Fludarabine Therapy in Macroglobulinemic Lymphoma

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Fludarabine, a fluorinated analogue of adenine, was given to 11 patients with macroglobulinemic lymphoma, all but one having failed prior standard chemotherapy. Five patients (45%) responded with more than a 50% reduction of immunoglobulin M (IgM) tumor mass for a projected median duration of longer than 1 year. The onset of remission was usually slow, with a median tumor halving time of 5.2 months in responding patients, emphasizing the importance of repeated courses of treatment. Fludarabine is an important new agent effective against macroglobulinemic lymphoma, and should be evaluated further in combination with other active modalities.

WALDENSTROM'S macroglobulinemia, or macroglobulinemic lymphoma, is a generalized chronic lymphoproliferative disorder characterized by the production of a monoclonal immunoglobulin M (IgM) by well-differentiated plasmacytic lymphocytes.[1-3] Clinical features include hyperviscosity syndrome, anemia, splenomegaly, lymphadenopathy, and peripheral lymphocytosis. Treatment has consisted usually of plasmapheresis for hyperviscosity and combinations of alkylating agents and steroids for the malignancy.[2-5] No guidelines or effective therapies have been promulgated for the treatment of patients resistant to standard regimens.

Fludarabine (9-β-d-arabinofuranosyl-2-fluoro-adenine monophosphate) is a fluorinated analogue of adenine. The antitumor activity may be due to inhibition of DNA polymerase and ribonucleotide reductase by the active phosphorylated product, fludarabine triphosphase, as well as by its incorporation into DNA, producing inhibition of DNA synthesis and cell death. Fludarabine has been the most active single agent for chronic lymphocytic leukemia[6] and has also demonstrated antitumor efficacy in other indolent lymphomas.[7] In this article, we report on the high frequency of response induced by fludarabine in patients with macroglobulinemic lymphoma, most of them having failed prior standard therapy.

PATIENTS AND METHODS

Eleven patients with macroglobulinemic lymphoma were treated with fludarabine after informed consent was obtained according to institutional guidelines. The diagnosis was confirmed by the presence of (1) unequivocal infiltration of well-differentiated lymphocytes and atypical or lymphocytic plasma cells in biopsies from involved organs, and (2) a monoclonal IgM peak on immunoelectrophoresis. The patients' characteristics are shown in Table 1. Median age was 57 years (range, 43 to 67 years), and eight (73%) were males. The median time from diagnosis to the start of therapy was 40 months (range, 0 to 94 months). The median IgM level was 2,500 g/100 mL (range, 930 to 8,600 g/100 mL). Seven patients had bone marrow involvement, four of them having peripheral lymphocytosis. Despite the presence of less than 30% lymphocytes in the bone marrow in patients 4, 7, 8, and 11, two of them (patients 7 and 8) had evidence of monoclonal lymphocytic proliferation in the bone marrow by immunophenotyping. The other two patients did not have immunophenotyping done on their marrows. One patient (patient 2) had palpable splenomegaly 25 cm below the costal margin (bcm). Two patients (patients 2 and 5) had palpable hepatomegaly 2 cm and 5 cm bcm, respectively. Three patients (patients 4, 9, and 10) had peripheral lymphadenopathy. The patients' median hemoglobin was 10.1 g/dL (range, 7.1 to 13.5 g/dL), and their median white blood cell (WBC) count was $4.8 \times 10^3/\mu L$ (range, 1.4 to $17.9 \times 10^3/\mu L$). Three had platelet counts below $100 \times 10^3/\mu L$ (Table 1). All but one had received multiple courses of prior chemotherapy with combinations of alkylating agents, steroids, anthracyclines, and interferons. The median number of prior regimens was four. Disease progression, defined as greater than 25% increase in tumor mass while on the immediate previous therapy, was observed in 7 of 10 patients (Table 1).

Fludarabine was given in a dose of 30 mg/m^2 intravenously over 30 minutes daily for 5 consecutive days. Courses were repeated every 4 weeks, provided the white blood cells had recovered to $2.5 \times 10^3/\mu L$ and the platelets to $100 \times 10^3/\mu L$, unless low values were attributed to extensive marrow infiltration by lymphocytes.

Response criteria were similar to those applied in evaluating therapeutic results in multiple myeloma.[8] Response was defined as a sustained decrease in the production rate of monoclonal IgM on electrophoresis by more than 50%, on at least two measurements at 2-week intervals with at least a partial response (PR) in all other involved organ sites.[9] Patients with mixed responses were considered failures.

