Cyclosporine Therapy for Advanced Langerhans Cell Histiocytosis

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Prompted by evidence that Langerhans cell histiocytosis (LCH) is a nonmalignant disorder of immune regulation, we used cyclosporine (12 mg/kg/d orally) to treat three young children with advanced multisystem LCH. All three patients had partial responses to cyclosporine within 2 months of therapy, as evidenced by complete resolution of organ dysfunction and regression of the majority of lesions. Complete responses were attained by adding relatively nontoxic chemotherapy (ie, prednisone and vinblastine). Toxicity from cyclosporine comprised mild and reversible elevations of the serum creatinine and blood urea nitrogen. These results indicate that further evaluation of cyclosporine for the treatment of patients with advanced LCH is warranted.© 1991 by The American Society of Hematology.

ANGERHANS CELL histiocytosis (LCH), previously termed histiocytosis X, is characterized by aberrant proliferation of a specific dendritic (Langerhans) cell belonging to the monocyte-macrophage system.1-3 The clinical manifestations of LCH, which result in part from tissue infiltration by or activation of Langerhans cells, range from solitary lytic bone lesions to multisystem disease with liver, lung, and bone marrow dysfunction. Although the disease often resolves when treated with minimal chemotherapy, the prognosis is very poor in children younger than 2 years with multisystem disease and organ dysfunction.3 These high-risk patients usually present with fever, wasting, skin rash, hepatosplenomegaly, generalized lymphadenopathy, anemia, and organ dysfunction.

The standard therapeutic approach to multisystem LCH (combination chemotherapy, low-dose irradiation, or both) parallels that for malignant diseases. This approach has come into question with mounting evidence that LCH is essentially a nonmalignant disorder of immune regulation.4-6 Based on this evidence, we used cyclosporine to treat three children with advanced-stage LCH. Our goal was to induce a complete remission or inhibit disease progression. We chose cyclosporine, a cyclic endecapeptide immunosuppressant of fungal origin, because of its ability to selectively inhibit adaptive immune responses. This agent blocks transcription and synthesis of lymphokines such as interleukin-2 (IL-2) and interferon-γ (IFN-γ),7 inhibits the accessory cell function of Langerhans cells,8 decreases the capacity of dendritic cells to enhance mitogenic stimulation of lymphocytes,9,10 and induces secretion of thymic hormone.11 Thus, cyclosporine could inhibit cytokine-mediated cellular activation that may contribute to the pathogenesis and progression of this disease. Here we describe the clinical responses of three patients whose acute multisystem LCH resolved or regressed with cyclosporine therapy.

MATERIALS AND METHODS

LCH diagnosis in all three patients was based on the presence of characteristic Langerhans cells in stained biopsy material, and positive S100 stain. Staining for peanut agglutinin was performed in patients 2 and 3, and showed cytoplasmic positivity. All cases were stage IV by the Osband et al classification,11 which requires age less than 2 years, ≥4 organs involved (any combination of skeleton, skin, liver, spleen, lymph nodes, lung, pituitary, and bone marrow), and the presence of any organ dysfunction (hepatic, hematopoietic, or pulmonary dysfunction) as defined by Lahey’s criteria.1

Treatment

The treatment plan specified two daily oral doses of cyclosporine, 6 mg/kg/dose, for 6 months. This dosage was intended to maintain a trough plasma level between 150 and 250 ng/mL, as measured by radioimmunoassay (TDx assay; Sandoz, Basel, Switzerland). If complete remission was achieved, cyclosporine therapy was continued at this dosage for a total of 6 months; the dosage was then reduced to 6 mg/kg/d to maintain a trough level between 100 and 150 ng/mL for the remainder of the 12-month treatment period.

Progressive disease at any time during the treatment course or the absence of any response to cyclosporine after 2 months of therapy were indications for stopping cyclosporine treatment. In patients with a partial response at 3 months, oral prednisone (2 mg/kg/d) was added to cyclosporine treatment for 2 months. Vinblastine, administered intravenously at 5 mg/m²/wk, was substituted for prednisone in patients who failed to achieve complete remission after this 2-month period. Patients with a complete response after the addition of prednisone received cyclosporine alone for the remainder of the 12-month treatment period, whereas those who required vinblastine continued to receive this drug together with cyclosporine for the duration of the trial.

