

Treatment Recommendations in Waldenstrom's Macroglobulinemia: Consensus Panel Recommendations From the Second International Workshop on Waldenstrom's Macroglobulinemia

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This presentation represents consensus recommendations for the treatment of patients with Waldenstrom's macroglobulinemia (WM), which were prepared in conjunction with the second International Workshop held in Athens, Greece during September 2002. The faculty adopted the following statements for the management of patients with Waldenstrom's macroglobulinemia: (1) Alkylating agents, nucleoside analogues, and rituximab are reasonable choices for first line therapy of WM. (2) Both cladribine and fludarabine are reasonable choices for the therapy of WM. (3) Combinations of alkylating agents, nucleoside analogues, or rituximab should at this time be encouraged in the context of a clinical trial. (4) In WM, rituximab can cause a sudden rise in serum IgM and viscosity levels in certain patients, which may lead to complications, therefore close monitoring of these parameters and symptoms of hyperviscosity is recommended for WM patients undergoing rituximab therapy. (5) For relapsed disease, it is reasonable to use an alternate first line agent or re-use of the same agent; however, since autologous stem cell transplantation may have a role in treating patients with relapsed disease it is recommended that for patients in whom autologous transplantation is seriously being considered, exposure to alkylator or nucleoside analogue drugs should be limited. (6) Combination chemotherapy for patients who can tolerate myelotoxic therapy, thalidomide alone or with dexamethasone, can reasonably be considered to have relapsed. (7) Autologous stem cell transplantation may be considered for patients with refractory or relapsing disease. (8) Allogeneic transplantation should only be undertaken in the context of a clinical trial. (9) Plasmapheresis should be considered as interim therapy until definitive therapy can be initiated. (10) Rituximab should be considered for patients with IgM-related neuropathies. (11) Corticosteroids may be useful in the treatment of symptomatic mixed cryoglobulinemia. (12) Splenectomy is rarely indicated but has been used to manage painful splenomegaly and hypersplenism.

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THE SECOND International Workshop on Waldenstrom's Macroglobulinemia was held in Athens, Greece, on September 26 to 30, 2002. This conference brought together a faculty with extensive clinical and scientific experience in Waldenstrom's macroglobulinemia (WM). Four

consensus panels were convened to define four specific areas. The charges of the other three consensus panels were to provide a clinicopathological definition for WM (Consensus Panel 1); to define prognostic markers and criteria to initiate treatment of WM (Consensus Panel 2); and to formulate uniform response criteria in WM (Consensus Panel 4). Consensus Panel 3 was charged with defining treatment recommendations in WM and is the subject of this report.

What Are the Treatment Options for First-Line Therapy of WM?

Statement I

Reasonable choices as first-line agents for the therapy of WM include alkylating agents (eg, chlorambucil), nucleoside analogues (cladribine or fludarabine), and the monoclonal antibody rituximab. There are insufficient data to recommend the use of one first-line agent over another; however, individual patient considerations, including 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 agent. For patients who are candidates for high-dose chemotherapy and autologous transplantation, and in whom such therapy is being seriously considered, exposure to alkylating or nucleoside analogue therapy should be lim-

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ited. Clinical trial participation should be considered a high priority for this patient population.

Discussion

An extensive body of literature exists on the use of alkylating agents,^{1,2} purine nucleoside analogs,³⁻¹⁴ and rituximab¹⁵⁻²⁰; however, no prospective randomized data exist in the literature to direct a treatment choice as initial therapy for this disorder. The data are clear that the use of both alkylating agents and purine nucleoside analogs can deplete hematopoietic stem cells, and the long-term use of these therapies is contraindicated in patients who are candidates for stem cell mobilization.^{21,22}

Statement 2

There are no comparative data to recommend the use of a particular nucleoside analogue, and the selection of either cladribine or fludarabine should be regarded as a reasonable choice if nucleoside analogue therapy is being considered.

Discussion

It is not clear in B-cell chronic lymphocytic leukemia (CLL) whether the purine nucleoside analogs are non-cross-resistant agents.^{23,24} The published literature does not permit selection of one agent as the preferred modality.^{25,26}

Statement 3

There are no comparative data to recommend the use of alkylating, nucleoside analogue, or monoclonal antibody therapy in combination with each other, or in combination with another agent at this time. The use of combination drug therapy should be undertaken in the context of a clinical trial until more data are forthcoming. The published response rates to purine nucleoside analogues range from 31% to 100%. The published response rates to alkylating agents range from 68% to 100%. Because of differences in study size and patient population, these numbers are not directly comparable. For patients in need of rapid tumor control, purine nucleoside analogues have been shown to achieve response in a shorter time interval.

