

## 2-Chlorodeoxyadenosine Therapy for Disseminated Langerhans Cell Histiocytosis

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• **Objective:** To evaluate the efficacy of 2-chlorodeoxyadenosine (2-CDA), a purine nucleoside analogue, in treating disseminated Langerhans cell histiocytosis (LCH).

• **Patients and Methods:** We retrospectively reviewed the clinical records of 5 patients who were seen at our institution for histologically confirmed disseminated LCH, including 1 patient with central nervous system parenchymal involvement. These patients were treated consecutively with 2-CDA chemotherapy between December 1994 and January 2001. The patients ranged in age from 19 to 81 years, and the median pretreatment duration of disease was 23 months. Median follow-up after initiation of 2-CDA treatment was 33 months. 2-Chlorodeoxyadenosine was used as frontline therapy for 1 patient and as salvage therapy for the other patients. Patients

generally received 0.7 mg/kg over 5 or 7 days; the median number of courses was 4.

• **Results:** Complete responses were achieved in 3 patients, including the patient with central nervous system disease, which, to our knowledge, has not been described previously. Two other patients achieved partial responses. The overall response rate was 100%. Toxic effects consisted mainly of myelosuppression; 1 patient developed dermatomal herpes zoster infection.

• **Conclusion:** Our experience confirms the reported efficacy of 2-CDA in the treatment of LCH; however, the optimal timing and schedule of therapy remain to be determined.

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2-CDA = 2-chlorodeoxyadenosine; LCH = Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a clonal proliferative disorder that results in the accumulation of tissue histiocytes in 1 or multiple organs or tissues. Clinical presentation is heterogeneous and varies from isolated osseous, pulmonary, mucocutaneous, or hypothalamic-pituitary involvement to more extensive multisystemic disease.<sup>1-3</sup> Conventional therapy is mainly palliative and spans the spectrum from corticosteroids, single or combination systemic chemotherapeutic agents including vinca alkaloids, alkylating agents, and antimetabolites, to immunomodulatory approaches, to, at the extreme end of the cytotoxic spectrum, hematopoietic stem cell transplantation.<sup>4,5</sup>

2-Chlorodeoxyadenosine (2-CDA [cladribine]), a purine nucleoside analogue, was recently reported to have major clinical activity in both pediatric and adult patients with LCH.<sup>6-9</sup> We retrospectively reviewed the clinical response of 5 adults with histologically proven LCH who were treated with 2-CDA at our institution. Although case 2 has been reported previously,<sup>10</sup> additional treatment and follow-up data are available.

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### PATIENTS AND METHODS

Between December 1994 and January 2001, 5 patients with biopsy-proven disseminated LCH were consecutively treated with 2-CDA at the Mayo Clinic in Rochester, Minn. We retrospectively reviewed their records to assess for clinical response to 2-CDA therapy, after obtaining approval from the Mayo Foundation Institutional Review Board. The ages of the 3 men and 2 women ranged from 19 to 81 years, and the median pretreatment duration of disease was 23 months (range, 4-24 months). In one patient, 2-CDA was used as frontline therapy; in the other patients, 2-CDA was used as salvage therapy. Generally, patients received 0.7 mg/kg of treatment over 5 or 7 days; the median number of courses was 4 (range, 3-9). Median follow-up since initiation of 2-CDA treatment was 33 months (range, 11-74 months).

### REPORT OF CASES

#### Case 1

A 38-year-old man presented with a 2-week history of progressive headaches. Magnetic resonance imaging of the brain showed an irregular, enhancing mass involving the right caudate nucleus with considerable surrounding edema associated with mass effect and midline shift (Figure 1). Pathologic review of tumor tissue obtained by stereotactic biopsy confirmed LCH (Figure 2). The patient was given high-dose corticosteroids, subsequently underwent pri-

