Primary Therapy of Waldenström's Macroglobulinemia With 2-Chlorodeoxyadenosine

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Purpose: **To assess the activity of 2-chlorodeoxyadenosine (2CdA) as primary therapy for patients with Waldenström's macroglobulinemia.**

Patients and Methods: **2CdA was given to 26 consecutive, previously untreated and symptomatic patients with Waldenström's macroglobulinemia. Two courses were 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. Responding patients were followed up without further therapy and were scheduled to receive two additional treatments with 2CdA on disease relapse.**

Results: **Twenty-two of 26 patients responded to the 2CdA therapy (85%; 95% confidence interval [CI], 65% to 96%), including three patients who achieved a complete response and 19 patients who had a partial response. Treatment was well tolerated, with no acute hematologic toxicity. A marked and sustained reduction of CD4+ lymphocytes occurred in all patients and may have contributed to a fatal infection with disseminated herpes simplex in one patient. With a median follow-up of 13 months, five patients have relapsed and all re-treated patients have responded again to 2CdA.**

Conclusion: **2CdA is highly active in previously untreated patients with Waldenström's macroglobulinemia. A limited program of treatment induced responses of good quality and long duration in more than 80% of patients.**

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WALDENSTROM'S macroglobulinemia is a small-cell lymphocytic lymphoma that produces monoclonal immunoglobulin M (IgM). The disease usually affects older persons and may cause symptoms due to anemia, lymphadenopathy, or elevated serum viscosity.[1-3] Chemotherapy with alkylating agents and steroids has been the standard therapy for patients with symptomatic macroglobulinemia and has induced responses in about one half of previously untreated patients. Courses have been usually administered intermittently for long periods and have exposed patients to the risks of myelosuppression and rarely secondary leukemia.[2-6]

We have recently reported that the nucleoside analog 2-chlorodeoxyadenosine (2CdA) was active in 40% of patients with macroglobulinemia who had failed previous therapies.[7] A few previously untreated patients were included in this study, and their disease appeared to be sensitive to this agent. Based on this encouraging experience, we studied 2CdA as the initial therapy for a larger number of patients with Waldenström's macroglobulinemia.

PATIENTS AND METHODS

Between January 1991 and March 1994, 26 previously untreated patients with Waldenström's macroglobulinemia were treated with 2CdA (R.W. Johnson Pharmaceutical Company, Ortho Biotech Inc, Raritan, NJ) after informed consent was obtained according to institutional guidelines. Patients' characteristics are shown in Table 1. The median age was 65 years (range, 35 to 88 years), and 16 were male. The primary reasons for treatment were worsening anemia (nine patients); lymphadenopathy or organomegaly (eight patients); hyperviscosity syndrome (five patients); weight loss, night sweats, or fever (two patients); cryoglobulinemia (one patient); and peripheral neuropathy (one patient). Two patients were referred to us with advanced Waldenström's macroglobulinemia and concurrent metastatic adenocarcinoma of unknown primary origin (diagnosed 3 months earlier) and metastatic squamous cell carcinoma of the skin (diagnosed 10 months earlier). Because none of the patients had previously received chemotherapy and because both had severe anemia and hyperviscosity syndrome, they were treated with 2CdA.

All patients had baseline evaluations that included blood counts, hepatic and renal function tests, bone marrow aspirate, immunophenotype and biopsy, quantitation of CD4+ and CD8+ blood lymphocytes, serum and urine protein electrophoreses, quantitation of serum Igs and β_2-microglobulin. Chest x-ray and computed tomography of the abdomen and pelvis were also performed. While on treatment, patients were followed up with weekly blood cell counts; serum electrophoretic studies were repeated monthly and complete restaging was done after completion of therapy.

2CdA 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 and responding patients were followed without further therapy until disease relapse when treatment with two courses of CdA was resumed. Patients who did not respond to primary therapy with 2CdA were treated with a combination of chlorambucil and prednisone.

Response criteria were adapted from those used at our center in evaluating patients with multiple myeloma and from previously published studies of Waldenström's macroglobulinemia.[2-4] Partial response was defined as a sustained decrease by at least 50% of monoclonal IgM concentration for at least 2 months; responding patients were also required to achieve more than 50% reduction of

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Table 1. Patient Characteristics

	Patients		Response*	
	No.	%	No.	%
Total	26		22	85
Age > 60 years	15	58	12	80
Lymphadenopathy	12	46	11	92
Splenomegaly	6	23	4	67
Hemoglobin < 100 g/L	14	54	14	100
β_2-microglobulin > 4.0 mg/L	8	32	8	100
Serum peak > 20 g/L	15	58	13	87
Bone marrow lymphocytes > 25%	12	46	11	92

*Response defined by reduction of serum monoclonal IgM level to < 50% of pretreatment level.

tumor infiltrate at all involved sites. Complete response was defined as disappearance of the monoclonal protein by immunofixation, resolution of lymphadenopathy and splenomegaly, and less than 20% lymphocytes in the bone marrow.