Throughout therapy with cyclosporine, trimethoprim-sulfamethoxazole was administered three times weekly as chemoprophylaxis for Pneumocystis carinii pneumonia.

Evaluation of Responses

Patients were evaluated monthly for the extent and pattern of their therapeutic responses, and weekly for cyclosporine toxicity. Responses were defined as described below.

Complete response. The lack of symptoms of LCH, normal physical and radiologic findings (excluding bony lesions, which should indicate healing as evidenced by sclerosis or trabeculation),12 and the absence of new lesions.

Partial response. A ≥50% reduction in organ involvement (either extent of disease or number of organs involved) and resolution of any organ dysfunction.

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No response. A less than 50% reduction in organ involvement or the persistence of organ dysfunction attributable to LCH.

Progressive disease. The involvement of additional organs or greater than 50% progression of disease in two or more involved organs (excluding bony lesions), any new organ dysfunction, or worsening of any existing dysfunction attributable to LCH.

Patients were closely monitored for side effects of therapy by regular testing of kidney function (serum electrolytes, creatinine, uric acid, and blood urea nitrogen), liver function (serum bilirubin, aminotransferases, and alkaline phosphatase), complete blood count, and cyclosporine plasma trough levels. Toxicity was considered mild if laboratory values were increased to less than twice the normal values for age, moderate if they were two to three times normal, and severe if they were more than three times normal.

CASE REPORTS

Patient 1

A 23-month-old white girl presented with a generalized rash; skin biopsy was diagnostic of LCH. Hepatosplenomegaly, a lytic bone lesion, bone marrow histiocytic infiltration, and hematopoietic and hepatic dysfunction were present (Table 1). She had a partial response to cyclosporine during the first 3 months of therapy, as evidenced by a marked improvement in her skin rash, decreased liver and spleen size, resolution of bone marrow disease, and improvement of hepatic and hematopoietic dysfunction. A plain roentgenogram of the left mastoid bone at 3 months showed signs of healing (both sclerosis and decrease in the size). However, because of residual skin disease, oral prednisone was added to her regimen, and 2 months later vinblastine was substituted for prednisone. The patient attained complete remission, and was taken off of treatment at 1 year. Side effects included mild reversible elevation of blood urea nitrogen (BUN) and serum uric acid secondary to cyclosporine therapy, and cushingoid appearance associated with oral prednisone.

Patient 2

This 5-month-old white boy presented with multisystem LCH characterized by skin and lung involvement, generalized massive lymphadenopathy, multiple bone lesions, bone marrow infiltration, and pulmonary and hematopoietic dysfunction (Table 1). The diagnosis was confirmed by inguinal lymph node biopsy, and cyclosporine therapy was initiated. There was immediate constitutional improvement, evidenced by resolution of fever, decreased respiratory distress, weight gain, and increased physical activity. By 1 month, the patient’s skin rash had disappeared, his enlarged lymph nodes had decreased in size, and his hemoglobin level had increased from 6.9 to 8.3 g/dL. Langerhans cells were not detected in bone marrow aspirates. Despite attaining a partial response, a chest computed tomography (CT) scan at this point showed substantial bilateral lung involvement with multiple granulomas and destructive lesions. Because of the severity of these findings, both prednisone and vinblastine were added to his treatment regimen in an attempt to induce complete remission while avoiding lung destruction and scarring by the disease process. The patient had complete resolution of lymphadenopathy, pulmonary granulomas, and bone lesions after 5 months of this modified treatment. One month later, a chest CT scan showed marked improvement without lung scarring. Cyclosporine toxicity was limited to a mild increase of BUN, which returned to normal after dose adjustment. This child remains in complete remission at 3 months after discontinuation of therapy.

