

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Cladribine Activity in Adult Langerhans-Cell Histiocytosis

By Alan Saven and Carol Burian

Langerhans-cell histiocytosis (LCH) results from the accumulation of tissue histiocytes derived from the same progenitor cells as monocytes. Because cladribine is potentially toxic to monocytes, we conducted a phase II trial of cladribine. Cladribine was administered to 13 LCH patients at 0.14 mg/kg per day by 2-hour intravenous infusion for 5 consecutive days, every 4 weeks for a maximum of six courses. Median age was 42 years (range, 19 to 72) and median pretreatment disease duration was 99 months (range, 6 to 252). One patient was untreated, one had received prior prednisone only, one prior radiation only, six prior radiation and chemotherapy, and four prior surgery, radiation, and chemotherapy. Seven patients had cutaneous involvement, six multifocal osseous, six pulmonary, two each with soft tissue and nodal involvement, and four had diabetes insipi-

du. Of 13 patients, 12 were evaluable for response and all for toxicity. After a median of three courses (range, 1 to 6), seven (58%) patients achieved complete responses (two pathologic and five clinical) and two (17%) patients achieved partial responses; overall response rate, 75%. Median response follow-up duration was 33 months (range, 1 to 65). Seven patients experienced grade 3 to 4 neutropenia. Only one patient had a documented infection, dermatomal herpes zoster. At a median follow-up of 42 months (range, 5 to 76), 12 patients remain alive and one patient has died. Thus, cladribine has major activity in adult LCH and warrants further investigation in both pediatric and adult LCH as a single agent and in combination with other drugs.

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LANGERHANS-CELL histiocytosis (LCH) results from the clonal proliferation and accumulation of tissue histiocytes, clinically manifested as osteolytic lesions, hypothalamic insufficiency, and seborrheic and vesiculopustular lesions on the scalp, perineum, rectum, and vulva.^{1,2} The clinical presentation and course of individual patients varies from indolent to aggressive and from spontaneous remission to rapid death. Prognosis is determined by the number of affected organs and their dysfunction.^{3,4} The diagnosis is established by identifying Langerhans or histiocytosis X cells, associated occasionally with multinucleated giant cells, in affected lymph nodes, bones, skin and lungs by microscopy or immunohistochemical staining, such as positivity for the S-100 protein.⁵ Birbeck granules seen on electron microscopy and characterized by the indentation across the nucleus of mononuclear cells, are pathognomonic.

Treatment of LCH is principally palliative. The therapeutic modalities most frequently used are corticosteroids, alkylating agents, antimetabolites, vinca alkaloids, combination chemotherapy, irradiation, and immunotherapy.⁶⁻⁸ 2-Chlorodeoxyadenosine (2-CdA) (cladribine, Leustatin [Ortho Biotech, Raritan, NJ]), a purine analogue with activity in indolent lymphoproliferative disorders^{9,10} and myeloid leukemias^{11,12} is potentially toxic to monocytes *in vitro*.¹³ Cladribine was approved by the Food and Drug Administration (FDA) in 1993 for the treatment of hairy cell leukemia, an uncommon chronic B-cell lymphoproliferative disorder characterized by mononuclear cells displaying cytoplasmic projections, as single courses of treatment induce long-lasting complete remissions in the vast majority of patients treated.⁹ Because tissue histiocytes and circulating monocytes have common progenitor cell origins, cladribine was a rational therapeutic option. Previously, we reported on three patients with LCH, all of whom obtained complete and durable remissions after cladribine administration.^{14,15} We, therefore, conducted a phase II study evaluating the efficacy and toxicity of cladribine in larger numbers of patients with LCH.

MATERIALS AND METHODS

Eligibility Criteria

Patients were required to have a histologic diagnosis of LCH with clinically or radiologically measurable disease and symptoms. The

histopathologic diagnostic criteria used were those previously proposed by the Writing Group of the Histiocyte Society.¹⁶ Definitive diagnosis required the finding of Birbeck granules in lesional cells by electron microscopy or demonstration of CD1a antigenic determinants on the surface of lesional cells. Diagnosis was justified when the lesion was characteristic by light microscopy and the lesional cells showed the presence of two or more of the following features: positive stain for adenosine triphosphate (ATPase), S-100 protein, or alpha-D-mannosidase or characteristic binding of peanut lectin in lesional cells. Presumptive diagnosis was warranted when findings, on study of conventionally stained biopsy material alone, were merely "consistent" with those defined in the literature. All pathologic materials were reviewed by the pathologists at Scripps Clinic.

