Combination Chemotherapy (M-2) Protocol (BCNU, Cyclophosphamide, Vincristine, Melphalan, and Prednisone) for Waldenström's Macroglobulinemia: Preliminary Report

By Delvyn C. Case Jr.

Fourteen consecutively referred, symptomatic patients with Waldenström's macroglobulinemia (ages 52–87 yr) have been treated with the 5-drug M-2 protocol (BCNU, cyclophosphamide, vincristine, melphalan, and prednisone). Three patients were previously treated and 11 patients were untreated. The majority of patients were symptomatic from hyperviscosity. All patients have responded to therapy. Two patients have achieved complete remissions and 12 patients partial remissions to date. None of the patients with symptomatic hyperviscosity has required plasmapheresis since therapy with the M-2 has been initiated. Lymphadenopathy, hepatosplenomegaly, and anemia have also responded to treatment. Follow-up data are limited, with survival from initiation of therapy with the M-2 ranging from 2 + to 35 + mo (median 17 + mo) (2 +–40 + mo from time of diagnosis). Combination chemotherapy for Waldenström's macroglobulinemia with the M-2 protocol appears to increase the response rate in patients with symptomatic disease. Further survival analysis will be carried out.

Waldenström's macroglobulinemia was first described in 1944 as a disease with insidious onset occurring in late adult life, characterized by anemia, bleeding diathesis, variable lymphadenopathy and hepatosplenomegaly, elevated sedimentation rate, infiltration of the marrow by lymphocytoid plasma cells, and abnormal elevation of serum globulins, later identified as macroglobulinemia.

Recent reviews have stressed the clinical and laboratory variability, the association with other malignancies, hyperviscosity, and the spectrum of disease in patients with Waldenström's-like disorder secreting IgG or IgA rather than IgM.

Macroglobulinemia is considered a chronic disease with a relatively good prognosis. However, chlorambucil, the usually employed alkylating agent, has failed to produce a high response rate. Patients, whether or not responding to chlorambucil therapy, have frequently required repeated plasmapheresis for the symptomatology of hyperviscosity. In one series, 5 of 9 patients responded to chlorambucil or another alkylating agent with or without prednisone; the median survival in the 9 patients was 34 mo from the time of diagnosis.

In other series, 42% of patients responded to alkylating agents: the average survival was 49.2 mo in the responding groups and 24.1 mo in the nonresponders. A median survival of 9 + mo was found in a series of patients with Waldenström's-like disorder without an IgM paraprotein but the patients are still responding.

In an attempt to establish criteria for prognosis in this variable disorder, the character of bone marrow involvement has been evaluated. Those patients with diffuse pattern of involvement had a median survival of 35 mo, whereas those with a nodular pattern had a 75-mo median survival.

Because of the low response rate to single alkylating agent therapy and the limited survival of patients, particularly the nonresponders, a phase II study of combination chemotherapy was devised for patients with active symptomatic Waldenström's macroglobulinemia. Because of the high response rate and improvement in survival produced by the M-2 protocol (BCNU, cyclophosphamide, vincristine, melphalan, and prednisone) in multiple myeloma and response in chronic lymphocytic leukemia, this program was utilized for the management of previously treated and previously untreated patients with Waldenström’s macroglobulinemia. The preliminary results of this study are the basis of this report.

MATERIALS AND METHODS

Selection of Patients

All consecutively referred patients with symptomatic active Waldenström's macroglobulinemia, previously treated or untreated, were eligible for this study. A diagnosis of active Waldenström's macroglobulinemia was made in patients presenting with signs and symptoms including weight loss, bleeding, lymphadenopathy, peripheral neuropathy, anemia, or hyperviscosity, with a monoclonal increase in IgM in the serum and with a diffuse infiltrate of lymphocytoid plasma cells in the bone marrow. Patients with associated malignancies were not included.

Treatment Studies

Pretreatment evaluation included careful history and complete physical examination, complete blood count with platelet count, renal and liver function studies, coagulation screen, chest x-ray, abdominal ultrasound and/or lymphangiogram if applicable, serum and urine immunoglobulin electrophoresis, bone survey, bone marrow aspiration with biopsy, and serum viscosity. Viscosity measurements were done with an RBC pipette viscometer with a solvent
and then 0.5 mg/kg x7) were given orally. Attenuated doses were used with patients having low leukocyte and/or platelet counts. For a white count of 3000/cumm or less, and/or platelet count of < 100,000/cumm or less, the dose of melphalan was reduced to 0.16 mg/kg and the doses of cyclophosphamide and BCNU were reduced by one-half.