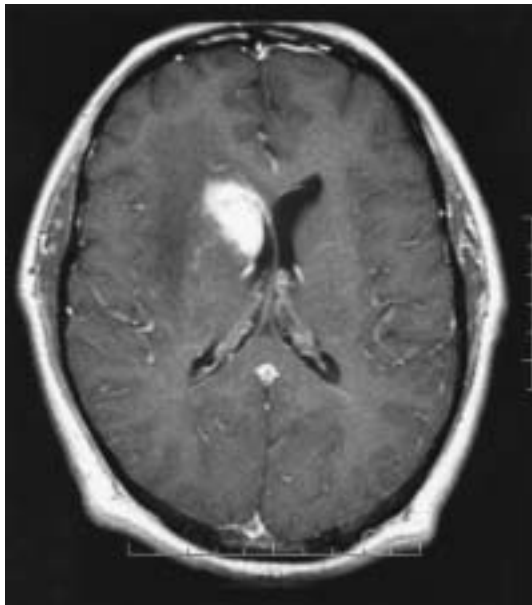


Figure 1. Case 1. Magnetic resonance image of the brain showing Langerhans cell histiocytosis lesion of the central nervous system.

primary external beam radiation therapy (2.035 Gy in 11 fractions plus a 0.54-Gy tumor boost), and had considerable symptomatic relief. Follow-up magnetic resonance imaging confirmed a decrease in the size of the primary lesion and reduced edema. Two months later, repeated brain imaging showed multifocal relapse of central nervous system disease with multiple new, enhancing lesions in both cerebral hemispheres, in the left basal ganglia, and in the right cerebellar hemisphere. Restaging confirmed that disease was confined to the brain, and 2-CDA therapy was initiated (0.09 mg/kg per day; 7-day calculated dose

given over 5 days as a 2-hour infusion per day). After the first course of 2-CDA, a small left-sided retinal hemorrhage developed and modestly reduced visual acuity in that eye. After a second course of 2-CDA, the patient was followed up expectantly. Repeated imaging, performed 6 weeks after the second course of chemotherapy, confirmed a considerable decrease in the size and contrast enhancement of all lesions. Ten months after the second course of chemotherapy, routine magnetic resonance imaging of the brain showed that, although all the old lesions had resolved, a new lesion had appeared in the left centrum semiovale, for which treatment with 2-CDA was reinitiated. The patient received 4 more courses of 2-CDA therapy, which he tolerated without complications. At last follow-up, 30 months after initial presentation, he had no neurologic symptoms and was working full-time. Follow-up magnetic resonance imaging of the brain showed complete resolution of the central nervous system lesions.

## Case 2

A 44-year-old man presented with a widespread rash, manifesting as small erythematous pruritic papules. Skin biopsy findings were indeterminate. Treatment was expectant and symptomatic for the next few years because of the relatively indolent nature of the process. Progressive skin disease eventually developed, manifesting mainly as a generalized erythematous rash with intense pruritus and axillary lymphadenopathy. Biopsy of a right axillary lymph node revealed LCH.

Treatment was initiated with vinblastine (6 mg/m<sup>2</sup>, day 1) and prednisone (60 mg/m<sup>2</sup>, days 1-7) given every 3 weeks for about 6 months. Although modest symptomatic relief (decreased pruritus) was evident initially, the rash eventually progressed despite further treatment. Therapy

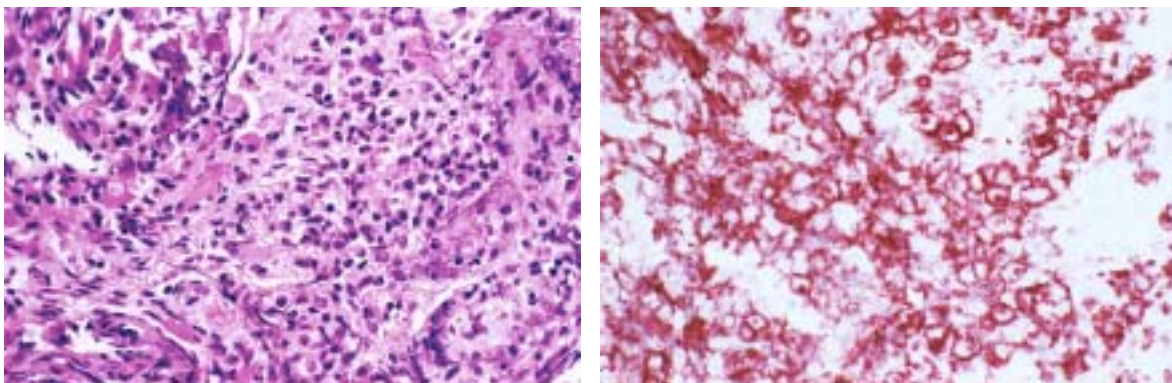


Figure 2. Case 1. Histopathologic findings in Langerhans cell histiocytosis of the central nervous system (A, hematoxylin-eosin, original magnification  $\times 240$ ; B, anti-CD1a immunostain, original magnification  $\times 240$ ). Criteria for histologic diagnosis include morphologic identification of pathologic Langerhans cells in characteristic infiltrates. Immunostains against CD1a or S-100 antigens are used to confirm the diagnosis.<sup>11</sup>

