Low-Dose Oral Etoposide Monotherapy in Adult Langerhans Cell Histiocytosis

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Background: The purpose of this study was to test the disease-controlling effect of low-dose oral etoposide monotherapy in adult-onset multisystem Langerhans cell histiocytosis. There are no previous reports of low-dose etoposide monotherapy for this condition.

Observations: A 27-year-old man with a 7-year history of multifocal chronic Langerhans cell histiocytosis presented with severe disabling ulcers in intertriginous areas. He had previously been treated with 2 different regimens of antitumoral chemotherapy; one had to be discontinued due to myelosuppression and the other had proved ineffective. We treated with oral etoposide monotherapy at 50 mg/d (22 mg/m² per day) for 21 days. The treatment was repeated at 28-day intervals for a total of 6 cycles. A rapid initial response with subtotal diminution of the involved skin area was found. No adverse effects were observed. The clinical picture has remained stable during the 7 months following cessation of therapy.

Conclusion: Low-dose oral etoposide treatment is an adequate therapeutic measure for prolonged disease control in adult-type Langerhans cell histiocytosis.

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Since 1987, Langerhans cell histiocytosis (LCH) has been the term used for those diseases previously classified as “histiocytosis X.” Whether this condition is a neoplastic or a reactive process has not yet been determined. During the past few years, this discussion has affected the way in which the more severe forms are treated, with a shift of goals from cure to control.1

Etoposide has been used by pediatricians for about 10 years for the treatment of the more frequent juvenile LCH.2-6 However, experience with etoposide in the rare, disseminated adult LCH is sporadic and limited to single cases treated by high-dose or combination schedules.7-11 Disseminated adult LCH is commonly organ destructive, but, in contrast to the juvenile type, has a more benign character with a slowly progressive or undulating course. This favors prolonged treatment with minimal adverse effects, until a curative drug or schedule has been established. The clinical responses to low-dose oral etoposide in malignant diseases encouraged us to try the same, obviously well-tolerated, monotherapy in a case of chronic disseminated LCH in an adult patient.

REPORT OF A CASE

A 27-year-old white man with a 7-year history of chronic LCH visited our clinic in March 1995. In 1988, he had experienced a spontaneous fracture of the right femur. In 1990, he developed diabetes insipidus, which responded well to twice-daily desmopressin inhalations. Computed tomography revealed a suprasellar tumor. The diagnosis of LCH was finally established in 1993 after a biopsy of a relapsing bone lesion of the right femur was performed. Subsequently, x-ray therapy of this femur and the sellar region was performed successfully, but additional chemotherapy (vinblastine and prednisolone) had to be abandoned because of myelosuppression. In 1994, he noticed signs of viscerocranial involvement with a tender swelling of the maxilla and gum infiltration. An eosinophilic granuloma was diagnosed from a biopsy specimen of the latter region. Three cycles of chemotherapy with cyclophosphamide, vincristine, procarbazine, and prednisone (COPP de Vita) did not produce any effect. Two months later, the patient experienced perianal soreness and ulceration that was unresponsive to local antibacterial and antifungal treatment.

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On initial examination at our department, the patient was an overweight man (123 kg and 168 cm) with deep painful suppuring ulcers of the bilateral inguinal, perianal, and right axillary regions. The largest lesions were 2 deep oozing ulcers in the natal cleft dorsal to the anus (Figure 1) and a punched-out purulent granulating ulcer in the right axilla (Figure 2, A). Maxilla and mandible showed swelling of the gums without mucosal ulceration. Furthermore, the patient had a mild exophthalmia and keratosis follicularis–like yellowish scaling papules in the seborrhoeic areas. Both symptoms are characteristic of the presented disease. In particular, he was immobile and complained of nutritional and defecation problems. The patient's general condition was poor. His family history was unremarkable for LCH, malignant tumors, autoimmune disorders, or skin diseases.

INVESTIGATIONS

Computed tomography revealed an involvement of both jawbones and established the reossification of the irradiated area of the right femur where the manifestation of the disease formally occurred. The suprasellar tumor described above was no longer evident. No other active lesions of organs or body regions were detected (computed tomography of thorax, abdomen, and femur, and abdominal sonogram). As a result of x-ray therapy of the sellar region, the patient developed hypopituitarism with a low level of insulinlike growth factor (63.7 ng/mL [reference range, 158-583 ng/mL]), labile thyrotropin (0.03-0.45 µIU/mL [reference range, 0.40-4.20 µIU/mL]), impaired mineralocorticoid axis (corticotropin, 3.8 pmol/L [reference range, 5.5-15.1 pmol/L]; cortisol, 122.60 nmol/L [reference range, 138-690 nmol/L 9 at AM]), and hypogonadotropic hypogonadism (small [9 mL] and tender testes), as well as azoospermia (serum testosterone, 0.35 nmol/L [reference range, 9.9-39.9 nmol/L]; follicle-stimulating hormone, 1.12 IU/L [reference range, 1.6-11 IU/L]). Microbiological investigation of skin smears from inguinal and axillary ulcers demonstrated the presence of Pseudomonas aeruginosa.