Follow-up studies included physical examination, complete blood count and platelet count, serum viscosity, and serum and urine immunoglobulin electrophoresis before each cycle. Once a remission was achieved, the serum viscosity and serum and urine electrophoresis were examined every other cycle. Repeat bone marrow was done when the immunoglobulins became normal and the M-component disappeared. X-rays were repeated as appropriate to check remission status.

Treatment Protocol

The M-2 protocol was given as previously reported: BCNU (1 mg/kg i.v.), cyclophosphamide, (10 mg/kg i.v.), and vincristine, (0.03 mg/kg iv.) were given on day I of each 5-wk cycle. Melphalan (0.25 mg/kg q.d. x4) and prednisone (1 mg/kg q.d. x7 and then 0.5 mg/kg x7) were given orally. Attenuated doses were used with patients having low leukocyte and/or platelet counts. For a white count of 3000/cumm or less, and/or platelet count of 100,000/cumm or less, the dose of melphalan was reduced to 0.16 mg/kg and the doses of cyclophosphamide and BCNU were reduced by one-half.

Treatment was continued every 5 wk. If a complete remission was achieved, treatment was then given every 10 wk for 1 yr and then discontinued. If only a partial remission was obtained, treatment was continued every 5 wk until relapse.

Evaluation of Responses

All patients entered were considerably evaluable. No patient was to be deleted from the study if early death occurred.

Therapeutic response (partial response—PR) was defined as a 50% reduction in the serum IgM level as well as a 50% reduction in the size of lymphadenopathy, splenomegaly, and a reduction in the serum viscosity (if increased) to one-half or less of the original determination. A complete remission (CR) was defined as complete normalization of the serum IgM as well as complete disappearance of the M-component, normal physical findings, normal bone marrow, and serum viscosity as well as x-ray findings.

RESULTS

Response to Therapy

Fourteen consecutively referred symptomatic patients with Waldenström's macroglobulinemia have been treated with the M-2 protocol after preliminary studies. Patient characteristics are noted in Tables 1 and 2. The patients ranged from ages 52 to 87 with a mean of 72 yr. Three patients had been previously treated with chlorambucil; therapy was changed to the M-2 because of treatment failure with continued hyperviscosity symptoms requiring plasmapheresis.

All 14 patients have responded to therapy with the M-2 protocol (Table 2). Twelve of the 14 responses have been partial: the total IgM level has either returned to normal, but a small IgM M-component can still be demonstrated or the IgM is near normal. These 12 patients are otherwise normal, except for changes in hematologic parameters related to treatment. The patients presenting with marked anemia also have had...
full recovery of normal hemoglobin values. Serum viscosity has become normal in all patients. One patient achieved a complete response but demonstrated reappearance of the M-component after therapy was discontinued. At the time of relapse, the total protein was normal. The bone marrow became positive again when the M-component reappeared. Retreatment has achieved a second complete remission. A second patient achieved a complete remission after 2 yr of therapy. All three patients previously treated with chlorambucil responded. These three patients required repeated plasmapheresis during chlorambucil therapy. After one cycle of the M-2, plasmapheresis was not required in any of the patients. In the previously untreated group, 3 patients required plasmapheresis before therapy was initiated. None of those patients required plasmapheresis after the M-2 was begun. Other patients with hyperviscosity were started on the M-2 protocol without plasmapheresis and responded without the need for subsequent plasmapheresis.

Significant partial remissions were noted after 1 or 2 cycles of therapy. Survival from initiation of therapy with the M-2 protocol is 2+–35+ mo (median 17+). Survival from diagnosis is 2+–40+ mo (median 17+). All patients continue in remission. Treatment will continue every 5 wk until relapse or until complete remission. Patients in complete remission are receiving therapy every 10 wk and treatment will be discontinued in 1 yr.

Toxicity

Toxicity has been modest, as previously seen in the studies on myeloma treated with M-2.10–13 Hematologic toxicity is noted in Table 3. Leukopenia infrequently required the reduction of the myelosuppressive drugs. Infectious complications related to treatment did not occur. Anemia and thrombocytopenia were modest. Two patients required red blood cells once treatment was initiated.