Relapse was defined by at least a 25% increase of monoclonal protein from the lowest value or reappearance of lymphadenopathy or anemia. Progression-free survival, overall survival, and disease-specific survival were calculated using the method of Kaplan and Meier.[8] In the calculation of progression-free survival, patients who died in remission from an unrelated cause were censored at the time of death.

RESULTS

Response

Of 26 patients, 19 achieved a partial response and three a complete response for an overall response rate of 85% (95% confidence interval [CI], 65% to 96%). The median time to a 50% reduction of IgM synthesis was 1.2 months (range, 0.2 to 2.5 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 (Table 2, Fig 1). Thus, lymphadenopathy was reduced by more than 50% in all 11 responding patients and resolved in eight patients. Bone marrow lymphocytosis was reduced by at least 50% in all 11 responding patients with more than 25% infiltration. Hemoglobin values of less than 100 g/L increased by at least 20 g/L in 12 of 14 responding patients (Table 2). Serum β_2-microglobulin values of greater than 4 mg/L were also reduced in all responding patients. Throbmocytopenia resolved in 2 patients with this abnormality. Four patients did not respond to 2CdA therapy. One died of cardiorespiratory arrest before further therapy was given and 3 patients remained resistant to a chlorambucil-prednisone combination.

Progression-Free Survival

With a median follow up of 13 months (range, 2+ to 39+ months), five patients (19%) have relapsed after 8 to 18 months (Fig 2). One relapsing patient has not yet received further treatment; the remaining four patients responded again to retreatment with 2CdA. One of these patients died of disseminated herpes simplex infection after 16 months of a second remission and the other three remain in a second unmaintained remission for 6+, 8+, and 12+ months.

Toxicity

Treatment was well tolerated and myelosuppression was mild and reversible; the median lowest neutrophil count was 1.2×10^9/L (range, 0.3 to 5.0×10^9/L) and the median lowest platelet count was 150×10^9/L (range, 38 to 350 10^9/L). The second course of treatment was administered 4 weeks after the first course without delay in all patients. One patient developed neutropenic fever, two patients developed nonneutropenic bronchitis, and one patient developed dermatomal herpes zoster. One patient developed fatal disseminated herpes simplex 16 months after retreatment with 2CdA, which was given because of recurrent disease.

A marked decrease in the number of lymphocytes ex-

Table 2. Clinical Response Pattern of 22 Patients

Patient No.	% of Pre Rx IgM Peak	Reduction of		% BM Lymphocytes		Hemoglobin (g/L)	
		LN	Spleen	Before RX	After RX	Before RX	After RX
1	0	CR	—	45	10	78	148
2	0	CR	—	22	18	130	124
3	5	PR	PR	20	7	91	123
4	10	CR	CR	13	15	96	135
5	28	CR	—	93	27	68	115
6	29	CR	—	30	14	120	139
7	33	PR	PR	16	10	113	120
8	34	CR	—	94	45	97	157
9	46	PR	CR	66	15	84	143
10	48	CR		33	14	119	128
11	49	CR	—	47	12	94	130
12	0	—	—	36	18	120	142
13	22	—	—	20	20	93	110
14	25	—	—	85	8	72	134
15	32	—	—	35	12	97	124
16	33	—	—	22	17	114	137
17	35	—	—	11	10	130	124
18	37	—	—	40	11	95	125
19	38	—	—	20	14	96	130
20	40	—	—	24	14	98	116
21	41	—	—	82	40	85	111
22	46	—	—	11	10	102	118

Abbreviations: Rx, treatment; IgM peak, serum monoclonal IgM component; LN, lymph nodes; BM, bone marrow; CR, complete response; PR, partial response; —, not applicable.