Histological examination (Figure 3, A) of the inguinal, perianal, and mandibular regions showed a deep dermal infiltrate composed of large, rounded, S-100 and CD1a-positive histiocytelike cells with abundant, slightly eosinophilic cytoplasm and accumulations of eosinophilic granulocytes. Lymphocytes, neutrophilic granulocytes, and eosinophilic granulocytes were present in the upper edematous dermis and epidermis. Langerhans cells (inguinal and mandibular) with characteristic Birbeck granules could be identified ultrastructurally in the deeper dermis, thus confirming the diagnosis of LCH (Figure 3, B).

Image cytometry DNA analysis on Feulgen-stained 6-µm-thick sections (as described by Klappperstuck and Wohlrab12) revealed a euploid tumor cell population with 6-µm-thick sections (as described by Klapperstuck and Wohlrab12) revealed a euploid tumor cell population with a diploid G0/1 stem line and a few proliferating cells.

TREATMENT

We started treatment with potassium permanganate baths, hydrogen peroxide lavage, and zinc oxide ointments in combination with oral antibiotics using ofloxacin 2 × 200 mg (Tarivid, Hoechst Bad Soden, Germany). With this regimen the ulcers cleared of their purulent character and bacterial contamination (negative culture) but there was no effect on shape and size after 3 weeks. Subsequently, we commenced oral treatment with 1 capsule of 50-mg etoposide every morning for 21 days (Vepeside, Bristol-Myers Squibb, Munich, Germany). Six cycles were repeated at 28-day intervals. The etoposide plasma profile on day 21 of the first cycle of therapy is given in the following tabulation.

<table>
<thead>
<tr>
<th>Time After Administration, h</th>
<th>Total Etoposide, µg/mL</th>
<th>Free Etoposide, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.57</td>
<td>0.050</td>
</tr>
<tr>
<td>5</td>
<td>0.72</td>
<td>0.020</td>
</tr>
<tr>
<td>20</td>
<td>0.30</td>
<td>0.009</td>
</tr>
</tbody>
</table>

During the treatment period neither glucocorticoids nor other adjuvant drugs with known anti-LCH potential were used.

The first therapeutic effects, with a remarkable diminution of all ulcers, occurred after 2 weeks. After the third cycle (12 weeks), all flexural and oral affections had completely healed except the deepest ulcer located in the dorsal region, which had been reduced from 4 × 2-3 cm (length × width × depth) to a remaining erythematous area with an erosion of 2 × 0.3 cm (Figure 2 and Figure 4). After the fifth cycle, the underlying LCH nature of this persistent skin lesion was still detectable by

Figure 1. Two painful, extended, and deep ulcers at the rima ani that caused immense defecation problems. A, Superior; B, inferior, next to the anus, 4 × 1 cm wide and 2 to 3 cm deep (bar = 1 cm).

Figure 2. Punched-out purulent granulating ulcer in the right axilla, 3 × 2.5 cm wide and 1 to 2 cm deep (A) that healed completely with etoposide therapy (B) (bar = 1 cm). Arrow indicates the former localization of the ulcer shown in part A.
conventional histological study and electron microscopy. During the same period, the swelling and subjective symptoms of the jawbones decreased and computed tomography revealed signs of diminution and partial reossification. Nevertheless, the last 3 cycles did not produce any additional effect on the remaining lesion, although the etoposide dose was increased to 100 mg/d in cycles 5 and 6. The ongoing healing of the local lesions was accompanied by a general recovery and independence from nursing care. In addition, most of the abnormal laboratory values investigated improved. Erythrocyte sedimentation rate and C reactive protein level decreased from 62/120 to 40/90 and 38.6 mg/L to 13.9 mg/L, respectively (before and after therapy). A mild anemia and leukopenia improved, with the following pretreatment vs posttreatment values: total CD3+ T lymphocytes, 0.19 × 10^9/L vs 0.35 × 10^9/L; CD3-CD8- T lymphocytes, 0.08 × 10^9/L vs 0.21 × 10^9/L; CD3-CD8+ T lymphocytes, 0.11 × 10^9/L vs 0.15 × 10^9/L; CD4/CD8 ratio, 0.7 vs 1.4; and recall antigen test (Multitest Merieux, Pasteur-Merieux MSD, Leimen, Germany), 3 mm vs 8 mm (reference, >9 mm). Bone marrow was normocellular with regenerative details and no significant changes following etoposide treatment.

Diabetes insipidus and hypopituitarism were not affected by the therapy. Daily drinking volume and urinary volume (tested under desmopressin pause) did not change significantly: drinking volume/urinary volume was 7.4/6.7 L before therapy vs 6.5/5.9 L after 3 months of therapy. During the therapy period, the desmopressin demand remained between 20 and 40 µg/d without significant change. Testosterone and follicle-stimulating hormone levels remained at the same low levels as given in the “Investigations” section, with values of 0.95 nmol/L and 0.92 IU/L, respectively, after 6 months of therapy. Levels of corticotropin and cortisol showed no significant improvement after 6 months of therapy, with values of 4.30 pmol/L and 115.60 nmol/L, respectively.

The clinical picture of the involved skin has remained stable for about 7 months after discontinuation of therapy. However, the flexural and oral LCH manifestations subsequently relapsed gradually at the former locations.

**ADVERSE EFFECT MONITORING**

The patient was followed up each week for adverse effects. Physical examination, blood cell count, determination of liver enzymes, creatinine, urea, uric acid, and urinary sediment, and microbial culture of ulcer smear were performed. Monitoring of possible immunosuppressive drug effects (recall antigen test, lymphocyte typing) and clinical neurological examination were performed at the beginning of etoposide treatment and after 2 and 6 cycles. Bone marrow biopsy was performed before therapy and after the sixth cycle. No noticeable adverse effects were detected.

**COMMENT**

Etoposide is a semisynthetic epipodophyllotoxin derivative that is effective in the treatment of malignant neoplasms of the monocyte-macrophage lineage, bronchial carcinoma, advanced breast cancer, mycosis fungoides, prostatic cancer, ovarian cancer, and Kaposi sarcoma and is also used for the treatment of resistant or relapsing LCH. It acts as a DNA topoisomerase II inhibitor and induces G2 arrest and S-phase delay in a dose-dependent manner.13 The long-term low-dose therapy was established in the 1980s in small cell lung cancer, lymphomas, and germ cell tumors following the surprising observation that prolonged low-dose administration and previously inaugurated high-dose schedules with some potent antitumor drugs, including etoposide, are equivalent in efficacy.14,15 The advantage of this new therapeutic approach is its much better tolerance. Experience with low-dose etoposide in the treatment of leukemia, multiple myeloma, advanced breast cancer, and other childhood and adult tumors is now also available. An oral dose of 50 mg/m² per day, administered in 21-day cycles is favored. The disadvantage of orally administered etopo-
side is its variable bioavailability. On the other hand, it appears that the lower the oral dose of etoposide, the higher the relative bioavailability. A comparatively low oral daily dose of 22 mg/m² was administered initially. With this regimen, the etoposide serum levels in our patient seemed to be acceptable when compared with results of in vitro investigations that demonstrated tumor cytotoxicity at levels ranging from 0.5 to 1.0 µg/mL.

Image cytometry DNA analysis has not identified aneuploidy in the biopsy material from our patient. This is consistent with the results of other investigations, and is of particular interest because of the ongoing discussion about the nature of LCH. To date, there has only been 1 case report in which flow cytometry revealed an aneuploid peak, distinguishing that case from most LCH cases. The effect of the therapy chosen for our patient can be considered to be successful in regard to partial remission because of the clear diminution of the skin area involved and the response of the jawbone destruction. The fact that the systemic disease (diabetes insipidus and hypopituitarism) did not improve is not surprising if the former x-ray therapy of the sellar region is taken into account.

Interestingly, the remission status of the disease has remained stable for 7 months after cessation of therapy. However, low-dose etoposide was not able to cure LCH completely. The most likely explanation might be the development of drug resistance, which is a well-known phenomenon in low-dose chemotherapy, including etoposide. A solution might be found by using a strategy of more aggressive initiation, as supported by recent investigations in disseminated childhood LCH. Further alternatives are a combination of etoposide with other antitumoral drugs, calcium channel blockers, or with immune-modulating agents such as prednisolone, cyclosporine, interferon gamma, or thalidomide.

Chronic LCH in the adult is a rare and difficult-to-treat disease. The results presented herein suggest that low-dose oral etoposide does not have a complete curative effect, but a disease-controlling effect. This was demonstrated for 12 months (5 during therapy and 7 thereafter) in our patient.

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