Patients could have received prior chemotherapy, steroids, radiation therapy, red blood cell or platelet transfusion support, but had to be off chemotherapy or radiation therapy for more than 4 weeks. Adequate renal (serum creatinine < 2.0 mg/dL) and hepatic function (bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) < 2 times normal) were required. Patients also had to be more than 15 years of age and accessible for follow-up.

Approval was obtained from the Institutional Review Board for these studies. Informed consent was provided according to the Declaration of Helsinki.

Baseline and Follow-Up Studies

Before the initiation of cladribine, patients underwent a complete history and physical examination, complete blood count with differen-

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tial and platelet count, chemistry panel, serum fibrinogen, erythrocyte sedimentation rate, thyroid functions, early morning serum cortisol, bone marrow aspiration and biopsy, chest x-ray, bone survey, computerized tomographic (CT) scan of the abdomen, and biopsy of affected tissue or organs. In those patients with subcutaneous lesions, patients underwent baseline photographs of involved areas. During therapy and subsequent follow-up, patients underwent a complete history and physical examination before each course of cladribine and monthly thereafter. All patients underwent a complete blood count with differential and platelet count on days 1, 3, and 5 while receiving cladribine and weekly thereafter. The full chemistry panel was redrawn on the first and third day of cladribine and monthly thereafter. Four weeks after the completion of the third course of cladribine, patients were clinically restaged to assess response. Complete blood counts, chemistry panel, serum fibrinogen, bone survey, bone marrow aspiration and biopsy, CT scan of the abdomen, and chest x-ray were repeated after three courses of cladribine, if previously abnormal, and again at maximum response.

Response Criteria

A complete response was defined as the absence of active disease on physical examination and imaging studies.¹⁷ Disease activity was established on clinical grounds.¹⁷ Active disease was defined as chronic progression, new symptomatic, histologically verified organ manifestations or local disease recurrence after initially successful therapy. Inactive disease was defined as no lesion/disease, stable asymptomatic, or stable symptomatic, but not progressive disease. Cutaneous lesions did not require repeat biopsy to document histologic resolution. A partial response was defined as a reduction by more than 50% of all measurable and active disease for more than 1 month. Any response less than partial was designated as no response. All clinical assessments were made by the author (A.S.), and all imaging studies were reviewed by the radiologists at Scripps Clinic.

Cladribine Therapy

Cladribine was administered at 0.1 mg/kg daily for 7 days by continuous intravenous infusion (patients 1 and 2) and 0.14 mg/kg per day over 2 hours intravenously daily for 5 consecutive days (patients 3 to 13), with courses repeated every 4 weeks, toxicity permitting. If, 4 weeks after the completion of the third course of cladribine, the patient did not achieve a partial or complete response, then no further cladribine was administered. The patient was then switched to alternative therapy if deemed appropriate. If, 4 weeks after the completion of the third course of cladribine a partial response had been achieved, cladribine was administered until maximum response or prohibitive toxicity was encountered. If a complete response had been achieved, then the patient received no further cladribine until documented disease recurrence, when this occurred. The total number of courses of cladribine administered did not exceed a maximum of six courses.

Toxicity

The National Cancer Institute Common Toxicity Criteria were used for the evaluation of toxicity with grade 3 and 4 being considered significant.¹⁸ The initiation of cladribine therapy was delayed for an absolute granulocyte count $< 1.0 \times 10^9$ per liter, or a $> 50\%$ reduction in the pretreatment platelet count. Cladribine was then held until the platelet count was more than 75% of the pretreatment value, or if the platelet count was $> 100 \times 10^9$ per liter, cladribine could be administered regardless.

