Update on Treatment Recommendations From the Fourth International Workshop on Waldenstrom’s Macroglobulinemia


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 therapies, 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.

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. Patients with a disease-related hemoglobin level of less than 100 g/L, platelet count of less than 100 × 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. Initiation of therapy should not be based on serum monoclonal protein levels alone, and asymptomatic patients should be observed. Asymptomatic patients with a low β₂-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). 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 therapy.
therapy with nucleoside analogs, nucleoside analogs plus alkylating agents, or rituximab with combination chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone or dexamethasone, rituximab, and cyclophosphamide. Such regimens may be particularly effective for the treatment of relapsed disease.

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 intravenously (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 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 lim-
iting 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 rituxi-
imb 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 re-
ported 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 Coopera-
tive 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 lena-
lidomide, the Waldenström’s Macroglobulinemia Clinical Trials
Group (WMCTG) conducted two phase II clinical trials in symptom-
atic 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 adminis-
tered 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 FcγRIIA–
158 polymorphism status (81% v 71% for VV/VF, 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, respec-
tively). Dose reduction of thalidomide was required in all patients and
led to discontinuation in 11 patients. Among the 11 patients experi-
encing ≥ 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 syncopated
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, bort-
ezomib, 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, sen-
sory 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 previ-
ously treated disease. Patients in this study received bortezomib using
the standard schedule until they either demonstrated progressive dis-
cease 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 vari-
obus B-cell malignancies. In an ongoing trial by the WMCTG, bor-
tezomib 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 WMTCG 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 cyclophosphamide/methylprednisolone or equivalent prophylaxis. A median of 33 infusions (range, 15 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 WMTCG 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 35% and 61%, respectively. Similar results have been reported by Dhedin et al31 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 26 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.35

**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
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 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 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 also be an appropriate 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.

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

<table>
<thead>
<tr>
<th>Therapeutic Class and Agents</th>
<th>Evidence for Efficacy</th>
<th>Level of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside analogs plus alkylators*</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Cladribine or fludarabine plus cyclophosphamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogs plus rituximab*</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Fludarabine plus rituximab; cladribine plus rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogs plus alkylators and rituximab*</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Cladribine, cyclophosphamide, and rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludarabine, cyclophosphamide, and rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentostatin, cyclophosphamide, and rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide-based combination therapy plus rituximab</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>CHOP and rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide, dexamethasone, and rituximab</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Immunomodulatory drugs plus rituximab</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Thalidomide and rituximab</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Rituximab (standard or extended schedule)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogs*</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Cladribine or fludarabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylator agents*</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Chlorambucil</td>
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</table>

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.

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### Table 3: Recommendations From the Fourth International Workshop on Waldenström’s Macroglobulinemia for the Management of Newly Diagnosed Symptomatic Waldenström Macroglobulinemia Patients

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplantation candidate</td>
<td>DRC, rituximab + thalidomide</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>R-CHOP, DRC</td>
</tr>
<tr>
<td>High M-protein</td>
<td></td>
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<tr>
<td>Non-transplantation candidate</td>
<td>DRC, rituximab + thalidomide</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>Nucleoside analogs + rituximab; nucleoside analogs + cyclophosphamide</td>
</tr>
<tr>
<td>High M-protein</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Low M-protein and cytopenias</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Older age and slow progression</td>
<td>Chlorambucil</td>
</tr>
</tbody>
</table>

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

| 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 | IIA | 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†† | IIA | B |
| Bortezomib | | |
| Bortezomib alone†† | IIA | B |
| Stem-cell transplantation‡ | | |
| High-dose chemotherapy and autologous stem-cell transplantation‡ | IIA | B |
| Allogeneic stem-cell transplantation‡ | 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.

AUTHOR CONTRIBUTIONS

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Manuscript writing: Meletios Athanasios Dimopoulos
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REFERENCES


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


22. Treon SP, Soumerai JD, Patterson CJ, et al: Bortezomib, dexamethasone and rituximab (IBDR) is a highly active regimen in the primary therapy of Waldenström’s macroglobulinemia: Planned interim results of WMCTG Clinical Trial 05-180. Blood 108: 2765, 2006 (abstr)


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

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>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</td>
</tr>
<tr>
<td>Partial response</td>
<td>A ≥ 50% reduction of serum monoclonal IgM concentration on protein electrophoresis and ≥ 50% decrease in adenopathy/organomegaly on physical examination or on CT scan; no new symptoms or signs of active disease</td>
</tr>
<tr>
<td>Minor response</td>
<td>A ≥ 25% but &lt; 50% reduction of serum monoclonal IgM by protein electrophoresis; no new symptoms or signs of active disease</td>
</tr>
<tr>
<td>Stable disease</td>
<td>A &lt; 25% reduction and &lt; 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</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>A ≥ 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 ≥ 38.4°C, drenching night sweats, ≥ 10% body weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis)</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; WM, Waldenström macroglobulinemia; IgM, immunoglobulin M.

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

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

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

<table>
<thead>
<tr>
<th>Grades of Recommendation</th>
<th>Evidence Level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ia, Ib</td>
<td>Required: at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation</td>
</tr>
<tr>
<td>B</td>
<td>Iia, Iib, III</td>
<td>Required: availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
<td>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</td>
</tr>
</tbody>
</table>