Table 1. Baseline and Posttreatment Laboratory Data for Langerhans Cell Histiocytosis Treated With 2-Chlorodeoxyadenosine\*

Laboratory value	Case 1		Case 2		Case 3		Case 4		Case 5	
	Pre Rx	Post Rx	Pre Rx	Post Rx	Pre Rx	Post Rx	Pre Rx	Post Rx	Pre Rx	Post Rx
Hgb (g/dL)	14.9	14.4	11.9	13.5	9.0	11.5	8.9	12.2	11.0	12.9
WBC ( $\times 10^9/L$ )	6.3	7.0	5.1	7.0	10.7	2.5	7.6	7.2	6.3	4.2
ANC ( $\times 10^9/L$ )	4.0	5.3	3.6	5.3	7.5	2.0	6.0	2.8	3.9	2.6
ALC ( $\times 10^9/L$ )	1.3	0.9	0.8	0.9	1.8	0.1	0.7	0.8	1.4	1.0
AMC ( $\times 10^9/L$ )	0.6	0.5	0.6	0.5	0.4	0.2	0.8	3.6	0.4	0.5
Platelet count ( $\times 10^9/L$ )	218	197	197	197	372	98	189	146	245	183
ALP (U/L)	...	...	...	...	2998	1820	...	...	...	...
AST (U/L)	...	...	...	...	142	116	...	...	...	...
ALT (U/L)	...	...	...	...	149	93	...	...	...	...
Bilirubin (mg/dL)										
Total	...	...	...	...	22.6	16.8	...	...	...	...
Direct	...	...	...	...	15.8	10.2	...	...	...	...
LDH (U/L)	...	...	...	...	272	180	...	...	...	...

\* ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMC = absolute monocyte count; ANC = absolute neutrophil count; AST = aspartate aminotransferase; Hgb = hemoglobin; LDH = lactate dehydrogenase; Pre Rx = before treatment; Post Rx = after treatment; WBC = white blood cell. Ellipses = normal levels.

with 2-CDA was initiated at a dosage of 0.1 mg/kg per day for 7 days as a continuous infusion. Treatment was well tolerated and led to considerable clearing of the rash with decreased pruritus. The response lasted 14 months, after which new skin nodules were noted. A second course of 2-CDA (7-day calculated dose given over 5 days as a 2-hour infusion per day) resulted in a dramatic response with near-complete resolution of the rash. Two years later, the second relapse of LCH manifested as gradual appearance of innumerable new skin nodules. A third course of 2-CDA led to complete resolution of these nodules. Treatment-related toxicity was limited to uncomplicated grade 1 leukopenia (Table 1). At last follow-up, 38 months after the last course of 2-CDA, the patient remained in complete clinical remission.

### Case 3

A 58-year-old woman presented to our institution with multisystemic disease. Three years earlier, idiopathic diabetes insipidus had been diagnosed, and during the next few months, results of liver function tests became progressively abnormal and dysphagia developed as a result of thyromegaly. Biopsies of the thyroid and liver lesions showed LCH. Treatment with corticosteroids and oral etoposide failed over the course of a year, with development of overt jaundice, cachexia, and general clinical decline. Subsequently, the patient noted swelling around both ears, and progressive bilateral hearing loss developed.

On presentation at our institution, the patient had pronounced jaundice (bilirubin: total, 22.6 mg/dL; direct, 15.8 mg/dL) (Table 1) with associated hepatomegaly (liver span, 13 cm), and she had bilateral parotid gland enlarge-

ment. Computed tomography of the head showed marked multinodular enlargement of the parotid glands with a destructive lesion involving the mastoid, temporomandibular joint, and auditory canal on the left. Biopsy of the left parotid gland confirmed LCH. Endoscopic retrograde cholangiopancreatography showed an irregular common bile duct with a long, diffuse stricture.