RESULTS

Response. Five of eleven patients (45%) responded with a greater than 50% reduction of monoclonal IgM production; three had a 75% or greater reduction. In addition, all five patients had at least a PR in other sites of disease involvement (Table 2). In patient 6, IgM levels decreased from 8,600 mg/100 mL to 4,175 mg/100 mL after three courses of fludarabine with normalization of blood and bone marrow lymphocytosis. He was considered unresponsive because only one electrophoresis was conducted during remission. Therapy was withheld because of non-A, non-B hepatitis, and his disease relapsed 2 months later.

The median time of tumor halving among responders was 5.2 months (range, 1.6 to 6.8 months). Figure 1 shows changes in calculated tumor mass in two responding patients. Responses have lasted for 9, 10+, 10+, 14+, and 19+ months, respectively.

Considering the small number of patients, we could not demonstrate any trends between patient characteristics, such

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Table 1. Patient Characteristics

Patient No.	Age (yrs)/Sex	Duration of Disease (mos)	Pretreatment: Hemoglobin (g/dL)	Pretreatment: Platelet Count ($\times 10^3/\mu L$)	Pretreatment: WBC Count ($\times 10^3/\mu L$)	Pretreatment: Peripheral Lymphocyte (%)	Pretreatment: Marrow Lymphocytes (%)	Pretreatment: IgM (g/100 mL)	Prior Therapy	Disease Status	Response/Duration (mos)	Status/Survival (mos)
Responders												
1	52/F	90	10.1	135	3.9	55	30	1,110.0	Chl,P,IFN-A	Stable	Response/19+	Alive/22+
2	49/F	0	7.2	101	4.4	54	52	9,060.0	—	—	Response/14+	Alive/17+
3	66/M	74	10.1	24	17.9	90	81	7,000.0	Melphalan,P,VCAP,Chl,IFN-G, splenectomy,VAD	Progressive	Response/9	Dead/21
4	59/M	94	10.1	199	3.9	27	14	1,185.0	Chl,CVP,VAD,IFN-A,MTX,V-D	Progressive	Response/10+	Alive/13+
5	53/M	32	9.9	79	4.1	94	87	1,010.0	C,MTX,V,P,IFN-A	Progressive	Response/10+	Alive/13+
Nonresponders												
6	67/M	40	7.3	8	1.4	41	61	8,600.0	IFN-A,Chl,P,CVP,A	Progressive	Fail	Dead/7
7	49/M	15	13.5	320	6.8	43	20	930.0	VAD	Progressive	Fail	Alive/5+
8	57/F	93	9.9	355	4.9	6	29	4,050.0	C,Chl,P,IFN-A	Progressive	Fail	Alive/4+
9	59/M	33	7.1	185	7.0	18	60	1,700.0	Chl,IFN-G,VAD	Progressive	Fail	Dead/3+
10	64/M	66	10.9	172	4.8	32	69	2,500.0	Chl,IFN-G	Stable	Fail	Dead/12
11	43/M	14	11.8	145	5.3	31	27	3,800.0	BCNU,C,P,V	Stable	Fail	Alive/19+

Abbreviations: V, vincristine; C, cyclophosphamide; A, Adriamycin; Chl, chlorambucil; P, prednisone; MTX, methotrexate; VAD, vincristine-Adriamycin-dexamethasone; IFN-A, alfa interferon; IFN-G, gamma interferon.

Table 2. Response Patterns

Patient No./ No. Courses	Time to Therapy	IgM (g/100 mL)	IgM Reduction (%)	Site of Involvement: Hemoglobin (g/dL)	Platelets ($\times 10^3/\mu L$)	Marrow Lymphocytes (%)	Peripheral Lymphocytes (%)	Absolute Lymphocyte Count ($\times 10^3/\mu L$)	Other Organs	
1/2	Pre	1,110		10.1	135	30	55	2.1		
	Post	198	94	11.1	135	5	25	0.5		
									Spleen (cm bcm)	Liver (cm bcm)
2/9	Pre	9,060		7.2	101	52	54	2.4	25	3
	Post	2,910	87	12.8	167	13	11	0.3	0	0
3/8	Pre	7,000		10.1	24	81	90	16.1		
	Post	1,275	75	10.8	126	20	10	0.9		
									Axillary LN (cm)	Inguinal LN (cm)
4/5	Pre	1,185		10.1	199	14	27	1.1	3 × 3	3 × 3
	Post	310	59	12.1	116	10	16	0.7	0	0
									Liver (cm bcm)	Abdominal LN (cm)
5/6	Pre	1,010		9.9	79	87	94	3.9	5	≤6
	Post	370	57	13.2	376	11	21	0.5	0	≤2

Abbreviations: LN, lymph nodes; bcm, below costal margin.