Discussion

A small feasibility study has been published combining cladribine, cyclophosphamide, and/or

prednisone.^{27,28} A dose-escalation study in CLL and non-Hodgkin's lymphoma has also been published.²⁸ These feasibility studies were performed to establish the dose of combinations but do not provide information on time to progression and overall survival to suggest that there is any benefit to combining active agents as opposed to their sequential use in the management of WM.

Statement 4

Abrupt and transient increases in serum IgM levels and serum viscosity may occur in some patients with WM who are receiving rituximab therapy; therefore, close serial monitoring of IgM levels and serum viscosity, if indicated, should be undertaken in patients receiving rituximab therapy.

Discussion

Anecdotal observations of a possible flare phenomenon after administration of rituximab have been reported. It is unknown whether this is the result of release of intracellular IgM in the circulation following the destruction of the lymphoplasmacytic clonal cells. Because of this phenomenon, it is important that physicians not abandon the therapy as a failure until sufficient time has passed to allow for clearance of the IgM monoclonal protein.^{17,29}

What Are the Treatment Options for Relapsed and Refractory Disease in WM?

Statement 5

For patients in relapse or who have refractory disease, the use of an alternate first-line agent may be reasonable. For patients in relapse who demonstrated a durable response of 1 year or more following cessation of initial therapy, the re-use of the same agent(s) may also be reasonable. However, for those relapsing patients for whom high-dose chemotherapy and autologous transplantation is contemplated, further exposure to stem cell-damaging agents (ie, many alkylating agents and nucleoside analogue drugs) should be minimized. Agents that are not toxic to stem cells, such as rituximab, would be preferable if stem cells have not been previously harvested.

Discussion

Patients with WM who relapse off therapy frequently maintain their chemotherapy sensitivity

and can have remission reinduced by the readministration of the identical agent that produced the first response.³⁰ However, in relapsed disease, preliminary data suggest that stem cell transplantation may have a role, and further exposure to stem cell-toxic agents should be avoided if stem cell transplantation is an appropriate consideration.³¹⁻³³

Statement 6

If the options in statement 5 are not applicable, limited published reports suggest that thalidomide as a single agent, and in combination with dexamethasone and/or clarithromycin is active in WM, and may be a reasonable choice for those patients who have failed first-line therapies, or for those relapsing patients who are not candidates for alkylating or nucleoside analogue therapy, or who are pancytopenic.

Myelotoxic combination chemotherapy (eg, cyclophosphamide, vincristine, prednisone [CVP]; cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]; cyclophosphamide, doxorubicin, prednisone [CAP]; and cyclophosphamide, vincristine, prednisone [COP]) may also be reasonable therapy for those relapsing patients who can tolerate such therapy.

Limited published and anecdotal reports suggest that high-dose dexamethasone or α -interferon therapy may also be of benefit in WM patients, and therefore may be a reasonable choice for use in patients who have experienced multiple relapses or who have pancytopenia that would preclude myelotoxic therapy. This may be an ideal patient population for participation in innovative trials of new agents.

Discussion

An extensive body of literature exists on the use of thalidomide and dexamethasone for the treatment of multiple myeloma.^{34,35} Similar data are now appearing on the use of these agents for the treatment of WM.³⁶⁻³⁸ Since these agents produce little or no myelosuppression, they are particularly well suited for patients who have extensive marrow infiltration resulting in dangerous cytopenias that would increase the morbidity of myelosuppressive chemotherapy.

Is There a Role for High-Dose Chemotherapy and Autologous, Allogeneic, and Nonmyeloablative Allogeneic Transplantation?

Statement 7

There is encouraging but no comparative published data on the use and timing of myelosuppressive chemotherapy with autologous stem cell support for the treatment of WM, and this treatment modality should be considered for eligible patients with primary refractory disease, relapsing disease, or complicating amyloidosis.

Discussion

Since disease recurrence in WM is inevitable and frequently drug resistance develops, the use of high-dose therapy in an attempt to overcome drug resistance is reasonable. Small numbers of patients have been transplanted, and although no comparative data exist, the reported treatment-related mortality is low, indicating this technique is worthy of further evaluation.³⁹

Statement 8

Encouraging but very limited results have been reported with the use of allogeneic transplantation (including nonmyeloablative allogeneic transplantation) in WM. In view of the high mortality and/or morbidity risks associated with these modalities of therapy, such patients should be treated in the context of a clinical trial.

Discussion

The median age of patients with WM is 67 years; so the majority of patients would not be suitable candidates for human leukocyte antigen (HLA)-matched stem cells as a source of hematopoietic reconstitution. However, in younger patients with macroglobulinemia, instances of successful allogeneic transplant have been reported,³⁹⁻⁴¹ but the known morbidity and mortality and uncertainty of durable remissions should limit this technique to patients whose outcomes will ultimately be reported in the peer-reviewed literature.

