Treatment of Waldenstrom Macroglobulinemia with 2-Chlorodeoxyadenosine

Meletios A. Dimopoulos, MD; Hagop Kantarjian, MD; Elihu Estey, MD; Susan O'Brien, MD; Kay Delasalle, BS; Michael J. Keating, MB, BS; Emil J. Freireich, MD; and Raymond Alexanian, MD

■ *Objective:* To evaluate the activity of 2-chlorodeoxyadenosine (2CdA) in the treatment of patients with Waldenstrom macroglobulinemia.

■ *Design:* Uncontrolled phase II trial.

■ *Setting:* Tertiary, referral cancer center.

■ *Patients:* Twenty-nine consecutive, symptomatic patients with Waldenstrom macroglobulinemia, of whom 9 were previously untreated.

■ *Intervention:* 2-Chlorodeoxyadenosine was administered as a continuous intravenous infusion at a dose of 0.1 mg/kg body weight per day for 7 days. Only two courses of 2CdA were given and responding patients were then followed without further treatment.

■ *Measurements and Main Results:* A total of 17 (59%) patients responded, including all of those who were newly diagnosed and 40% of those who had failed previous therapies. Treatment was well tolerated except for one death in a patient who had presented with severe pancytopenia. With a median follow-up of 7 months, only one responding patient has relapsed.

■ *Conclusion:* 2-Chlorodeoxyadenosine is a nucleoside analog that was effective in most patients with Waldenstrom macroglobulinemia and was associated with little toxicity.

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From the University of Texas M. D. Anderson Cancer Center, Houston, Texas. For current author addresses, see end of text.

Waldenstrom macroglobulinemia is a low-grade lymphoid malignancy composed of mature plasmacytoid lymphocytes that produce a monoclonal IgM. The disease usually affects older persons and may produce anemia, lymphadenopathy, elevated serum viscosity, or a combination of these (1). Chemotherapy with alkylating agent-steroid combinations has induced responses in approximately 50% of previously untreated patients, with a subsequent median survival of about 5 years (1-3). Fludarabine monophosphate, a nucleoside analog with antitumor efficacy in chronic lymphocytic leukemia and indolent lymphoma, has induced responses in 40% of patients with macroglobulinemic lymphoma who were resistant to standard therapies (4).

2-Chlorodeoxyadenosine (2CdA), a deoxyadenosine analog that is phosphorylated by deoxycytidine kinase, accumulates as chlorodeoxyadenosine triphosphate (chlorodATP) in cells rich in deoxycytidine kinase (5). ChlorodATP inhibits enzymes important in DNA repair, leading to DNA strand breaks that may accelerate the process of programmed cell death (apoptosis) (6). 2-Chlorodeoxyadenosine has been effective in several lymphoid malignancies, the most striking results being in patients with hairy cell leukemia in whom prolonged remissions have occurred after one course of therapy (7, 8). We evaluated the activity of this compound in patients with Waldenstrom macroglobulinemia, a disorder immunophenotypically similar to hairy cell leukemia (9). A marked cytoreductive effect was achieved in all newly diagnosed patients and in many patients with resistant disease, with little toxicity. The high frequency of response provides an opportunity for the study of a sequence of effective regimens in patients with Waldenstrom macroglobulinemia and other low-grade lymphatic malignancies.

Methods

Between January 1991 and February 1992, 29 symptomatic patients with Waldenstrom macroglobulemia were treated with 2CdA (R. W. Johnson Pharmaceutical Company, Raritan, New Jersey) after informed consent was obtained according to institutional guidelines. The primary reasons for treatment were symptoms from worsening anemia (nine patients); weight loss, night sweats, or fever (six patients); hyperviscosity syndrome (five patients); lymphadenopathy (three patients); palpable purpura and arthralgias due to cryoglobulinemia (two patients); hypercalcemia (two patients); cold agglutinin-induced hemolysis (one patient); and severe peripheral neuropathy (one patient) (Table 1). The median age was 65 years (range, 41 to 80 years), and 19 were men. Among the 20 previously treated patients, 9 had not responded to any previous regimen (primary refractory), 7 patients were relapsing despite chemotherapy (refractory relapse), and 4 patients were relapsing while followed without treatment. The median duration from initial treatment was 9 months for patients with primary refractory disease, and 40 months for patients with relapsing disease. All patients had baseline evaluations that included blood counts, hepatic and renal function tests, bone marrow aspirate and biopsy, immunophenotyping, quantitation of CD4+ and CD8+ lymphocytes, serum and urine protein electrophoreses, and quantitation of serum immunoglobulins. Computed tomography of the abdomen and the pelvis was also done when clinically indicated. Blood counts were repeated weekly, serum electrophoretic studies and quantitation of blood lymphocyte subgroups were repeated monthly, and complete restaging was done after completion of 2CdA therapy.

