Symptomatic Bone Langerhans Cell Histiocytosis Treated at Diagnosis or After Reactivation With Indomethacin Alone

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Summary: This study evaluated the outcome of patients with symptomatic bone Langerhans cell histiocytosis (LCH) treated with indomethacin alone, either at diagnosis or after reactivation (after recurrence with previous therapies). We evaluated the non-randomized use of oral indomethacin (2 mg/kg/d) in patients with symptomatic single-system bone LCH. From 1997 to 2012, 38 sequential patients were treated for a median of 4 months. Criteria of nonactive disease (NAD) after initial treatment (8 wk) were: no pain, no soft tissue involvement, no increase of size, or no new bone lesions. Twenty-two patients were treated at diagnosis: 18 showed NAD after initial treatment (2 patients who had bone reactivations were retreated with indomethacin and remain with NAD). Three patients improved and they are with NAD after treatment with indomethacin, steroids, or radiotherapy. One patient developed progressive bone disease and he is with NAD after treatment with steroids and chemotherapy. Sixteen patients were treated after reactivation, and all were with NAD after initial treatment: 5 reactivated and 4 remain with NAD after reactivation with indomethacin. Toxicity was not significant. We conclude that indomethacin is a well tolerated and active drug in patients with symptomatic bone disease. The results support the concept that chemotherapy may not be necessary for limited bone disease.

Key Words: indomethacin therapy, bone Langerhans cell histiocytosis, outcome

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Langerhans cell histiocytosis (LCH) is a rare disease with variable clinical manifestations. It may be self-limited in some patients, whereas in others intensive treatment is unsuccessful. The outcome depends on whether vital organ are compromised at diagnosis in which case the prognosis is poor.

The course of single-system LCH is usually benign. Bone is the commonest single organ involved in LCH. In bone disease, reactivations usually remain restricted to skeleton and do not influence survival. However, reactivations have an impact on morbidity as permanent consequences are mostly related to the site of disease activity.2

Many different strategies have been used for the treatment of bone LCH in children.3,4 From minimal strategies such as observation or steroid injections,5,6 to more aggressive approaches such as surgery, chemotherapy, or radiotherapy,7,8 Treatment strategies with lower incidence of adverse events while ensuring a successful cure are desirable in this cohort of patients.

Indomethacin is a nonsteroidal anti-inflammatory drug inhibitor of cyclo-oxygenase 1 and 2 enzymes that participate in prostaglandin synthesis from arachidonic acid.9 Prostaglandins are hormone-like molecules normally found in the body where they have a wide variety of effects, some of which lead to pain, fever, and inflammation.

The main use of indomethacin is as an anti-inflammatory drug in rheumatologic conditions. Prostaglandins (PG) have been implicated in the pathogenesis of histiocytic disorders. Purified LCH cells from bony lesions of LCH produce interleukin 1 and PG E2 in vitro and LCH cells in a case of disseminated LCH have been shown to produce PG D2 and thromboxane.10,11

On that basis Munn et al9 used indomethacin in patients with symptomatic bone LCH and they concluded that indomethacin was a useful therapy for LCH involving the bony skeleton and may have a role as first-line treatment in single-system bone disease. Other subsequent study also showed that indomethacin seems to be effective for treating isolated bone LCH in children avoiding morbidity associated with other treatment approaches such as chemotherapy or surgery.12 However, the systematic use of indomethacin in larger cohorts of children with LCH, including children with reactivation of the disease, has not been further explored.

Therefore, the aim of this study was to evaluate the outcome of patients with symptomatic bone LCH treated with indomethacin alone, either at diagnosis or after reactivation.

METHODS

A retrospective analysis of 38 LCH patients with persistent symptomatic single-system bone involvement at diagnosis (after bone aspiration, biopsy, or curettage) or after reactivation was performed. Patients treated at diagnosis had a proven definitive diagnosis of LCH according to the Histioyte Society criteria.13 Patients treated at reactivation were diagnosed according to the clinical symptoms/signs (pain, tumor) associated with new bone lesion(s) with or without adjacent soft tissue involvement showed by imaging.

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Patients were collected at 3 pediatric hospitals from August 1997 to January 2012. All patients with persistent symptomatic single-system bone involvement (up to 3 bone lesions) were treated with indomethacin alone at a dose of 2 mg/kg/d and the median duration of treatment was 4 (r, 2 to 24) months.

Patients with: (a) asymptomatic bone involvement after diagnostic biopsy, (b) ≥ 4 bone lesions at diagnosis, and (c) special-site bone involvement (lesions of craniofacial region) were not treated with indomethacin and were not included in this study.

All the patients treated with indomethacin (at diagnosis or reactivation) were evaluated separately and consecutively since day 1 of that drug. The 22 patients treated at diagnosis should have persistent (mild, moderate, or strong) or progressive pain after being biopsied to be included in the study.

The criteria of bone response after 8 weeks and at the end of treatment were: (a) no evidence of active disease (no pain, no tumor, no soft tissue involvement, no increase of size of bone lesions, no new bone lesions); (b) partial response; (c) stable disease; and (d) progressive disease.

The definition of disease status was according to the Histiocyte Society criteria. The time free of reactivation for newly diagnosed patients was defined as the time from no evidence of active disease after 8 weeks of treatment to reactivation or to the last follow-up; the follow-up time was defined as the time from diagnosis to the last follow-up. For patients treated at reactivation the time free of reactivation was defined as the time from no evidence of active disease after 8 weeks of treatment to the next reactivation and the follow-up time was defined as the time from diagnosis of reactivation to the last follow-up.

The duration of indomethacin therapy was not prospectively defined. Patients treated at reactivation or with partial response after initial treatment or with multifocal involvement were treated during longer periods of time.

All the reported patients were evaluated and reviewed by members of Pediatric, Radiology, and Hematology/Oncology Departments (clinical evaluation followed and radiologic measurements of all lesions confirmed the decrease, disappearance, persistence, or progression of bone lesions and soft tissue involvement). Imaging was not systematically reviewed for the purpose of this report. Data were collected from clinical and radiology reports.

Skeletal survey was performed in all the patients at diagnosis, at week 8 and at the end of treatment. Computed tomography scan was performed in all the patients with flat bone lesions and in some patients with long bone lesions. Radiologic procedures were repeated thereafter only if patients have new symptoms or signs (pain or tumor) compatible with reactivation. When clinical conditions overtly improved there was not need of costly studies, thus avoiding anesthesia in small children and unnecessary radiation exposure. This conservative policy is also recommended now by the Histiocyte Society protocol studies.

RESULTS

A summary of therapy response to indomethacin and the outcome of all patients are shown in Figure 1. The comparison of unifocal versus multifocal bone disease outcome is shown in Figure 2.

Patients Treated at Diagnosis

Twenty-two patients (female 11/male 11) with symptomatic bone LCH involvement (1 to 3 sites) were treated with indomethacin alone. Median age was 3.9 (r, 2 to 14.2) years. The median duration of treatment was 3 months (r, 2 mo to 1 y). Median time free of reactivation was 2.3 (r, 0.2 to 8.3) years and the median follow-up time was 3.7 (r, 0.5 to 8.5) years. The sites of the lesions are shown in Table 1.

Eighteen of the 22 (81.8%) patients had nonactive disease (NAD) after 8 weeks of treatment; 2 of those patients

FIGURE 1. Flow chart of patients treated with indomethacin (overall outcome). ARAC indicates cytarabine; IMT, indomethacin; NAD, no active disease; PD, progressive disease; PRED, prednisone; PR, partial remission; RT, radiotherapy; VCR: vincristine.
who had bone reactivations were retreated with IMT and they were with NAD at the last follow-up visit, with a time free of reactivation of 9 months and 4.4 years, respectively.

Three patients had a partial improvement of the disease after 8 weeks of treatment (all were retreated and they are with NAD: 1 patient continued with indomethacin for 2 y, and the other 2 patients were retreated with prednisone-indomethacin and prednisone-radiotherapy, respectively, with a time free of reactivation of 4.25 y, 9 mo, and 6 y, respectively). Finally, 1 patient had progressive multifocal bone involvement after initial treatment and was with NAD at the last follow-up after treatment with prednisone-vincristine-cytarabine with a time free of reactivation of 3 years.

**Patients Treated at Reactivation**

At initial diagnosis of LCH, 6 of these patients had multifocal bone involvement, 5 had low-risk involvement, 3 had unifocal bone involvement, and 2 belonged to the risk group. They had been previously treated at diagnosis and in previous reactivations, with prednisone-vinblastine (12 patients), vincristine-prednisone-cytarabine (3 patients), radiotherapy (3 patients), prednisone-vinblastine-etoposide (2 patients), prednisone-indomethacin (1 patient), intralesional steroids (1 patient), and wait and see policy (2 patients).

Seven patients received indomethacin, for the first time, at first reactivation, 3 at second reactivation, 3 at third reactivation, 2 at fourth reactivation, and 1 at sixth reactivation.

One patient received indomethacin at their sixth and seventh reactivations, 1 at their second, third, and fourth reactivations, and 1 at third and fourth reactivations.

After recurrence with previous treatments, 16 patients (male 9/female 7) with symptomatic bone LCH involvement (1 to 3 sites) were treated at reactivation with indomethacin alone. The median age was 5.65 (r, 1.9 to 13) years. The median duration of treatment was 9 months (r, 2 mo to 2 y).

The median time free of reactivation was 3.3 (r, 0.5 to 9.6 y) years, and the median follow-up time was 4.5 (r, 1.4 to 11.75 y) years. The sites of involvement are shown in Table 1.

All patients treated with indomethacin at reactivation had NAD after 8 weeks of initial therapy. Five of those patients had bone reactivations, 4 of them were retreated with indomethacin and the other one was retreated with vincristine, prednisone and cytarabine and they are with NAD with a time free of reactivation of 5.3 years, 10 months, 7.3 years, 1 month, and 1.3 years, respectively. The response to treatment of one of those patients is shown (Figs. 3A, B).