RESULTS

Patient Characteristics

Patient characteristics at the initiation of cladribine are shown in Table 1. Of the 13 patients treated, seven were men and six

were women. The median age at initiation of cladribine was 42 years (range, 19 to 72 years) and the median pretreatment duration was 99 months (range, 6 to 252 months). Using the histopathologic diagnostic criteria proposed by the Writing Group of the Histiocyte Society, five patients had a definitive diagnosis, four had a diagnosis and four had a presumptive diagnosis of LCH.¹⁶ One patient had received no prior therapy, one patient had received prior prednisone, one patient radiation only, six patients radiation and chemotherapy, and four patients surgery, radiation, and chemotherapy. Using the staging system as designated by Lavin and Osband,¹⁹ eight patients had stage I disease, four patients stage II disease, and one patient had stage III disease. The sites of active disease before the initiation of cladribine was skin in seven patients, bone (all multifocal) in six patients, lung in four patients, soft tissue in two patients, and lymph nodes in two patients. Four patients had prior diabetes insipidus, two patients had loss of teeth from gingival involvement, and two patients had marked pulmonary fibrosis. Patients 1 and 2 have been previously reported,^{14,15} as have been the pretreatment characteristics of patient 12.²⁰

Responses and Response Duration

Of the 13 patients treated, 12 were evaluable for response and all for toxicity. Patient 11, inevaluable for response, received only a single course of therapy and was not seen in follow-up. After a median of three courses of cladribine (range, 1 to 6), seven (58%) patients achieved complete responses (two pathologic and five clinical) and two (17%) patients partial responses, for an overall response rate of 75% (95% confidence interval, 43% to 95%). Three (25%) patients had stable disease and were scored as nonresponders. The median response follow-up duration was 33 months (range, 1 to 65+ months); the median follow-up response duration for complete responders was 33+ months (range, 1 to 65+ months), and the response follow-up duration for the partial responders was 36+ and 8+ months.

Individual patient responses and their duration are shown in Table 2. The cutaneous responses of patients 6 and 12 are shown in Figs 1 and 2. The pretreatment CT scan of the abdomen and pelvis in patient 6 showed asymmetric enlargement and fascial plane effacement of the musculature of the left buttocks, including the gluteal, pyriformis, obturator, and internis muscles, with extension through the sciatic notch and encroachment into the fat of the left ischioanal fossa. After cladribine, there was complete resolution with the absence of asymmetry on CT scan.

Toxicities, Late Events, and Survival

The principal acute toxicity was hematologic with seven patients experiencing grade 3 or 4 neutropenia (Table 2). In two of these seven patients, neutropenia was complicated by fever necessitating hospital admission for intravenous antibiotics. In both patients, cultures remained negative. No patients experienced grade 3 to 4 anemia or grade 3 to 4 thrombocytopenia. Patient 11, with a history of a seizure disorder, experienced chills, tightness in his chest, wheezing, hyperventilation, hypertension, and became briefly cyanotic after the acute administration of cladribine. It resolved spontaneously without treatment, and it is unknown if this event was related to cladribine or if the patient had experienced a seizure. Only a single patient, patient

Table 1. Pretreatment Patient Characteristics

Patient No.	Age/Sex (yrs)	Pretreatment Disease Duration (mos)	Pathologic Diagnosis ¹⁶	Prior Therapy	Stage at Start of Cladribine	Sites of Disease Involvement
1	33/F	204	Presumptive	Prednisone, vinblastine, azathioprine, VP-16, methotrexate Radiation	I	Skin, external auditory canals, mouth, vagina, diabetes insipidus
2	57/M	7	Definitive	Prednisone	II	Skin, neutropenia
3	20/M	176	Presumptive	Prednisone, vinblastine, suppressin A (experimental), VP-16 C5 vertebrectomy	I	Bone (vertebrae, orbits, skull, sternum, ribs and pelvis)
4	50/M	21	Presumptive	Prednisone Radiation Surgical debridement	I	Bone (mandible and ribs), gingiva, tooth loss, lung
5	42/F	133	Diagnosis	Prednisone, vinblastine Radiation Bowel resection, partial hepatic resection	I	Skin, mouth, vagina, colon, diabetes insipidus
6	35/M	99	Diagnosis	Topical nitrogen, mustard, VP-16 Electron beam radiation	I	Skin, soft tissue, diabetes Insipidus, pulmonary
7	72/M	34	Definitive	Prednisone, cyclophosphamide Radiation	I	Skin
8	47/M	114	Definitive	Radiation	II	Bone (mandible and maxilla), lung, edentulous
9	37/M	22	Diagnosis	Prednisone, vinblastine Radiation Pericardiectomy	III	Bone (mandible, radius and ribs), soft tissue, lung, lymphadenopathy, ascites, diabetes insipidus
10	68/F	64	Diagnosis	Vinblastine, methotrexate, 6-thioguanine Radiation	I	Skin, mouth, vagina, anemia
11	34/M	146	Definitive	Vinblastine, vincristine, interferon, methotrexate, VP-16, prednisone Radiation	II	Bone (skull, hips, vertebrae, clavicle, tibia and ribs), lung
12	46/F	253	Definitive	Vinblastine, methotrexate, isotretinoin, interferon Radiation	I	Skin
13	19/F	6	Presumptive	None	II	Bone (skull, femur, fibula and pelvis), lung, lymphadenopathy