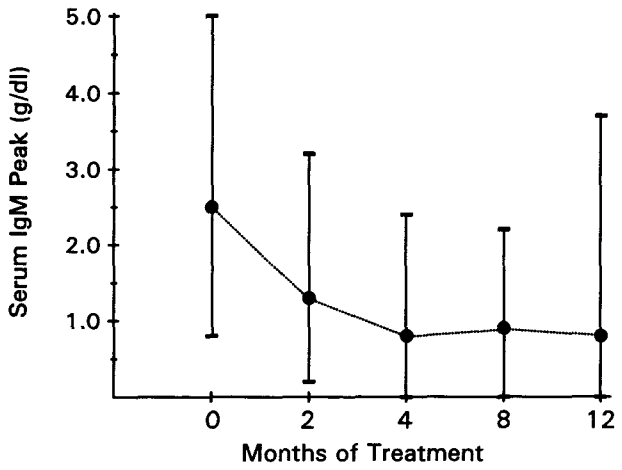

Fig 1. Sustained reduction of serum monoclonal component of IgM concentration after two courses of 2CdA. (Circles represent the median and solid lines the range of values.)

pressing CD4 surface antigen (helper phenotype) occurred in all patients with a less pronounced decrease in lymphocytes expressing CD8 surface antigen (suppressor phenotype) (Table 3). To evaluate the recovery of CD4+ lymphocytopenia with time, CD4 counts were remeasured 12 months after initiation of treatment in 9 patients who responded to 2CdA and remained in remission for at least 12 months. The median lowest value and that at 12 months were 103 × 10^3/L and 150 × 10^3/L, respectively, indicating sustained depression for as long as 1 year.

Table 3. Lymphocyte Subsets in Patients With Waldenström's Macroglobulinemia Treated With 2CdA

	Baseline	Nadir	P
CD4+ lymphocyte counts × 10^3/L*			
Median	764	112	< .01
Range	135-5,368	15-390	
No. ≤ 200	2	13	< .01
No. ≤ 50	0	3	
CD8+ lymphocyte counts × 10^3/L†			
Median	509	201	.04
Range	94-2,505	50-2,100	

*Normal range, 365 to 2,400 × 10^3/L.
† Normal range, 270 to 1,600 × 10^3/L.

Survival

With a median follow-up of 13 months, five patients (19%) have died. One patient died of disseminated herpes simplex and was rated as a treatment-related death. Four patients died of unrelated diseases that were present before the initiation of 2CdA therapy: the deaths of three responding patients were due to cerebral hemorrhage in a patient with severe hypertension, metastatic adenocarcinoma of unknown origin and metastatic squamous cell

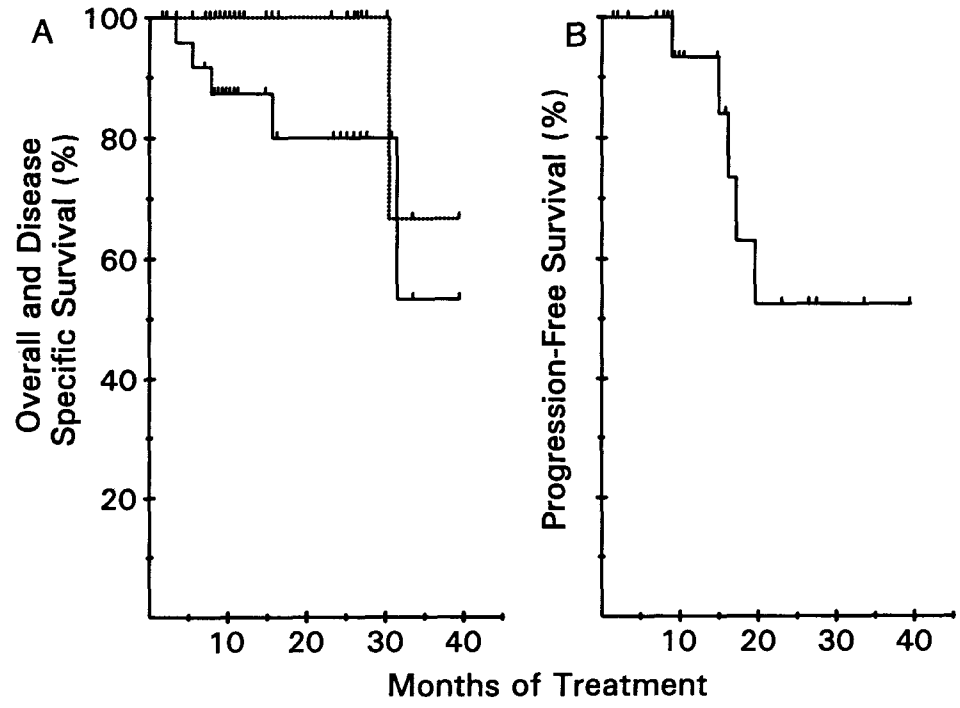

Fig 2. (A) Overall survival (solid line) and disease-specific survival (dotted line). (B) Progression-free survival of 22 patients with macroglobulinemia responding to 2CdA.

carcinoma of the skin. Despite control of the macroglobulinemia, the growth of both solid tumors was not affected and caused the deaths 2 and 8 months later. One resistant patient with severe chronic obstructive lung disease died of cardiorespiratory arrest. Fig 2 shows the overall and disease-specific survival.