Patient 3

A 4-month-old white boy presented with massive generalized lymphadenopathy and anemia with a hemoglobin level of 7.7 g/dL. The diagnosis of LCH was made by cervical lymph node biopsy. The disease process also involved liver, lungs, and bone, and

### Table 1. Early Clinical Course of LCH in Patients Treated With Cyclosporine

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2*</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mo</td>
<td>1 mo</td>
<td>2 mo</td>
</tr>
<tr>
<td><strong>Organs involved</strong></td>
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<td></td>
</tr>
<tr>
<td>Skin</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Bone</td>
<td>1 Lesion</td>
<td>NE</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Liver†</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Spleen†</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Lungs</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytes (×10³/L)</td>
<td>12.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>6.6</td>
<td>9.2</td>
</tr>
<tr>
<td>Platelets (×10³/L)</td>
<td>100.0</td>
<td>181.0</td>
</tr>
<tr>
<td>Serum protein (g/dL)</td>
<td>4.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.8</td>
<td>3.6</td>
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<tr>
<td><strong>Imaging results</strong></td>
<td></td>
<td></td>
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<tr>
<td>Chest roentgenogram</td>
<td>--</td>
<td>NE</td>
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<tr>
<td>Chest CT scan</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

Abbreviations: +, mild involvement by LCH; ++, moderate involvement; ++++, extensive involvement; --, absence of LCH; NE, not evaluated; ↑, progressing; ↓, resolving; ↑↑, mixed response.

*Prednisone and vinblastine added to cyclosporine at 1 month because of extensive lung disease apparent on CT scan.
†Palpable below costal margin (in centimeters).
hepatic, pulmonary, and hematopoietic dysfunction were apparent (Table 1). A CT scan of the chest at diagnosis showed bilateral multiple pulmonary granulomas and a large, lobulated, anterior mediastinal mass (Fig 1A). Two months after initiation of cyclosporine therapy alone, there was complete resolution of lymphadenopathy, hepatomegaly, and pulmonary, hematopoietic, and hepatic dysfunction. A follow-up CT scan of the chest disclosed a normalized thymus and a marked decrease in the size of parenchymal granulomas (Fig 1B). A skeletal survey showed a mixed response to therapy: four lesions had increased in size while five others had decreased. At 3 months of treatment, the disease was in partial remission; prednisone was added according to the treatment plan because of residual pulmonary infiltrates. Vinblastine was substituted for prednisone once the patient attained complete remission at 5 months of therapy. Side effects of cyclosporine therapy were limited to mild increases of BUN and serum creatinine. The patient has required neither blood products nor hospitalization since the commencement of therapy. He remains in complete remission with normal growth and development at 12 months from diagnosis.

![Fig 1. Chest CT scans of patient 3. (A) Large anterior mediastinal mass and bilateral axillary lymphadenopathy at diagnosis. (B) Marked disease regression after 8 weeks of single-agent therapy with cyclosporine.](image-url)
DISCUSSION

The treatment of LCH has been as varied as the clinical presentation of the disease. Historically, some investigators have advocated the use of antimicrobial therapy, based on the assumption that LCH is an infectious disease; others have recommended chemotherapy and irradiation because of the presumed malignant potential of this disorder.5,16 For systemic disease, administration of vinblastine in combination with corticosteroids is a common practice.16,18 The current approach for patients with chronic indolent disease is to use the least-toxic therapy possible. For solitary bone lesions, surgical curettage or low-dose radiation therapy has been the treatment of choice.

The value of conventional therapy for systemic LCH was brought into question by Greenberger et al,4 who reported no difference in survival between matched pairs of treated and untreated patients. Moreover, 7 of the 62 (11%) surviving treated patients in their series developed malignancies that were attributed to therapy with alkylating agents, radiation, or both. A review of published reports on a total of 132 patients with stage III or IV LCH showed that 75 (57%) died despite receiving treatment with conventional agents.3,17,24

More intensive multiagent therapy was evaluated in a large prospective cooperative study by German and Austrian groups. Twenty children with organ dysfunction (of 181 patients with newly diagnosed LCH) were intensively treated with vinblastine, prednisone, etoposide (VP-16), methotrexate and 6-mercaptopyrurine.24 Only eight patients (40%) had complete responses; eight died after failing to respond to initial therapy, and the remaining four children had chronic disease after treatment. Eight of nine patients presenting with hepatic dysfunction died despite aggressive therapy. In contrast, two of our patients presented with hepatic dysfunction, which corrected with cyclosporine alone, and remain alive in remission.

Broadbent et al25 recommended a conservative approach to treatment, based on their observation of two infants with early-stage disease whose disease spontaneously remitted. These investigators suggested that therapy should be withheld in children with multisystem LCH who have no evidence of constitutional symptoms and no failure of vital organs. This expectant approach, while having the potential advantage of decreasing treatment-related morbidity and mortality, would likely not be adequate for patients who are symptomatic and have organ dysfunction.

The rationale for use of cyclosporine in children with poor-prognosis advanced LCH is its recognized immunomodulatory effects on the afferent limb of the cellular immune system, especially the suppression of IL-2 and IFN-γ.28 Suppressor T-cell deficiency, attributable in part to thymic dysfunction and decreased serum thymulin (thymic factor), has been noted in many patients and could account for the increased proliferation and accumulation of Langerhans cells.15,26 Moreover, Langerhans cells from eosinophilic granulomas produce excessive amounts of IL-1 and prostaglandin E2 (PGE2), which can cause bone resorption through osteoclast activation.27-29 Finally, IL-1 causes the release of IL-2 and IFN-γ from CD4 lymphocytes, leading to stimulation of other lymphocytes and non-Langerhans histiocytes.30,31 Thus, multisystem LCH appears to reflect cytokine-mediated activation or proliferation of histiocytes and lymphocytes in distant tissues, in addition to the expansion of the local population of Langerhans cells.

Our results suggest that cyclosporine may provide an effective, nonmyelosuppressive therapy in conjunction with nonaggressive treatments currently in use for advanced LCH. As a single agent, cyclosporine rapidly produced objective, measureable benefit in three consecutive patients with stage IV disease. There was clear evidence of disease regression in the skin, liver, spleen, lymph nodes, lungs, thymus, and bone marrow. Pulmonary, hepatic, and hematopoietic dysfunction resolved promptly. Of further interest was the healing of pulmonary granulomatous disease without residual fibrosis or parenchymal destruction, a common sequela of therapy in patients with progressive disease treated with chemotherapy alone. These responses could not be attributed to spontaneous remission, which seldom occurs in patients with organ dysfunction.32 In general, cyclosporine was well tolerated in doses that effectively maintained the plasma trough level within the specified range. As in other studies,6 the toxicity we observed was primarily renal and was rated as mild, dose related, and reversible with dose adjustment.

The inability of cyclosporine to completely eradicate the disease in our patients should, perhaps, not be surprising and can be attributed in part to its selective immunosuppression and lack of a direct cytolytic effect. Failure to completely suppress proliferating Langerhans cells in primary sites, such as skin and bone, could be expected to lead to recurrences in some patients. Thus, the combination of cyclosporine with cytotoxic or nonselective immunosuppressive agents, such as vinblastine or prednisone, could be effective in destroying activated Langerhans cells and committed lymphocytes contributing to the disease process. Another possible explanation for the less-than-complete responses is the marked pharmacokinetic and pharmacodynamic variability of cyclosporine administered to patients. Although we attempted to maintain plasma trough levels between 100 and 250 ng/mL, the acknowledged therapeutic window for cyclosporine, we cannot discount the possibility that variability in the tissue distribution of or sensitivity to cyclosporine in different affected organs might have influenced treatment outcome.

The cyclosporine-induced effects we observed are suggestive of inhibition of key histiocyte and lymphocyte functions.8,10 We speculate that cyclosporine disrupts an abnormal cytokine-dependent activation of lymphocytes and histiocytes residing in the liver, spleen, lymph nodes, and bone marrow. This activation is most likely secondary to uncontrolled proliferation of Langerhans cells, with excessive production of IL-1 and PGE2,38 resulting in amplification of the effector limb of the immune system.

We acknowledge that conventional agents may be as
effective as cyclosporine in these patients, and that the data presented here merely suggest that cyclosporine has activity in this disease. Further study is required to better estimate the value of this agent and to establish its relative efficacy compared with conventional agents. Because of the rarity of advanced LCH, it is doubtful that any single group of investigators will accumulate enough patients to conduct a randomized clinical trial. Thus, we believe that the responses described merit further testing in a multicenter trial.

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REFERENCES

Cyclosporine therapy for advanced Langerhans cell histiocytosis [see comments]

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