1, had a documented infection, dermatomal herpes zoster, which occurred soon after the first course of cladribine and resulted in a delay in the second course. The course of patient 6 was complicated by diarrhea, which resolved spontaneously

without therapy. Patient 1 with a prior history of papillary carcinoma of the thyroid had disease recurrence 4 years after cladribine therapy. She had a preceding history of papillary carcinoma of the thyroid having undergone a resection for this 2

Table 2. Cladribine Treatment Outcomes

Patient No.	Response	Response Duration (mos)	No. of Cladribine Courses	Toxicities/Late Events	Status (follow-up in months)
1	CR	65+	4	Grade 4 neutropenia with fever Recurrence of papillary carcinoma of thyroid	Alive (76)
2	CR	36	2	Chronic myelomonocytic leukemia	Dead (41)
3	NR	—	3	Grade 3 neutropenia	Alive (39)
4	CR	46+	2	Grade 4 neutropenia	Alive (49)
5	CR (Pathologic)	5	3		Alive (47)
6	CR	33+	6	Grade 3 neutropenia	Alive (48)
7	CR (Pathologic)	1	6		Alive (47)
8	CR	10+	6		Alive (45)
9	PR	36+	6	Grade 4 neutropenia with fever	Alive (42)
10	NR	—	2	Grade 4 neutropenia	Alive (32)
11	NE	—	1	Possible acute allergic reaction to cladribine	Alive (16)
12	PR	8+	6	Grade 4 neutropenia	Alive (15)
13	NR	—	3		Alive (6)

Abbreviations: CR, complete response; PR, partial response; NR, no response; NE, not evaluable.

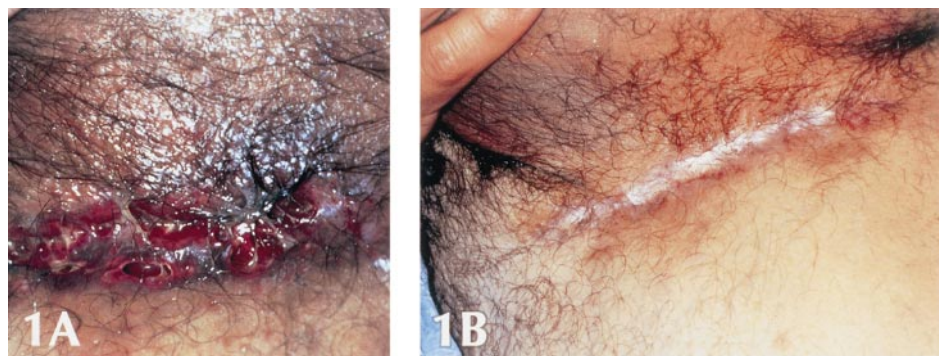


Fig 1. The inguinal area of patient 6 is shown before (A) and after (B) six courses of cladribine. Pretreatment, the area shows active cutaneous lesions, serosanguineous, and pustular drainage, which has resolved after treatment.

years before institution of cladribine therapy. Patient 2 developed chronic myelomonocytic leukemia 38 months after cladribine therapy. Bone marrow cytogenetics showed a normal male karyotype.