Vincristine-related neuropathy, constipation, and hair loss were not limiting. Hemorrhagic cystitis has not been seen.

DISCUSSION

Waldenström’s macroglobulinemia has been considered a chronic disease with a good prognosis that responds to single alkylating agent therapy, usually chlorambucil. However, recent studies demonstrate a 40%–60% response rate to chlorambucil with a median survival of 36 mo.4,8

In prior studies, the M-2 protocol (BCNU, cyclophosphamide, vincristine, melphalan, and prednisone) has shown an improvement in the response rate and survival compared to melphalan and prednisone in patients with a multiple myeloma, particularly in patients with advanced stages.10–13 Because of these results with the M-2 in myeloma and in another B-cell disorder, chronic lymphocytic leukemia,14,15 the M-2 protocol was selected for this study.

In the series presented, 14 patients consecutively referred with symptomatic Waldenström’s macroglobulinemia have been treated with the 5-drug M-2 protocol. The patients were elderly (mean 72 yr old). Three patients had failed chlorambucil therapy and required frequent plasmapheresis; 11 patients were previously untreated. In the entire group, 10 patients had symptomatic hyperviscosity, 10 had splenomegaly, and 9 had anemia. All patients had diffuse marrow involvement with plasmacytoid lymphocytes compatible with Waldenström’s macroglobulinemia. In this preliminary report, all patients have responded to therapy with the M-2 protocol. The total IgM protein level has returned to normal or near normal in all patients, but a small IgM paraprotein is still detectable in 12 of the 14 patients. None of the patients have required plasmapheresis for hyperviscosity symptoms after therapy has been initiated. Significant response could be documented after 1 or 2 cycles of therapy. Survival from initiation of therapy with the M-2 is 2+–35+ mo (median 17+); survival from the diagnosis is 2+–40+ mo (median 17+). All patients continue in remission. The treatment has been well tolerated.

At the present time, treatment is continuing regularly in patients with partial responses to maintain the remissions. Treatment will continue until relapse or until complete remission occurs. In one patient with a complete remission, therapy was discontinued after 1.5 yr. Relapse was detected 8 mo later. Despite a normal total IgM level, a small IgM paraprotein was detected and marrow involvement was documented again. The patient has reverted to normal with therapy given every 5 wk. A second patient has responded with a complete remission after 2 yr of therapy.

This preliminary report suggests that symptomatic patients with Waldenström’s macroglobulinemia with

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Table 3. Hematologic Toxicity

<table>
<thead>
<tr>
<th>Myelosuppression (nadirs)</th>
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<tbody>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>8.5–14 (median 10.6)</td>
</tr>
<tr>
<td>Leukocytes (cells/cu mm)</td>
<td>2,200–5,000 (median 4,300)</td>
</tr>
<tr>
<td>Platelets (cells/cu mm)</td>
<td>25,000–180,000 (median 140,000)</td>
</tr>
</tbody>
</table>

Patients with symptomatic myelosuppression

- RBC transfusions: 2
- Sepsis: 0
- Platelet transfusions: 0

*Includes patient who presented with platelet count 30,000/cu mm.
a pattern of diffuse marrow involvement may be candidates for combination chemotherapy and that response to the 5-drug M-2 protocol is more satisfactory than to single alkylating agent treatment. To date, all 14 patients treated with the M-2 protocol in this study have responded. There have not been any early disease-related deaths or significant treatment complications. All symptoms were rapidly controlled with drug therapy. Plasmapheresis was not required once the M-2 was started. The first two patients on study deteriorated during chlorambucil therapy and required repeated plasmapheresis; prompt remissions were achieved with the M-2. A third previously treated patient required plasmapheresis every 1–2 wk while on chlorambucil (5 mo). Since initiation of therapy with the M-2, plasmapheresis has not been required for the last 35 mo.

Combination chemotherapy for symptomatic Waldenström’s macroglobulinemia appears useful in increasing the response rate and reducing symptomatology, particularly hyperviscosity. Survival data will be analyzed and subsequently reported.

REFERENCES

15. Case DC Jr: Unpublished data
Combination chemotherapy (M-2) protocol (BCNU, cyclophosphamide, vincristine, melphalan, and prednisone) for Waldenstrom macroglobulinemia: preliminary report

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