2-Chlorodeoxyadenosine was administered to outpatients at a dose of 0.1 mg/kg body weight per day for a 7-day continuous infusion using a portable pump through a central venous catheter. Two courses of 2CdA were given 4 weeks apart, before removal of the central venous catheter. No further therapy was given during follow-up.

Response criteria were similar to those used in evaluating patients with multiple myeloma and in previously published studies of Waldenstrom macroglobulinemia (1, 2, 10). Response was defined as a sustained decrease by at least 50% of monoclonal IgM synthesis for at least 2 months with more than a 50% reduction of tumor infiltrate at all involved sites. Complete response was defined as disappearance of the abnormal

Table 1. Patient Characteristics

Characteristic	Newly Diagnosed Patients (n = 9)	Previously Treated Patients (n = 20)
Hemoglobin <100 g/L, n	8	11
Platelets <100 × 10^6/L, n	1	7
Lymphadenopathy, n	4	5
Palpable splenomegaly, n	0	3
Bone marrow lymphocytes median, % *(range)*	40 (16 to 94)	24 (10 to 90)

protein by immunofixation, resolution of lymphadenopathy and splenomegaly, and less than 20% lymphocytes in the bone marrow.

Results

Response Rate

Of 29 patients, 18 had a meaningful tumor reduction defined as a 50% reduction of IgM synthesis. One patient achieved a 95% reduction of tumor mass but died on day 70 with pancytopenia and aspergillus pneumonia, and the death was classified as a toxic death.

Thus, 17 of 29 patients responded to treatment (59%) (95% CI, 39% to 76%), of whom 1 patient achieved a complete response. All responding patients had rapid relief from the symptoms due to the disease, including the one patient each with cryoglobulinemia and peripheral neuropathy. Remission was induced in all previously untreated patients and in three of four patients relapsing without therapy (Table 2). Among nine patients with primary refractory disease, seven were treated with 2CdA within 12 months of diagnosis, and four patients responded; neither of the two patients with primary resistance for more than 12 months responded. Remissions were achieved in one of seven patients with refractory relapse (Table 2) and in one of four patients resistant to fludarabine monophosphate.

The median time for a 50% reduction of IgM synthesis in previously untreated patients was 1.0 month (range, 0.2 to 2.0 months) (Figure 1). The kinetics of IgM reduction for the nine previously treated patients who responded was identical (median time for 50% reduction, 1.2 months; range, 0.8 to 2.0 months). Even after 2CdA therapy was stopped, gradual reduction of abnormal protein continued in all responding patients along with disease reduction at all involved sites (*see* Figure 1). Thus, among patients with more than 25% infiltration, bone marrow lymphocytosis was reduced by at least 50% in all 10 responding patients but in only 1 of 5 unresponsive patients (Figure 2). Hemoglobin values of less than 100 g/L increased by at least 20 g/L in 10 of 11 responding patients but did not increase in any of the 8 unresponsive patients (Figure 2). Lymphadenopathy resolved in three of six responding patients and was reduced by more than 50% in the remaining three patients.

Table 2. Response by Disease Status

Disease Status	Patients	Response
	n	n (%)
Newly diagnosed	9	9 (100)
Relapse off therapy	4	3 (75)
Primary refractory	9	4 (44)
Refractory relapse	7	1 (14)
Total	29	17 (59)