DISCUSSION

The standard therapy of Waldenström's macroglobulinemia has been alkylating agents with or without glucocorticoids. These treatments induce a response in about one half of previously untreated patients and produce a median survival of about 5 years.[2-5] Although benefit has been reported in resistant patients who received high dose steroids, alpha or gamma interferon and fludarabine, these agents have not been studied adequately in previously untreated patients.[9-12]

2CdA is an adenosine deaminase-resistant purine analogue that is phosphorylated by deoxycytidine kinase and accumulates as chlorodeoxyadenosine triphosphate (chlorodATP) in cells rich in deoxycytidine kinase. ChlorodATP inhibits enzymes important in DNA repair, leading to DNA strand breaks that may accelerate the process of programmed cell death (apoptosis).[13] The observation that 2CdA exerts its cytotoxic effects independent of the cell cycle may explain its activity in patients with low-grade lymphoid neoplasms such as chronic lymphocytic leukemia, hairy-cell leukemia and low-grade B- or T-cell lymphomas.[14-18]

We have previously described the activity of 2CdA in patients with Waldenström's macroglobulinemia, most of whom were resistant to alkylating agent–based combinations.[7] In this study, a high frequency of response was observed in patients with previously untreated macroglobulinemia with only two courses of 2CdA. Eighty-five percent of patients responded and this frequency appeared higher than the 57% response rate obtained previously among similar patients treated with chlorambucil-prednisone.[19] However, since patient selection and supportive care could have played a role, a randomized trial would be necessary to identify any convincing differences between these treatments. Responses to 2CdA were usually rapid in onset and continued even after the completion of treatment. The reduction of monoclonal protein was associated with resolution of symptoms, of anemia, a significant decrease of organomegaly and lymphadenopathy, and clearing of bone marrow lymphocytosis. The resolution of clinical abnormalities occurred even when the reduction of serum IgM peak barely exceeded 50%, suggesting that a complete remission of low-grade lymphoma may be associated with a substantial residual tumor load. Despite limited treatment with only two courses of 2CdA, remissions appeared durable, in most patients. Furthermore, patients with disease relapsing off therapy remained sensitive to retreatment with 2CdA, indicating that several months of disease control may be achieved with limited treatment and without the use of alkylating agents.

A single course of 2CdA has induced durable responses in most patients with hairy-cell leukemia.[16] Multiple courses of 2CdA have been given recently to previously untreated patients with chronic lymphocytic leukemia.[20] Although a high response rate was observed, there was a high incidence of severe hematologic toxicity and 17% of patients developed severe opportunistic infections.[20] In our study, despite limiting the initial treatment to two courses, CD4 lymphocytopenia was marked and sustained even in patients followed without treatment for many months and one patient who received a total of four courses of 2CdA developed fatal disseminated herpetic infection. Because opportunistic infections may occur more frequently in patients who receive 2CdA, physicians should anticipate such complications to plan an early and effective treatment.[20,21]

The impact of 2CdA therapy on survival will require longer follow-up and eventually a controlled study. Four of our patients (15%) died of conditions that appeared to be unrelated to the underlying macroglobulinemia or its therapy. Two patients died of preexisting metastatic carcinomas while their macroglobulinemia was responding to 2CdA. Although 2CdA did not appear to affect the rate of progression of the unrelated tumors, this question could not be definitively clarified by the study of only two patients. A similar frequency of unrelated deaths has been reported previously for patients with macroglobulinemia treated with alkylating agent-based therapy and for patients with chronic lymphocytic leukemia and hairy-cell leukemia.[19,22] This indicates the need to report both overall and disease-specific survival when evaluating studies of low-grade lymphoid neoplasms in older patients. Although second primary tumors appear to develop at a higher than predicted frequency among patients with low-grade lymphoproliferative disorders, the possible effects of 2CdA on this incidence requires further study.[2,5,23,24]

In summary, 2CdA is a promising agent in the primary treatment of patients with Waldenström's macroglobulinemia, inducing a high frequency of remission with minimal acute toxicity after only two courses of treatment. Longer follow-up is required to assess the clinical sig-

nificance and the reversibility of cell-mediated immunosuppression as well as the impact of 2CdA on the survival of patients with Waldenström's macroglobulinemia.

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