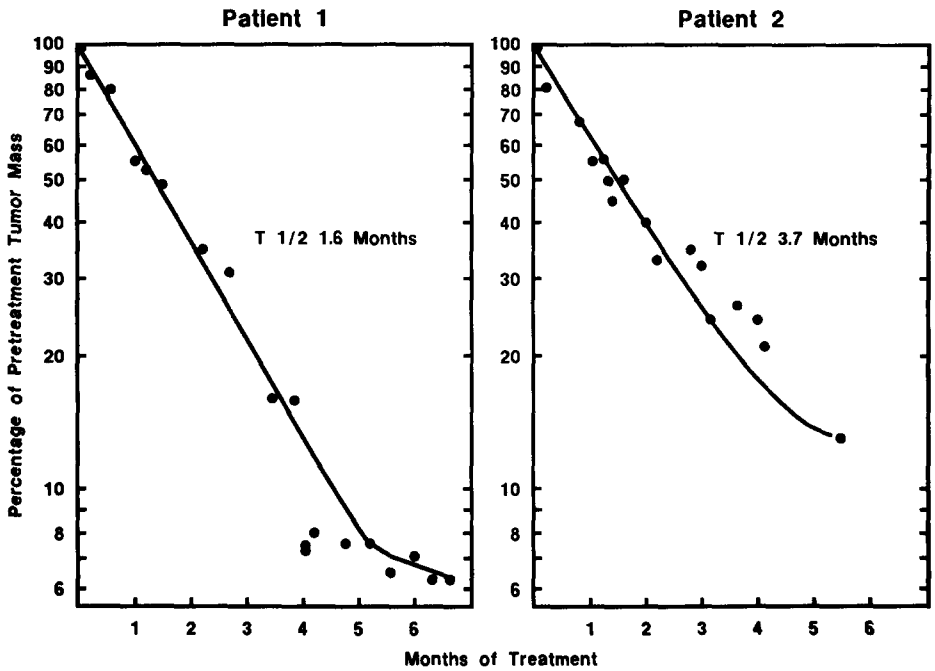

Fig 1. Reduction of calculated tumor mass in two patients with macroglobulinemic lymphoma responding to fludarabine.

as age, duration of disease, extent of prior therapy, or IgM levels, and response to fludarabine (Table 1).

The details of the response patterns among the five responders are shown in Table 2. After two courses of fludarabine, patient 1 obtained a 94% reduction in the IgM tumor mass, and a decrease of the peripheral lymphocytosis from 55% to 25%. She remains in remission 14 months after discontinuation of therapy. Patient 2 has achieved a nodular partial response (residual lymphoid nodules) in the bone marrow, and complete response of her massive splenomegaly. In addition, the IgM tumor mass was reduced by 87%. She continues to receive fludarabine therapy. Patient 3 achieved a complete remission in the peripheral blood and bone marrow, in addition to a 75% tumor mass reduction. Treatment was stopped after eight courses of fludarabine. He developed a second primary malignancy, a squamous cell carcinoma of the glottis and larynx, and died 13 months after treatment was discontinued. Patient 4 has received a total of five courses of fludarabine, achieving a complete regression of bilateral axillary lymphadenopathy from 3 × 3 cm to nonpalpable, and a partial regression of bilateral inguinal lymph nodes from 3 × 3 cm to 1 × 1 cm. IgM tumor mass was also reduced by 59%. Patient 5 is continuing on therapy. After six cycles of fludarabine, he had obtained a complete response in the peripheral blood, marrow, and liver and a PR in the extensive abdominal lymphadenopathy consisting of numerous (more than 10) enlarged lymph nodes up to 6 cm each, which have all decreased to 2 cm or less.

Toxicity. The side-effects associated with treatment were usually mild and reversible. Mild thrombocytopenia (50 to 100 × $10^3/\mu L$) was observed in two patients, and infections occurred in three patients. One patient developed fever with normal granulocyte counts that responded to antibiotic therapy; another patient (patient 6) developed a dental abscess and non-A, non-B hepatitis; a third developed a herpes simplex infection during the fourth course, bronchitis during the seventh course, and herpes zoster during the ninth course.