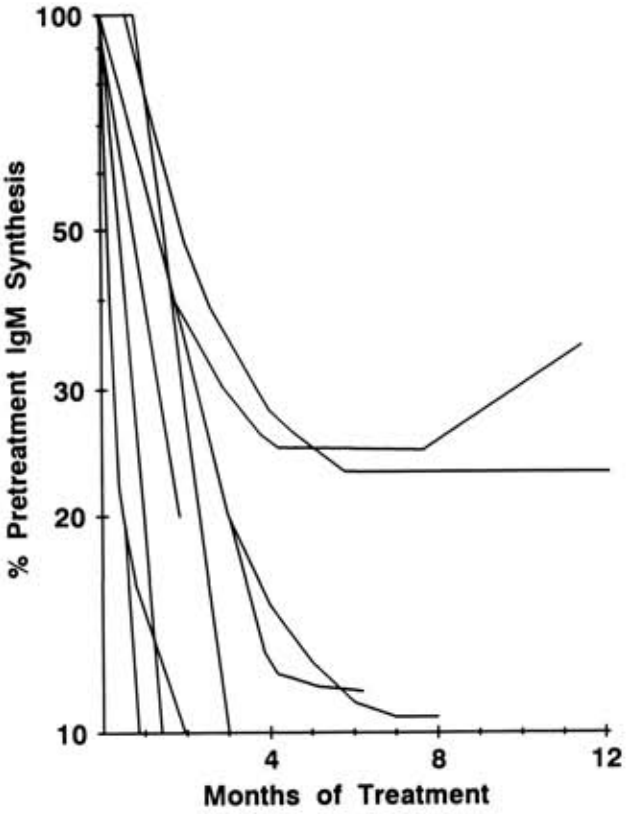

Figure 1. Immunoglobulin M synthesis with 2-chlorodeoxyadenosine treatment in the nine previously untreated patients.

With a median follow-up of 7 months (range, 2 to 16 months), one patient has had a relapse after 9 months, and the earliest treated patient remains in remission after 16 months. One patient died in remission of metastatic adenocarcinoma of unknown origin, and two patients died of resistant macroglobulinemia.

Toxicity

Treatment was well tolerated without serious drug-associated toxicity in all but one patient who was severely pancytopenic before and after 2CdA treatment and died on day 70 with aspergillus pneumonia. Among all patients, the median lowest neutrophil count was 1.5 × 10^6/L (range, 0.1 to 5.5 × 10^6/L), and the median lowest platelet count was 170 × 10^6/L (range, 8 to 331 × 10^6/L). The second course of treatment was administered without delay 4 weeks later in 25 patients; in 3 patients, the second course was delayed 1 to 3 weeks and was omitted in 1 patient because of thrombocytopenia that had preceded 2CdA. Four patients required platelet transfusions, three patients developed bronchitis that responded to antibiotics, and two patients developed herpes zoster.

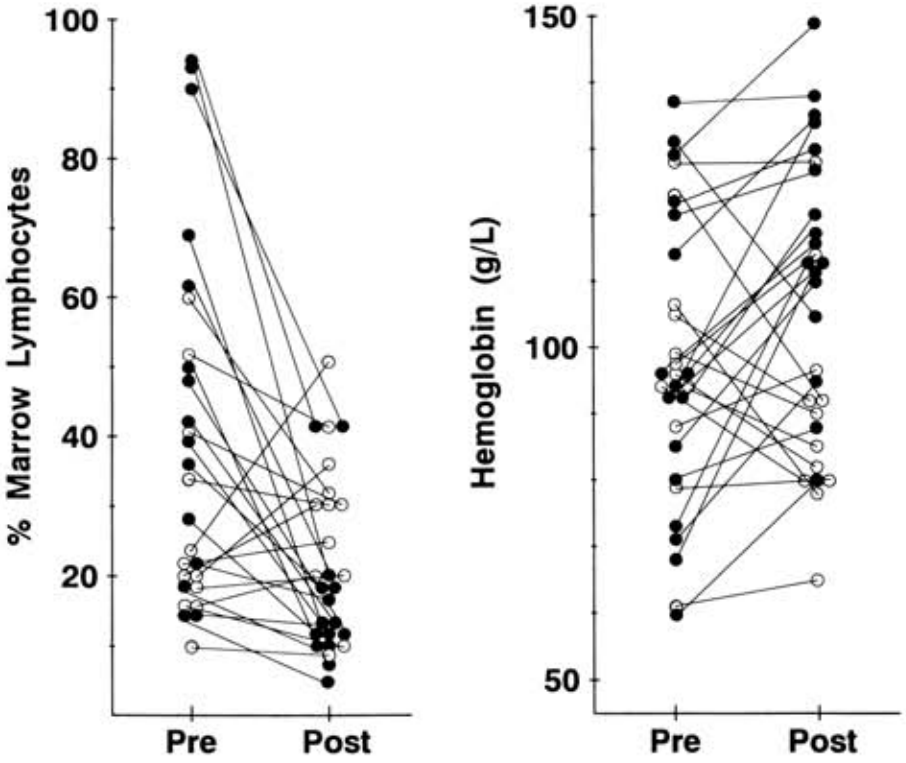

Figure 2. Marrow lymphocytes and hemoglobin levels in patients before and after treatment with 2-chlorodeoxyadenosine. Left. Changes in marrow lymphocytes with 2-chlorodeoxyadenosine (2CdA) in responsive patients (●—●) or unresponsive (○—○) patients. **Right.** Changes in hemoglobin level with 2CdA in responsive patients (●—●) or unresponsive (○—○) patients.

