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, signifi-
cant 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 char-
acterized by bone marrow infiltration with lympho-
plasmacytic cells and by production of monoclonal
immunoglobulin M (IgM). Supportive, but not nec-
essary, 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 manifesta-
tions 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 <100g/l, platelet count <100 × 10⁹/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••].

### 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].