**MANAGEMENT OF IgM-RELATED
DISORDERS: HYPERVISCOSITY, IgM
NEUROPATHIES, CRYOGLOBULINEMIA,
AND AMYLOIDOSIS**

Statement 9

The use of plasmapheresis is indicated for the treatment of symptomatic hyperviscosity, and limited data support its use for the treatment of certain complications associated with IgM monoclonal proteins such as moderate to severe neuropathy, symptomatic cryoglobulinemia, or light chain cast nephropathy. In such circumstances, plasmapheresis should be regarded as interim therapy until definitive therapy can be initiated and shown to control disease.

Rituximab has been reported to be of benefit in patients with IgM autoantibody-related neuropathies and may be regarded as a reasonable choice for treating patients who demonstrate clinical or laboratory evidence of moderate to severe IgM autoantibody-related neuropathies. For patients with mild IgM neuropathies, the use of supportive measures, including analgesics, anticonvulsants such as gabapentin, and antidepressants such as amitriptyline, may be incorporated. Patients should be encouraged to participate in clinical trials.

Discussion

Plasmapheresis has been demonstrated to successfully reduce the complications and morbidity associated with hyperviscosity.⁴²⁻⁴⁴ Hyperviscosity is a direct result of immunoglobulin production by the tumor clone; therefore, cytoreductive therapy should be considered the primary modality of managing hyperviscosity, and plasma exchange should be considered an interim management tool to prevent life-threatening hemorrhage or irreversible central nervous system complications while primary therapy is used to reduce the production of the IgM monoclonal protein. Peripheral neuropathy is a serious and disabling complication associated with IgM monoclonal gammopathies. Plasmapheresis has been demonstrated to produce symptomatic and objective benefit in these patients and is valuable in the management of this problem.⁴⁵⁻⁴⁸

Patients with IgM-associated disorders such as neuropathy do not generally fulfill the criteria for an overt malignancy. Their bone marrow will

demonstrate only small numbers of clonal lymphocytes/plasma cells, and they will not have associated anemia or lymphadenopathy as is seen in WM. Cytotoxic chemotherapy may be inappropriate because the clinical course will be dominated by the neurologic syndrome. Therapies that do not carry a risk of secondary malignancy or long-term immunosuppression such as rituximab have been reported to successfully lead to regression of neuropathy, although its use is usually unnecessary in patients whose symptoms are limited to mild paresthesias of the feet without evidence of motor changes.⁴⁹⁻⁵²

Statement 10

The use of corticosteroids in symptomatic WM and IgM-related disorders in patients with symptomatic mixed cryoglobulinemia with immune complex deposition may be of particular benefit based on limited published experiences.

Discussion

IgM monoclonal gammopathies are invariably present in type II mixed cryoglobulinemia. This immune complex disorder results in systemic vasculitis involving the skin, kidneys, liver, and joints. The primary therapy in patients with hepatitis-associated cryoglobulinemia is interferon. However, deposition of immune complexes resulting in significant morbidity can be effectively managed with the use of high-dose corticosteroid therapy. It is important to recognize that patients with IgM monoclonal gammopathies may have an associated cryoglobulinemia with immune-related manifestations unrelated to overall tumor mass.⁵³⁻⁵⁶

Is There A Role for Splenectomy in the Management of WM?

Statement 11

Splenectomy is rarely indicated, but limited case reports exist suggesting it may be helpful for managing symptomatic splenomegaly, including hypersplenism and painful splenomegaly.

Discussion

Splenectomy does not address the primary issue of WM: the direct marrow infiltration with lymphoplasmacytic cells. Rare patients have been reported in whom splenectomy has led to a hema-

tologic response. Massive splenomegaly where splenectomy led to disappearance of the monoclonal IgM has also been described. Splenectomy can be considered in patients who have severe cytopenias that would increase the risk of cytotoxic drugs or who have symptoms related to their enlarged spleen.⁵⁷⁻⁵⁹

CONCLUDING COMMENTS

Clear-cut guidelines cannot be issued for all patients because of the lack of randomized phase 3 studies. The mainstays of therapy remain alkylating agents and purine nucleoside analogues, usually administered singly or in sequence. The available data do not permit selection of one modality over another. Whether combinations will be shown to be superior to sequential single agents is unknown. The ultimate role of rituximab in the management of WM remains to be defined. The hope is that new targeted therapy may improve the outcome for these patients. Further revisions of these guidelines are planned at the next Waldenstrom's International Meeting to be held in 2004.

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