At a median follow-up of 42 months (range, 5 to 76), 12 patients remain alive and one patient (patient 2) has died.

DISCUSSION

This phase II study has demonstrated that single-agent cladribine has major activity in the treatment of adults with LCH, and this was achieved with a favorable toxicity profile. Responses were documented in patients with cutaneous, oral,

osseous, soft tissue, lymph node, and pulmonary sites of involvement. The majority of responses were complete, generally durable, and unmaintained. These results confirm and extend the observations made previously in three adults with LCH treated with cladribine.^{14,15}

Other investigators have also reported in small numbers of patients on the successful application of cladribine to the treatment of LCH.^{21,22} Dimopoulos et al²³ administered cladribine to a 34-year old patient with LCH who was resistant to corticosteroids and etoposide. After four courses of cladribine, the patient achieved a complete remission, which was ongoing for 12 months. Stine et al²⁴ reported on three children with



Fig 2. These photographs show the purple-colored, nodular cutaneous lesions of patient 12. Her face, with the nasal disfigurement, and her right shoulder is shown before (A and C) and after six courses of cladribine therapy (B and D).

LCH, all of whom achieved complete responses after cladribine therapy. As expected, myelosuppression was the principal toxicity.

Cladribine is an antimetabolite that uniquely destroys resting and dividing lymphocytes equally.²⁵ It is also potently toxic to monocytes,¹³ which may explain its potential application to the treatment of monocyte-derived neoplasms and chronic inflammatory conditions, like multiple sclerosis.^{26,27} A further potential mechanism of action of cladribine in LCH may be through T-cell depletion, as cladribine is potently immunosuppressive.^{28,29} It is thought that the activity of cyclosporine in LCH is mediated through its immunosuppressive effects.³⁰ It should be noted that children with congenital adenosine deaminase deficiency, in which there is only an absence or immunologic incompetence of lymphocytes, do not have monocytopenia.³¹ Additionally, 2'-deoxycoformycin, a tight-binding inhibitor of adenosine deaminase that in some ways simulates the defects of severe combined immunodeficiency disease and has a similar spectrum of activity against indolent lymphoproliferative disorders as that of cladribine, is not toxic to monocytes.³²

Because cladribine is powerfully immunosuppressive, reducing CD4 lymphocytes for up to 2 years and its incorporation into DNA is potentially mutagenic,^{25,33} it was speculated that cladribine might be responsible for an increased incidence of second cancers.^{28,34} A long-term follow-up analysis at Scripps Clinic of patients with hairy cell leukemia treated with cladribine identified an observed-to-expected ratio of second malignancies of 1.88 (95% confidence interval, 1.24 to 2.74), a small but statistically significant increase.³⁵ Multiple other investigators have also investigated cladribine treatment in hairy cell leukemia and the incidence of second malignancies and have failed to establish such a causal relationship.^{36,37} It is thought that patients with hairy cell leukemia have an intrinsic susceptibility to developing second cancers, which is made manifest by the improved survivals that these patients now enjoy. In this report of cladribine use in adults with LCH, one patient developed chronic myelomonocytic leukemia and one patient had recurrence of papillary carcinoma of the thyroid gland. As has been described for hairy cell leukemia, a high incidence of associated malignancies has been documented in patients with LCH, including myelomonocytic leukemia,¹⁷ which could precede, be coincidental with, or occur after a diagnosis of LCH.³⁸ It should be emphasized that patients with hairy cell leukemia generally receive only a single course of cladribine treatment, while in this study, patients with LCH received a median of three courses of cladribine (range, 1 to 6). The multiple courses of cladribine might have a different effect on the incidence of second malignancies. Obviously, determination of potential long-term risks will require continued and meticulous follow-up of treated patients.

Thus, cladribine has significant activity in adults with LCH and warrants further investigation both as a single agent and in combination with other drugs in pediatric and adult LCH, as well as other histiocytic syndromes. Prospective randomized studies are now warranted to determine the role of cladribine in patients with LCH at relapse or even as front-line therapy in high-risk patients. The subcutaneous and oral bioavailability of

cladribine will further facilitate its administration to patients with LCH.^{39,40}

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