DISCUSSION

Few reports are available on the treatment of patients with macroglobulinemic lymphoma. Alkylating agents, such as chlorambucil and cyclosphosphamide, in combination with glucocorticosteroids, have been used most frequently as the primary treatment for the disease. Most patients respond to varying degrees and for various durations; the median survival time is about 4 years. No guidelines or effective therapies are available for patients resistant to these standard regimens.[1-5]

In this report, we describe the use of a new agent, fludarabine, which has produced remissions of good quality in a high proportion of patients with macroglobulinemic lymphoma resistant to standard therapy. Response criteria were rigid and based on unequivocal and sustained reductions of both monoclonal IgM production and tumor mass. Responses were usually slow in onset and required multiple courses of treatment, but were durable in nature. Complete disappearance of IgM tumor mass was not obtained, in contrast to the results with intensive chemotherapy (M2 protocol).[5] Side effects were infrequent, mild in degree, and reversible. The number of patients was too small to yield any prognostic trends regarding predictive factors for response to fludarabine. However, four of the five responding patients were either untreated (one patient), or had long periods of disease control with prior chemotherapy.

Because of the rarity of macroglobulinemic lymphoma, experience with chemotherapy or biologic treatment is fragmentary.[9-13] Gomez et al reported responses in two patients

who received vincristine, bleomycin, and prednisone.[9] Pihlstedt emphasized the value of plasma exchange and moderate doses of cytostatics in achieving durable responses.[10] One patient treated with pentostatin by Riddell et al also achieved a significant response.[11] Ohno et al described one responder among three patients who received recombinant alpha or lymphoblastoid interferon.[12] Finally, Quesada et al observed no objective responses among five patients treated with recombinant gamma interferon.[13]

In summary, this experience with fludarabine suggests a high level of antitumor efficacy in patients with advanced macroglobulinemic lymphoma, as was also seen among patients with other indolent B cell neoplasms.[6,7] The activity in patients resistant to standard therapy suggested even greater use might be shown in newly diagnosed patients, or among those in partial remission with other treatments. Further studies involving combinations of fludarabine and other active agents and during remission consolidation may improve the response rate and remission time of patients with macroglobulinemic lymphoma.

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REFERENCES

1. Waldenstrom J: Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia—a new syndrome? Acta Med Scand 117:216, 1944

2. McCallister BD, Bayrd ED, Harrison EG, McGuckin W: Primary macroglobulinemia—review with a report on 31 cases and notes on the value of continuous chlorambucil therapy. Am J Med 43:394, 1967

3. MacKenzie MR, Fudenberg HH: Macroglobulinemia—an analysis of forty patients. Blood 39:874, 1972

4. Fahey JL, Barth WF, Solomon A: Serum hyperviscosity syndrome. JAMA 192:464, 1965

5. Case DC Jr: Combination chemotherapy (M-2) protocol (BCNU, cyclophosphamide, vincristine, melphalan, and prednisone) for Waldenstrom's macroglobulinemia. Blood 59:934, 1982

6. Keating MJ, Kantarjian H, Talpaz M, Redman J, Koller C, Barlogie B, Velasquez W, Plunkett W, Freireich EJ, McCredie KB: Fludarabine: A new agent with major activity against chronic lymphocytic leukemia. Blood 74:19, 1989

7. Redman J, Cabanillas F, McLaughlin P, Hagemeister F, Velasquez W, Swan F, Rodriguez M, Plunkett W, Keating M: Fludarabine phosphate—a new agent with major activity in low grade lymphoma. Proc AACR 29:211, 1988 (abstr 840)

8. McLaughlin P, Alexanian R: Myeloma protein kinetics following chemotherapy. Blood 60:851, 1982

9. Gomez GA, Han T, Ozer H, Henderson ES: Treatment of refractory lymphoproliferative diseases with daily, low-dose vincristine, continuous infusion of bleomycin, and high-dose prednisone. Med Pediatr Oncol 12:239, 1984

10. Pihlstedt P: Plasma exchange and moderate dose of cytostatics in advanced macro(cryo)globulinemia. Acta Med Scand 212: 187, 1982

11. Riddell S, Johnston J, Rayner H, Israel L: Response of Waldenstrom's macroglobulinemia to pentostatin (2' Deoxycoformycin). Cancer Treat Rep 70:546, 1986

12. Ohno R, Kodera Y, Ogura M, et al: Treatment of plasma cell neoplasma with recombinant leukocyte A interferon and human lymphoblastoid interferon. Cancer Chemother Pharmacol 14:34, 1985

13. Quesada JR, Alexanian R, Kurzrock R, Barlogie B, Saks S, Gutterman JU: Recombinant interferon gamma in hairy cell leukemia, multiple myeloma, and Waldenstrom's macroglobulinemia. Am J Hematol 29:1, 1988