**Other Overall Results**

One of the patients treated at diagnosis developed a primary autoimmune hypothyroidism after treatment with indomethacin. Six of the patients treated at reactivation had endocrinological involvement; all of them had diabetes insipidus before the treatment with indomethacin. One of these patients developed a deficiet of thyroid-stimulating hormones and growth hormones, and the other patient developed a deficiet of adrenocortical-stimulating hormone after indomethacin therapy.

No reactivations during the treatment with indomethacin were found. After a new bone reactivation, 7 of the 38 patients were retreated again with indomethacin and are with NAD with a median time free of reactivation of 4.25 years (r, 1 mo to 7.3 y). Four patients were retreated with other medications (prednisone-cytarabine-vincristine, 2 patients; prednisone-indomethacin, 1 patient; and prednisone-radiotherapy, 1 patient).
In summary, 34 of all the 38 patients treated with 1 to 3 courses of indomethacin alone were without evidence of active disease.

Two of 38 patients evaluated had mild somnolence. No other significant toxicities were evident in the patients of the study. Three patients with spine involvement had a mild (grade 1) severity of sequelae. The estimated cost in our study of indomethacin therapy for a patient of 15 kg during 4 months of treatment in our setting was 93 US dollars.

DISCUSSION

Munn et al. showed in their study that indomethacin was an active agent for patients with LCH bone involvement. Nevertheless, the study was conducted in a reduced number of cases and some of them also received corticosteroids. The principal aim of that study was the symptomatic relief of bone disease. According to this report, whether indomethacin has a specific role in slowing disease progression or merely acts as an analgesic has not yet been established.

Our study evaluated the response to treatment with indomethacin in a significant number of cases with symptomatic unisystem bone disease not only at diagnosis but after reactivation. The principal objective of our study was the complete control of bone disease.

In agreement with Munn and colleagues, we used indomethacin trying to avoid the potential toxicity of the usual treatments (corticosteroids, chemotherapy, radiotherapy) used for these patients with an optimal possibility of survival.

Han et al. compared indomethacin therapy with other more aggressive approaches of anti-cancer chemotherapy and surgery in the treatment of isolated bone LCH. The treatment was effective avoiding the morbidities associated with other aggressive strategies. This study was not randomized like Han and colleagues’s series but included patients with 2 or 3 bone lesions (at diagnosis or reactivation) with similar good results. Other study showed sustained favorable clinical outcome in 2 patients with single-system bone disease treated with only PG inhibitors.

Two studies showed that bone was the most frequent site of reactivation; it is also associated with a high survival rate. Following these conclusions, we treated our patients at reactivation with a conservative strategy and a good response. As patients were managed on an ambulatory basis and many of them lived far from our center, some mild toxic effects might have been missed.

Bone response to therapy is usually a matter of controversy. Healing is slow and could not be in parallel with the disease response, although imaging may be initially inconsistent. The cutoff point of 8 weeks may be insufficient to evaluate the response of bone lesions. Therefore, the optimal duration of therapy is difficult to establish for these patients. The duration of indomethacin therapy was not uniform for all our patients. As it is reported, reactivation was associated with a higher rate of sequelae; therefore, the duration of treatment with indomethacin for these patients tended to be longer. The same occurred in cases with partial response, or with multifocal involvement.

The outcome of patients with unifocal bone disease did not show significant differences with that of multifocal involvement (Fig. 2). The small number of patients precluded any further analysis.

Patients treated with indomethacin as a single agent had a low incidence of late effects. Only 2 patients developed growth hormone, thyroid-stimulating hormone, and adrenocortical-stimulating hormone deficit, but they both had a previous pituitary involvement (diabetes insipidus) before indomethacin therapy. Reactivations occurring after the cessation of a first course of indomethacin were retreated with success using the same drug in the majority of cases. Better understanding of the optimal treatment duration of indomethacin may reduce such recurrences in the future.

Our results showed that the majority of these patients may be cured with this strategy with minimal side effects. Those who did not achieve a complete response or underwent a new reactivation were rescued with indomethacin alone, indomethacin plus prednisone, indomethacin plus radiotherapy, and only 2 were exposed to standard chemotherapy (vincristine, cytarabine, prednisone).

The use of an oral, well-tolerated, and low cost medication had, in our study, a favorable impact on these patients and their families and allowed to treat them with the concurrence of local pediatricians and general practitioners, which was heartily accepted by low-income families living far away from our center.
Indomethacin is a useful drug when used alone in LCH patients with symptomatic bone disease at diagnosis or after reactivation. The present analysis showed that indomethacin therapy was feasible and nontoxic. A complete control of the disease was achieved in the majority of cases. Beyond the incidence of recurrences, the use of indomethacin alone cured most of the patients included in this study.

Indomethacin may deserve to be evaluated as a first-line treatment in single-system bone disease in future controlled multicenter studies.

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