Therapy with 2-CDA was initiated at a reduced dosage (0.05 mg/kg per day over 7 days as a continuous infusion) because of the patient's poor performance status. A partial clinical response was noted in that parotid swelling and liver size had decreased and liver function had improved (bilirubin: total, 16.8 mg/dL; direct, 10.2 mg/dL). The patient received 3 additional courses of 2-CDA treatment at 0.1 mg/kg per day for 7 days repeated every 4 weeks. After the second course, the parotid swelling completely resolved. At the end of 4 courses, her performance status had dramatically improved (Eastern Cooperative Oncology Group score, from 3-4 to 1). Additionally, the patient had decreased hepatomegaly (33%) on physical examination, decreased pruritus, and an improved hemoglobin value. Treatment was well tolerated, and toxicity was limited to uncomplicated grade 1 leukopenia and thrombocytopenia and grade 3 lymphopenia (Table 1). At last follow-up, clinical response was sustained.

### Case 4

An 81-year-old man presented with a history of rash and purulent discharge from both ears of several months' duration. He had erythematous and scaly maculopapular lesions distributed over his neck, upper trunk, and arms as well as edema and deformity of both external auditory canals with

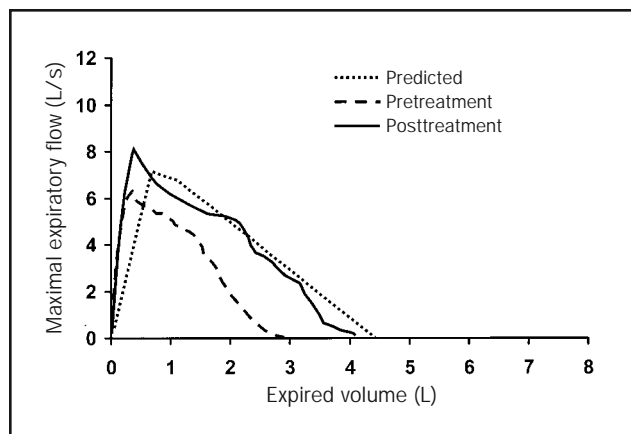


Figure 3. Case 5. Flow-volume curves obtained with spirometry before and after completion of 2-chlorodeoxyadenosine therapy. At baseline, forced vital capacity (FVC), forced expiratory volume in 1 second ( $FEV_1$ ), and adjusted diffusing capacity of lung for carbon monoxide (DLCO) were 66%, 68%, and 60% of predicted values, respectively. After therapy, FVC,  $FEV_1$ , and adjusted DLCO improved to 91%, 94%, and 73% of predicted values, respectively.

purulent discharge. On the basis of biopsy of a skin lesion, LCH was diagnosed. During the next year, the patient's clinical condition worsened; at intervals, he had purple nodules and plaques in the right axilla and chest wall, some of which eventually ulcerated, and axillary and inguinal lymphadenopathy. Also, he developed progressive dyspnea with bilateral moderate-sized pleural effusions detected on chest radiography, and supplemental oxygen was necessary. Biopsy of several skin lesions and inguinal and axillary lymph nodes confirmed LCH. Other staging studies, including bone marrow biopsy, showed normal findings. The patient underwent pleurodesis of the right pleural space. Because of his progressive course, treatment with 2-CDA was initiated at a dosage of 0.1 mg/kg per day (7-day calculated dose given over 5 days as a 2-hour infusion per day).

The skin lesions improved considerably with treatment, and the lymphadenopathy and pleural effusions resolved. Skin findings were reduced to erythematous macules in the axillary and inguinal regions, and the patient was weaned from supplemental oxygen. Response lasted 6 months, after which the skin lesions progressed. At relapse, idiopathic thrombocytopenic purpura had developed and was treated with corticosteroids. For the duration of treatment, the skin lesions remained stable (macular rash in the axillae and scaling of the torso); however, the patient experienced a second relapse when use of corticosteroid treatment was discontinued after 6 months. He received 2 more courses of 2-CDA treatment, and only residual macules persisted. Treatment was well tolerated, and uncomplicated grade 2

lymphopenia was the only documented toxic effect (Table 1). About 5 years after initial presentation, the patient died of complications related to a central nervous system vascular stroke that was unrelated to LCH.

