



Brief Report

ETOPOSIDE AS THE BASIC AND INTERFERON- α AS THE MAINTENANCE THERAPY FOR LANGERHANS CELL HISTIOCYTOSIS: A RTC

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□ *The treatment of patients who suffer from a disseminated form of Langerhans cell histiocytosis (LCH) is still controversial. So far, few larger randomized studies have been performed. The authors present 3 patients with a disseminated form of LCH—4 months, 9 months, and 2 years old, respectively. The lesional Langerhans cells in each patient showed positive immunohistochemical reaction to S-100 protein and the presence of Birbeck granules was confirmed by electron microscopy. All the patients were treated with etoposide (VP-16), 200 mg/m² for 3 consecutive days, with 15 cycles at intervals of 3 weeks between each cycle, followed by maintenance therapy with IFN- α . All 3 patients reached complete stable remission. The patients were young, at high risk, with multiple-organ involvement of LCH, and two of them had obvious signs of organ dysfunction at presentation, suggesting a poor prognosis. All remain disease-free several years after therapy. The results suggest that IFN- α may prevent recurrences in high-risk patients.*

Keywords. etoposide, IFN- α , Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a disease of unknown etiology and with an unpredictable clinical course. The disease mainly affects young children, most frequently those 1–3 years of age. The clinical picture varies from

Received 11 September 2000; accepted 4 December 2000.

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solitary bone lesions to a potentially lethal leukemia-like syndrome with signs of dysfunction of involved organs, or intermediate forms with characteristic bone, skin, and mucous membrane lesions [1]. Morphologically and phenotypically Langerhans cells (LC) found in the lesions are similar to dendritic antigen-presenting LC found in skin and other organs. The lesional cells express the CD1a glycoprotein and S-100 protein as well as Birbeck granules [2]. Several cytokines seem to have a role in the pathogenesis of the LCH lesions since proinflammatory cytokines, such as IL6, IL2, IL1, IL8, TNF- α , GM-CSF, and LIF, have been found in such lesions [3]. A viral infection as a key etiological factor has not been proven, although some viruses can induce production of cytokines and stimulate the growth of lesional LC [4].

The treatment of LCH is usually adapted to the extent of the disease. High-risk patients with early onset of symptoms and multiple-organ involvement are often given systemic treatment with corticosteroids and cytostatics. Many different treatment strategies and drugs have been used in such patients, but few studies have compared the efficacy of individual drugs.

In the first randomized chemotherapy trial, etoposide (VP-16), previously shown to be effective in LCH [5], was as effective as vinblastine in the treatment of multisystem LCH [6]. Interferon-alpha (IFN- α) has also been used in LCH patients with multisystem disease. In most reports IFN- α had been given as a salvage therapy in cases that have had recurrences or failed on conventional chemotherapy. Patients who seem to have responded have received IFN- α treatment for extended periods of time [7, 8].

In this report we present 3 patients with multisystem LCH who were treated with VP-16 and IFN- α . In all patients the diagnosis was confirmed by a positive immunohistochemical staining for S-100 protein and by the presence of Birbeck granules in the lesional cells [9]. All patients had high IgG titers against both EBV viral capsid antigen (VCA) and nuclear antigen (EBNA) and CMV. All patients were treated with VP-16 (200 mg/m² on 3 consecutive days) for 15 cycles at 3-week intervals, as recommended in the Italian protocol AIEOP-ICL 89 [10], followed by maintenance therapy with IFN- α 3,000,000 IU/m² daily. IFN- α was given subcutaneously for 1 year, and then 3 times weekly for 3 months.

CASE REPORTS

Case 1

A 2-year-old female was admitted at our department with high fever, enlarged lymph nodes (submandibular, occipital, axillary, and inguinal) without liver or spleen enlargement, and normal cerebrospinal fluid (CSF). X-rays of the skull and long bones showed multiple osteolytic lesions, and the bone marrow (BM) was infiltrated by multiple histiocytes showing phagocytosis of erythrocytes and leukocytes. After chemotherapy with VP-16 was

completed the girl reached partial remission. Complete remission was reached after 3 months of INF- α maintenance therapy. The girl is now without any signs of disease after 9 years off therapy.

Case 2

A 4-month-old female presented with high fever, anemia, leukocytosis with lymphomonocytosis, enlargement of submandibular and cervical lymph nodes on both sides, hepatomegaly (4 cm), and splenomegaly (2 cm). She had normal CSF findings. X-rays of the skull and long bones were normal. Bone marrow smears revealed an increased amount of histiocytes with erythrophagocytosis. When she finished chemotherapy (VP-16), she had reached complete remission and remains so now 6 years off therapy.

CASE 3

A 9-month-old female presented with high fever and an enormous enlargement of submandibular and cervical lymph nodes. Her axillary and inguinal lymph nodes were also enlarged at both sides and hepatomegaly (4 cm) and splenomegaly (3 cm) were also recorded. X-rays of the skull and long bones and a CSF cytopsin were all normal. A BM examination showed a large number of histiocytes without signs of phagocytosis. At the end of the chemotherapy (VP-16) she had reached complete remission. This girl is now still in complete stable remission 4 years off therapy.

DISCUSSION

Various hypotheses have been considered to explain the etiology of LCH. The role of cytokines and viral agents has been thoroughly investigated [3, 4]. The demonstration of clonality of LCH lesions has raised the question of whether LCH is a neoplastic disorder. However, in the absence clearcut evidence of the etiology of LCH, the treatment of disseminated LCH remains controversial.

All 3 patients in this report were young and had multiple-organ involvement of LCH at presentation, 2 of them with obvious signs of organ dysfunction. They thus belong to a high-risk group of patients that may have poor prognosis, particularly if the response to the initial therapy is poor [6]. Our patients responded to the initial chemotherapy, although one of them (case 1) still had signs of the disease at the end of the scheduled treatment with etoposide. All our patients remain disease-free several years after all therapy was finished. Although this is a small series of patients, our results indicate that IFN- α may prevent recurrences in high-risk LCH patients. The tolerability of IFN- α was excellent. As expected, a mild rise in body temperature during the first week of therapy was recorded.

The cumulative doses of etoposide in all patients were 9 g/m² given over a period of 45 weeks without any serious side effects or toxicity after several years. Since the first randomized trial, LCH-I has shown that etoposide has no advantage over vinblastine [6], and since there is a concern about the potential leukemogenicity of vinblastine, alternative chemotherapy regimens should be considered.

Prospective randomized studies are required to confirm the efficacy of IFN- α in preventing recurrences in patients who need chemotherapy. Long-acting (pegylated) IFN- α with more favorable pharmacokinetics, which is now becoming available, should perhaps be used in such studies.

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