A marked decrease in the number of lymphocytes expressing CD4 surface antigen ("helper" phenotype) occurred in all patients (median, 541 × 10^3/L reduced to 117 × 10^3/L) ($P < 0.01$) with slight decrease in lymphocytes expressing the CD8 surface antigen ("suppressor" phenotype) (median, 343 × 10^3/L reduced to 208 × 10^3/L) ($P = 0.04$). With the longest follow-up of 16 months, no recovery of either class of lymphocytes has occurred. No life-threatening opportunistic infections were associated with the marked and prolonged decline of CD4+ lymphocytes.

Discussion

For many years, a combination of an alkylating agent and a glucocorticoid has been considered the standard therapy for patients with Waldenstrom macroglobulinemia, inducing a response in about one half of previously untreated patients (1-3). Intermittent courses have usually been administered for long periods and have exposed patients to the risk for complications from pancytopenia and rare occurrences of secondary leukemia (11). There have been limited trials of other treatments, including doxorubicin (12), high-dose steroids (13), alpha- or gamma-interferon (14, 15), and deoxycoformycin (16), with occasional benefits reported. Fludarabine has induced responses in 40% of patients who had been resistant to previous treatments, a frequency similar to its activity in chronic lymphocytic leukemia (4).

We report a high frequency of response with 2CdA in Waldenstrom macroglobulinemia, primarily among newly diagnosed patients and those resistant for less than 12 months to previous chemotherapy with standard drugs. Responses were usually rapid in onset and continued even after the completion of treatment. Longer follow-up is needed to define any meaningful gain in remission duration and survival, especially because this disease has a long clinical course. Our positive results after only two courses of treatment that were free of serious toxicity support a major role for 2CdA in the treatment of patients with Waldenstrom macroglobulinemia. Despite our promising results, however, randomized, comparative trials are needed to confirm that 2CdA is the treatment of choice for newly diagnosed patients with Waldenstrom macroglobulinemia.

The therapeutic effect of 2CdA varies markedly among patients with different hematologic neoplasms. Although it is effective in about 90% of patients with hairy cell leukemia, less than one half of those with resistant chronic lymphocytic leukemia responded, a frequency similar to our results in comparable patients with Waldenstrom macroglobulinemia (17). None of 12 patients with multiple myeloma treated at our center has benefited (Dimopoulos M. Unpublished observations). Thus, 2CdA was effective in specific malignancies that derived from a narrow range of the B-cell maturation spectrum (9). Presumably, the antitumor effect results from a direct inhibition by 2CdA of DNA repair in monoclonal lymphocytes. In addition, malignant hairy cell and macroglobulinemic tumor clones may be sustained by normal T-lymphocytes, and the antitumor effect may also be mediated in part by a marked reduction of these lymphocytes.

In summary, 2CdA appears to be a promising modality in the treatment of patients with Waldenstrom macroglobulinemia, inducing a high frequency of remission with minimal toxicity after only two courses of treatment. Thus, multiple drugs have proven activity in patients with this disease, including alkylating agents and

fludarabine. Because these agents do not appear to show cross-resistance, sequential therapies seem worthy of study in an attempt to achieve more pronounced and durable remissions. Our findings also justify similar trials with 2CdA in newly diagnosed patients with other low-grade lymphatic malignancies.

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Requests for Reprints: Meletios A. Dimopoulos, MD, University of Texas M. D. Anderson Cancer Center, Box 1, 1515 Holcombe Boulevard, Houston, TX 77030.

Current Author Addresses: Drs. Dimopoulos, Kantarjian, Estey, O'Brien, Keating, Freireich, and Alexanian, and Ms. Delasalle: Department of Hematology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

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Now where correctness and incorrectness each have a defined limit, surely there must be an art. For absence of art I take to be an absence of correctness and incorrectness; but where both are present, art cannot be absent.

Hippocrates

Submitted by Daniel Sulmasy, MD
Washington, D.C.

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