### Case 5

A 23-year-old woman presented to our institution with multisystemic LCH. Diabetes insipidus had been diagnosed 4 years earlier, and during the next 2 to 3 years she had development of progressive lesions involving the scalp, perineum, vulva, external auditory canals, and gingivae. Biopsy of representative skin and gingival lesions revealed LCH. Staging work-up at the time was negative, except for an indeterminate bibasilar pulmonary infiltrate on chest radiography. During the next 24 months, the patient was initially treated with vinblastine plus methylprednisolone and then with oral etoposide. Although modest symptomatic relief (decreased pain and pruritus) was evident initially, the rash eventually progressed despite further therapy. Salvage external beam radiation therapy was needed for the progressive perineal lesions. Follow-up chest radiography revealed a new 3-cm opacity in the left upper lung, and high-resolution computed tomography of the chest revealed 3 additional smaller pulmonary nodules. The patient had minimal respiratory symptoms, limited to intermittent dry cough. Wedge resection of the dominant pulmonary nodule confirmed LCH.

The patient was given 2-CDA (0.7 mg/kg divided over 5 consecutive days as a 2-hour infusion per day). Response to the first several courses of 2-CDA was partial and transient, and the mucosal lesions (oral ulcers) recurred before the next course of treatment. After 9 courses of 2-CDA, she had complete clinical resolution of skin and mucosal lesions and improvement in lung function (Figure 3). Treatment responses were durable, and at last follow-up, about 22 months after her last course of 2-CDA, the patient remained free of symptoms. Grade 2 leukopenia, neutropenia, and thrombocytopenia and grade 3 lymphopenia developed with 2-CDA therapy, and an episode of dermatomal herpes zoster infection developed after the last course of 2-CDA.

### DISCUSSION

For patients with LCH who have refractory or relapsed disease or those with widespread multiorgan involvement and rapid progression of disease, new and effective therapies are necessary.

Among antimetabolites, 2-CDA is novel in that it appears to have activity against both resting and actively dividing lymphocytes.<sup>12</sup> Its ability to induce apoptosis in lymphocyte populations with low growth fractions is thought to underlie its substantial clinical activity in indo-

Table 2. Clinical Features, Therapy, and Outcome of Langerhans Cell Histiocytosis Treated With 2-CDA\*

Case	Age at diagnosis (y)	Sites involved	Time from diagnosis to 2-CDA (mo)	Prior treatment	2-CDA		Follow-up since start of 2-CDA (mo)	Response
					Dosage	Cycles		
1	38	Brain	4	EBXRT	0.09 mg/kg per day for 7 days	6	26	Complete
2	44	Skin, LN	9	VBL, corticosteroids	0.1 mg/kg per day for 7 days	3	74	Complete
3	56	DI, liver, EAC, parotid, thyroid, bone	24	Etoposide, corticosteroids	0.1 mg/kg per day for 7 days	4	11	Partial
4	81	Skin, EAC, LN, lung	23	None	0.1 mg/kg per day for 7 days	3	36	Partial
5	19	DI, skin, mouth, vagina, lungs, EAC	24	VBL, corticosteroids, etoposide	0.14 mg/kg per day for 5 days	9	33	Complete

\* 2-CDA = 2-chlorodeoxyadenosine; DI = diabetes insipidus; EAC = external auditory canal; EBXRT = external beam radiation treatment; LN = lymph node; VBL = vinblastine.

lent lymphoproliferative disorders, including hairy cell leukemia, chronic lymphocytic leukemia, low-grade non-Hodgkin lymphoma, and Waldenström macroglobulinemia.<sup>13</sup> Also, this agent has activity in myeloid malignancies, including recurrent acute nonlymphoblastic leukemia in children.<sup>14</sup> Approved by the Food and Drug Administration for the treatment of untreated or interferon-refractory hairy cell leukemia, 2-CDA induces durable complete remissions in the vast majority of patients in a single course and has a favorable toxicity profile.<sup>15</sup>

Toxic to monocytes *in vitro*, 2-CDA produces considerable, but transient, monocytopenia *in vivo*.<sup>16,17</sup> Its potent activity against circulating monocytes, which share a common progenitor cell of origin with histiocytes, has led to the investigation of this agent for treatment of LCH. Since the first report in 1993 of successful treatment with 2-CDA in an adult patient with LCH,<sup>6</sup> experience with use of this agent in LCH has increased gradually. A review of the published literature revealed an estimated 42 patients, including pediatric patients, who have been treated with 2-CDA. Although 2-CDA was used as salvage therapy in most of these patients, other patient characteristics, including treatment doses and schedules, were highly heterogeneous.

