antibody† | | |
| Rituximab (standard or extended schedule) | IIa | B |
| Alemtuzumab | IIa | B |
| Nucleoside analogs plus alkylators*† | | |
| Cladribine or fludarabine plus cyclophosphamide | IIa | B |
| Nucleoside analogs plus rituximab*† | | |
| Fludarabine plus rituximab | IIa | B |
| Nucleoside analogs plus alkylators and rituximab*† | | |
| Cladribine, cyclophosphamide, and rituximab | IIb | B |
| Fludarabine, cyclophosphamide, and rituximab | III | C |
| Pentostatin, cyclophosphamide, and rituximab | III | C |
| Combination chemotherapy plus rituximab | | |
| CHOP and rituximab | III | C |
| Thalidomide | | |
| Thalidomide alone or in combination with dexamethasone ¹⁸ | IIa | B |
| Bortezomib | | |
| Bortezomib alone ^{20,21} | IIa | B |
| Stem-cell transplantation‡ | | |
| High-dose chemotherapy and autologous stem-cell transplantation ³⁰ | IIa | B |
| Allogeneic stem-cell transplantation ^{32,33} | III | C |

Abbreviation: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*The choice of appropriate therapy should take into account the candidacy of a patient for high-dose chemotherapy because prolonged use of both alkylating agents and nucleoside analogs can deplete hematopoietic stem cells.

†Reuse of a first-line single agent or combination is reasonable if patient achieved a response duration of ≥ 12 months; otherwise, use of an alternate single agent or combination is reasonable.

‡For eligible patients with primary refractory or relapsed disease, high-dose chemotherapy with autologous stem-cell transplantation may be reasonable; allogeneic or nonmyeloablative allogeneic transplantation procedures should be cautiously approached in view of the associated high mortality and/or morbidity risks and should be undertaken in context of a clinical trial.

According to the IPSSWM, one third of patients belong to a high-risk group, with a median survival time of 3 years. For younger patients with high-risk disease, prospective trials should be considered that incorporate high-dose therapy in the up-front treatment strategy. Furthermore, all new randomized trials should stratify patients according to IPSSWM, and eventually, specific treatments may be evaluated for the different IPSSWM risk groups.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Summary of Updated Response Criteria From the Third International Workshop on Waldenström's Macroglobulinemia

| Response | Criteria |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Complete response | Disappearance of monoclonal protein by immunofixation; no histologic evidence of bone marrow involvement and resolution of any adenopathy/organomegaly (confirmed by CT scan), along with no signs or symptoms attributable to WM; reconfirmation of the complete response status is required at least 6 weeks apart with a second immunofixation |
| Partial response | A \geq 50% reduction of serum monoclonal IgM concentration on protein electrophoresis and \geq 50% decrease in adenopathy/organomegaly on physical examination or on CT scan; no new symptoms or signs of active disease |
| Minor response | A \geq 25% but < 50% reduction of serum monoclonal IgM by protein electrophoresis; no new symptoms or signs of active disease |
| Stable disease | A < 25% reduction and < 25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms caused by disease and/or signs of WM |
| Progressive disease | A \geq 25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings as a result of disease (ie, anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms attributable to WM (unexplained recurrent fever \geq 38.4°C, drenching night sweats, \geq 10% body weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) |

NOTE. Data from Kimby E, Treon SP, Anagnostopoulos A, et al. Clin Lymphoma Myeloma 6:380-383, 2006.
Abbreviations: CT, computed tomography; WM, Waldenström macroglobulinemia; IgM, immunoglobulin M.

Table A2. US Agency for Health Care Policy and Research: Levels of Evidence

| Level of Evidence | Type of Evidence |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ia | Evidence obtained from meta-analysis of randomized controlled trials |
| Ib | Evidence obtained from at least one randomized controlled trial |
| IIa | Evidence obtained from at least one well-designed controlled study without random assignment |
| IIb | Evidence obtained from at least one other type of well-designed quasiexperimental study |
| III | Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities |

Table A3. US Agency for Health Care Policy and Research: Grades of Recommendation

| Grades of Recommendation | Evidence Level | Recommendation |
|--------------------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A | Ia, Ib | Required: at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation |
| B | IIa, IIb, III | Required: availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation |
| C | IV | Required: evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality |