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Cyclosporine A Therapy for Multisystem Langerhans Cell Histiocytosis

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Background. Treatment of multisystem Langerhans cell histiocytosis (LCH) remains difficult. Various regimens of single and multiagent chemotherapy have been used, but a significant proportion of patients fail to respond to treatment. ***Procedure.*** We have evaluated the use of cyclosporine A (CSA) in a controlled group of patients, who had received a systematic primary therapy (LCH-I). Patients received CSA either as a single agent (10 patients) or in combination with vinblastine, etoposide, prednisolone, and/or antithymocyte globulin (16 patients). ***Results.*** Among the total of 26 patients treated, a single patient developed a complete response and three a partial response, whereas 85% (22 patients) had no response to CSA. ***Conclusions.*** CSA is at best of limited value in the treatment of patients with multisystem LCH, particularly those who had progressive disease while receiving chemotherapy. Med. Pediatr. Oncol. 33:482–485, 1999.

Key words: Langerhans cell histiocytosis; chemotherapy; cyclosporine A

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a reactive disorder characterized by infiltration and proliferation of dendritic cells bearing the phenotype of normal Langerhans cells, with still poorly understood etiology and pathogenesis. It is generally accepted that introduction of chemotherapy has improved prognosis of LCH. However, about 20% of patients with multisystem LCH (MS-LCH) do not respond to various chemotherapeutic regimens and have an extremely poor prognosis [1–4]. This was confirmed by the preliminary results of the First International Study on LCH (LCH-I; paper in press).

Cyclosporine A (CSA), a fungal metabolite with potent immunosuppressive activity, had been reported by Mahmoud et al. in 1991 to be an effective agent in treatment of LCH [5]. This observation was subsequently supported by other reports [6,7]. Here we report on 24 pediatric patients from the International LCH-I Study, whose salvage therapy contained CSA.

MATERIALS AND METHODS

Data files from 135 patients included in the international LCH-I Study were retrospectively reviewed to identify patients who had been treated with CSA at any time of their course, including two patients enrolled in the now closed salvage trial LCH-I-S (treated with a combination of prednisolone, antithymocyte globulin, and CSA). The LCH-I Study was initiated in April, 1991 [8]. Briefly, only newly diagnosed, previously untreated patients up to the age of 18 years with multisystem disease and a definitive diagnosis of LCH were eligible. According to the Histiocyte Society diagnostic criteria, definitive diagnosis LCH required presence of $CD1a^+$ and/or Birbeck granule-bearing Langerhans cells in stained biopsy tissue [9]. Informed consent was obtained before inclusion in the LCH-I Study. Multisystem disease was defined as involvement of two or more organs or systems. All study patients were randomly assigned to receive either etoposide (VP-16; 150 mg/m^2 i.v. over 2 h) given on 3 consecutive days every 3 weeks or vinblastine (6 mg/m^2 i.v. bolus) weekly for a period of 24 weeks. Each drug was administered as a single agent, combined with a single pulse of high-dose methylprednisolone. Different salvage therapies were applied in patients who did not respond to protocol therapy.

Twenty-eight of one hundred thirty-five study patients received CSA during their disease course. Twenty-six children, 12 male and 14 female, were evaluable. Two patients were excluded because of incomplete data. The

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median age at the time of LCH diagnosis was 13 months (range birth to 2 years 3 months). According to the LCH-I protocol, 13 of 26 patients were initially treated with vinblastine and 13 of 26 patients with etoposide. For 5 patients this was the only treatment prior to CSA. Thirteen patients were switched to the alternative protocol arm; 5 were treated with multiagent chemotherapy, and 2 with systemic steroids and 1 was splenectomized after the initial therapy failed. Seven patients experienced more than one therapy switch before CSA was instituted.

Despite such heavy pretreatment, at switch to CSA, 21 of 26 patients were assessed as having progressive disease and 4 patients as having stable disease. In 1 patient CSA was commenced in the presence of regressing disease. Involvement of liver, lung, spleen, and hematological system is strongly associated with poor prognosis [3,4,10], a fact confirmed by the LCH-I Study (paper in press). At least one of these organs was involved in 21/26 patients at the time of starting CSA. Details concerning mode, dose, and schedule of CSA treatment, response, and side effects were collected by special questionnaire.

Response to CSA had been assessed at a median of 2 months (range 10 days to 8 months) after its initiation. Disease state and response to CSA were assessed according to the criteria adopted by the LCH Study Group: nonactive disease (NAD), meaning complete disease resolution, and active disease (AD). The last category covered patients with signs of continuous regression (AD better), patients with evident disease progression (AD worse), and patients with intermediate response (AD intermediate). Patients were assigned to the AD intermediate group if stabilization of the disease was observed (AD intermediate stable) or regression at one site was accompanied by progression at the other (AD intermediate mixed). Response to CSA was defined as achievement of NAD or AD better. Patients with AD worse, as well as the 3 patients with AD intermediate mixed, were categorized as nonresponders.

RESULTS

There were considerable variations in mode of CSA treatment. Ten of twenty-six patients (38%) received CSA as a single agent. In 16 patients (62%) CSA was given concomitantly with steroids and either vinblastine, etoposide, and/or antithymocyte globulin. For all patients, the median CSA dose was 6 mg/kg/day (range 3–12), and it was given for median 4.5 months (range 10 days to 2 years 2 months). Plasma levels of CSA, reported in 5 patients, varied widely, between 100 and 600 ng/ml.

The response to CSA containing therapy is summarized in Table I. Complete disease resolution was achieved in only 1 patient (4%). In 3 patients (11%) therapy resulted in evident disease regression. In another 3 patients regression of old lesions was accompanied by development of new lesions, suggesting that the underlying process was not controlled by the therapy. No benefit was seen in 19 patients, in whom further disease progression was observed. Thus, 22 patients (85%) were qualified as nonresponders.

TABLE I. Response and Outcome

		Outcome		
Response category	Response	Alive disease-free	Alive with disease	Dead
AD worse	19	3[a]	4[a]	12
AD interm. mixed	3	1	1	1
AD better	3	2[b]	1	None
NAD	1	1	None	None

[a]All rescued with other therapy after CSA failure.
[b]One patient rescued by bone marrow transplantation.

Outcome correlated clearly with response to therapy (Table I). All patients who survived after CSA had failed to arrest the disease progress were rescued by additional therapy. This was chemotherapy (7 patients), bone marrow transplantation (1 patient), or addition of steroids and antithymocyte globulin to CSA (1 patient). Some of the patients experienced more than one switch after CSA. Only mild toxicity attributable to CSA (hypertrichosis and mild increase in blood pressure) was reported in 5 patients.

DISCUSSION

Overall prognosis in patients with MS-LCH has improved since chemotherapy was introduced [11–14]. However, careful review of the literature shows that little progress has been made in the treatment of patients with the most severe form of disease [15]. About 20% of patients with MS-LCH have a lethal outcome despite treatment with different chemotherapeutic regimens [3,4]. The International LCH-I Study showed that a small group of patients with a high risk of poor outcome can be identified very early in their course, after only 6 weeks of treatment. Use of experimental therapeutic approaches, rather than continuing the apparently unsuccessful therapy used to date seems to be justified for such patients.

It is now generally accepted that LCH is a reactive disease of immunologic dysequilibrium, and most of its clinical manifestations are possibly related to cytokine activation of lymphocytes and macrophages in distant tissues. Thus, strategies aimed at suppressing cell activity and decreasing production of certain cytokines are at least theoretically justified.

CSA is a noncytotoxic immunosuppressive agent with well-established application in bone marrow and organ transplantation as well as in the treatment of immune-

TABLE II. Cyclosporine A (CSA) Therapy for Multisystem Langerhans Cell Histiocytosis*

	Mahmoud et al. [5]	Aricò et al. [7]	Mahmoud and Broadbent [6]	Colella et al. [16]	Present group
No. of patients	3	11	24	10	26
Age at diagnosis	23 m, 5 m, 3 m	Med. 9.5 m (3 m to 4 years)[a]	Med. 14 m (1 m to 14 years)[a]	Med. 6 years	Med. 13 m (birth to 2 years 3 m)[a]
Risk organs	3/3	9/11	21/24	n.a.	21/26
Prior therapy	None	All[b]	All[b]	n.a.	All[b]
CSA dose (mg/kg/day)	12	12	Med. 6 (5–12)[a]	12	Med. 6 (3–12)[a]
Application					
CSA alone	3/3	11/11	12/24	10	10/26
CSA comb.[c]	None	None	12/24	9	16/26
CSA duration	n.a.	12 m	n.a.	≥12 Weeks	Med. 4 m (10 days to 2 years 2 m)[a]
Response to CSA					
CR (%)	none	3 (27)	3 (13)	n.a.	1 (4)
PR (%)	3 (100)	4 (36)	3 (13)	n.a.	3 (11)
NR (%)	none	4 (36)	18 (74)	6 (60)	22 (85)

*CR, complete response; PR, partial response; NR, no response; n.a., not available; med., median; m, months.
[a]The numbers in parentheses reflect the corresponding value ranges.
[b]All patients pretreated with chemotherapeutic regimens containing Pred ± VBL ± VP16.
[c]CSA combined with other agents (i.e., steroids, vinblastine, etoposide, ATG).

mediated diseases. Series published thus far are summarized in Table II. In 1991, Mahmoud et al. [5] reported successful treatment with CSA in 3 newly diagnosed untreated patients with MS-LCH. However, only partial resolution was achieved with CSA alone, and complete response in all cases was attained by adding steroids and/or vinblastine. Aricò et al. [7] reported 12 patients, 11 of whom had MS-LCH. All patients were pretreated with chemotherapy including vinblastine and/or etoposide or steroid and received oral CSA (12 mg/kg/day) as a second-line therapy. CSA treatment was associated with clinical response in 8 of 12 patients (67%); however, only 3 patients had a complete response. Five patients had partial response, and 3 patients experienced disease reactivation requiring additional CSA courses after a favorable response to the first course. Another cohort was reported by Colella et al. [16]. Six of nine evaluable patients responded neither to 12-week monotherapy with CSA nor to addition of etoposide. It is remarkable that these disappointing results were observed in a group of patients with median age 6 years.

H. Mahmoud and V. Broadbent [6] in 1993 presented results of a cyclosporine salvage therapy questionnaire circulated among members of the Histiocyte Society. Their cohort (24/29 patients had MS-LCH and were evaluable for therapy response) compares quite well to ours. CSA failed to control disease process in 18 of 24 (74%) of their patients vs. 22 of 26 (85%) in our group. This resulted in almost equal mortality rates in both groups: 13 of 24 (54%) vs. 13 of 26 (50%). It should also be stressed that 3 of 11 (27%) and 5 of 13 (38%) of the survivors, respectively, had no involvement of risk organs at start of CSA therapy.

No difference could be found in terms of response and outcome by comparing patients treated with CSA alone or in combination with other agents in the group of Mahmoud and Broadbent. In our study CSA combined with other agents appeared to have a slightly better effect than did CSA alone (responders 4/16 vs. 0/10, survivors 9/16 vs. 4/10). However, this observation should be interpreted cautiously in view of the small patient sample.

The optimal dosage and schedule of CSA application in MS-LCH is not known. It is also not known if earlier institution of CSA will result in better efficacy. CSA could be more effective as a part of immunosupressive combinations aimed to achieve global inhibition of cytokine production. Unfortunately, such immunosupressive regimens, consisting of prednisone, antilymphocytic globulin, and CSA proposed in the LCH Study Group's salvage protocol (LCH-I-S), could not be evaluated. This trial failed to recruit patients and had been prematurely closed.

In historical series [10,12,14,17] lungs, liver, and hematological system involvement have been reported to confer poor prognosis, and this has been confirmed prospectively in the LCH-I Study. In our series 21 of 26 patients had involvement of at least one of these organs, and a 50% mortality rate would be expected in this negatively selected group. However, more disappointing is the fact that disease course remained uninfluenced by CSA in 85% of the patients. This was the case in all patients who died and in 9 of 13 (69%) of the survivors. It should be added that only 8 of 13 survivors (62%) had involvement of risk organs at switch to CSA, and 5 of them were switched to another therapy later because of

nonresponse to CSA. Regression attributable to CSA was observed in only 15% of the patients.

CONCLUSIONS

Our results suggest that CSA is of limited value in high-risk patients with progressive disease, especially if they have been heavily pretreated, and that new salvage therapy agents must be evaluated.

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