A survey by the International Histiocyte Society identified 15 patients with LCH (12 pediatric patients) treated with 2-CDA.<sup>9</sup> The overall response rate was 60% (40% complete, 20% partial), and there was 1 early death. The dosage of 2-CDA varied from 0.1 mg/kg per day (approximately 3 mg/m<sup>2</sup> per day) by continuous infusion to 13 mg/m<sup>2</sup> per day by continuous infusion for 5 days, and the number of cycles varied from 2 to 6. Toxic effects were mild and primarily limited to transient myelosuppression; there were no treatment-related deaths. Dermatomal herpes zoster infection developed in 2 patients, and 1 patient had thrombocytopenia that lasted more than 6 months. Saven

and Burian<sup>8</sup> described 13 adults with LCH who were treated with a median of 3 courses of 2-CDA at a dosage of 0.14 mg/kg per day by 2-hour infusion for 5 consecutive days. The overall response rate was 75% (58% complete, 17% partial). The principal toxic effect was hematologic; 7 of 13 (54%) patients had grade 3 or 4 neutropenia (2 with neutropenic fever), and 1 patient had dermatomal herpes zoster infection. These 2 studies are important in that they confirm that the considerable clinical activity of 2-CDA in LCH in previously published case reports was not due to reporting bias.

A recent report in the Spanish literature described 9 patients with LCH treated with 2-CDA.<sup>18</sup> Most patients received 2-CDA at a dosage of 0.1 mg/kg per day for 5 consecutive days. The overall response rate was 66% (22% complete, 44% partial). Treatment-related neutropenia and thrombocytopenia (grade >2) were noted in 5 (56%) of the 9 patients, and 4 (44%) had infections (1 fatal). Other investigators also have reported small numbers of patients with LCH treated with 2-CDA.<sup>19-23</sup>

The novel contributions of our report include the first description of 2-CDA therapy for LCH of the central nervous system and a description of its use as first-line therapy for aggressive, multisystemic LCH.

Patient characteristics before the initiation of 2-CDA treatment and best treatment response are summarized in Table 2. One of our patients received 2-CDA as first-line therapy, and 4 patients received it as salvage therapy. Of the 5 patients, 3 (60%) achieved a complete response, and 2 (40%) achieved a partial response (overall response rate, 100%). All patients received a dosage of approximately 0.1 mg/kg per day given either as a continuous infusion or as a 7-day total calculated dose over 5 consecutive days as a 2-hour infusion per day. Treatment was well tolerated (Table 1), and only 1 patient (case 5) had development of an

opportunistic infection, despite the limited use of prophylactic antimicrobial therapy (1 patient [case 3] received trimethoprim-sulfamethoxazole and acyclovir).

Involvement of the central nervous system by LCH in adults is distinctly uncommon,<sup>2</sup> and the efficacy of 2-CDA in this setting is unknown. One study reported that 2-CDA penetrated the blood-brain barrier, resulting in cerebrospinal fluid levels that were 25% of plasma levels.<sup>24</sup> A review of the published English literature revealed no report of histologically documented LCH involvement of the central nervous system that was treated with 2-CDA. One of our patients (case 1) presented with an enhancing intraparenchymal, space-occupying lesion in the basal ganglia (type IIb lesion; ie, gray matter lesion with enhancement, according to the LCH–central nervous system study classification of central nervous system lesions).<sup>25</sup> In contrast to the previously described associations of LCH and central nervous system disease,<sup>25</sup> this patient did not have multi-systemic disease or skull lesions, and diabetes insipidus did not develop at any point during the course of his illness. This patient received salvage 2-CDA for relapsed disease after the failure of primary external beam radiation treatment. He received 6 courses of 2-CDA and had a complete, durable response.

## CONCLUSION

The developing opinion is toward the use of 2-CDA for refractory or relapsed LCH or even as first-line therapy for patients with high-risk disease, although the latter practice is not universally accepted because of the potential for acute and long-term toxic effects associated with this agent. 2-Chlorodeoxyadenosine is potently immunosuppressive, and its incorporation into DNA renders it potentially mutagenic.<sup>8</sup> Sustained follow-up of patients is required for an accurate assessment of the long-term risks of 2-CDA treatment. Although this agent clearly has activity in LCH (>50% responses in heavily pretreated patients), the dose-response relationship and the timing and schedule for therapy have yet to be defined. These issues need to be studied prospectively.

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