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Does Adjunctive Chemotherapy Reduce Remission Rates Compared to Cortisone Alone in Unifocal or Multifocal Histiocytosis of Bone?

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Abstract

Background Langerhans cell histiocytosis (LCH) is a rare disorder that can affect almost any organ, including bone. Treatment options include local corticosteroid infiltration in isolated bone lesions and oral corticosteroids and chemotherapy in multifocal bone lesions. Several studies show local corticosteroid injection in unifocal bone lesions heal in more than 75% of patients with minimal side effects. Therefore, it is unclear whether chemotherapy adds materially to the healing rate.

Questions/purposes We therefore compared overall survival, remission rate, and recurrence rate in patients with bone LCH treated with chemotherapy and corticosteroids or corticosteroids alone.

Methods We retrospectively reviewed the records of 198 patients with LCH since 1950. Median age at diagnosis was 5 years, male-to-female ratio was 1.33, and the most frequent symptom was local pain (95%). We recorded the disease presentation, demographics, treatment, and clinical evolution of each patient. Minimum followup was 4 months (median, 24 months; range, 4–360 months).

Results The survival rate of the systemic disease group was 76.5% (65 of 85) while the survival rate in the unifocal and multifocal bone involvement groups was 100% at a median 5-year followup. All patients with unifocal bone involvement and 40 of 43 (93%) with multifocal bone involvement had complete remission. One of 30 patients with multifocal bone involvement treated with chemotherapy and oral corticosteroids did not achieve remission whereas two of six receiving only corticosteroids did not achieve remission.

Conclusions Our observations suggest intralesional corticosteroid injection without adjunctive chemotherapy achieves remission in unifocal bone LCH but may not do so in multifocal single-system bone involvement. Larger series would be required to confirm this observation.

Level of Evidence Level IV, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.
Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
This work was performed at University of São Paulo and Boldrini Cancer Center.

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Introduction

Langerhans cell histiocytosis (LCH), as renamed from histiocytosis X by the Histiocyte Society in 1987 [23], refers to a group of conditions with different clinical

courses, characterized by abnormal proliferation of pathologic Langerhans cells (LCs) [27]. Although the stem cell has been identified, the pathogenesis remains unclear [10, 23]. While it has been suggested LCH is a primary neoplastic disorder of the LC [29], more recent evidence points toward an immunologic aberration [2, 5, 10]. LCH can occur at any age but is predominantly seen in children and in males [27]. It affects almost any organ and, especially in the bone, can be unifocal or multifocal [17].

The disease is characterized by a disorder of the regulation of antigen-presenting dendritic cells (LCs), which are derived from the bone marrow and are normally present in the lymph nodes and other organs, such as lungs, liver, and spleen [29]. The proliferation of these pathologic LCs occurs most frequently in the bone, especially in children [29].

LCH has been classified according to the extent and location of the disease [24]. Multisystem involvement is rare and includes Hand-Schüller-Christian disease [25], which includes the triad of cranial lesions, diabetes insipidus, and exophthalmos. Even more unusual is Letterer-Siwe disease [30, 31], which is a more severe presentation, characterized by earlier onset (younger than 3 years), wasting, hepatosplenomegaly, generalized lymphadenopathy, pancytopenia, and rash.

The overall mortality rate for the systemic forms ranges from 6% to 21% [8, 18, 20] for all systemic forms [4, 12] and from 40% to 69% for the Letterer-Siwe form. There is a subgroup of patients (nonresponders to initial therapy) with extremely poor prognosis (mortality rate of 90%) [9, 14, 16, 19]. Most patients with LCH, however, have a good prognosis [26], except those with multisystem involvement: most of the lesions resolve completely, some of them even without treatment [20, 27].

Several modalities are used to treat the different presentations of the disease [9, 11, 14, 20, 21]. Local corticosteroid infiltration is frequently used in isolated bone lesions, with a reported remission rate of greater than 75% [7, 22, 28]. Oral corticosteroids and chemotherapy are used in multifocal bone lesions and multisystem involvement, with long-lasting complete remission with minimal or no adverse effects [1, 3, 6]. Low-dose radiation therapy may be used as well, with more than 43% of local control, but the risk for secondary malignancy exists [15]. Some authors suggest this treatment method should no longer be recommended [1].

We compared patients with LCH with bone involvement treated with chemotherapy and corticosteroids or corticosteroids alone in terms of (1) overall survival, (2) remission rate, and (3) recurrence rate. Our objective was to describe a large series of this rare disease and the different treatment modalities used during a six-decade period.

Patients and Methods

We conducted a cross-sectional, retrospective study based on the medical records of patients from three tertiary hospitals in the state of São Paulo, Brazil, treated between 1950 and 2009. We retrospectively identified 203 patients who had LCH of bone diagnosed and treated at the Institute of Orthopaedics and Traumatology of the University of São Paulo by the Orthopaedic Oncology Group (n = 36), at the Institute of Pediatric Cancer Care of the University of São Paulo by the Pediatric Oncology Group (n = 23), and at the Pediatric Oncologic Center of Campinas at Boldrini Institute (n = 144) between 1950 and 2009. We crossreferenced the three sources to eliminate duplicate patients. We included all patients whether the disease involved unifocal or multifocal bone lesions or was multisystem. The patients were aged 11 months to 60 years (median, 5 years) at the time of diagnosis, with 159 of 203 (78%) between 1 and 7 years. There were 117 males and 86 females (male-to-female ratio: 1.36). Five patients were lost to followup and were excluded from the study: a 2-year-old boy with a solitary lesion in the left humerus who did not return after the biopsy; an 8-year-old boy with a solitary lesion in the left clavicle who did not return after the biopsy; a 60-year-old man with a solitary lesion on the right femur who was treated by curettage and never returned after release from the hospital; a 4-year-old boy with a solitary lesion in the jaw who was treated with oral corticosteroids and was last seen 2 weeks after beginning of treatment; and a 1-year-old girl with multisystem involvement, including multiple viscerae and multiple bone sites, who began treatment with oral corticosteroids and never returned to the doctor. The minimum followup of the 198 patients was 4 months (mean, 50 months; range, 4–360 months). No patients were recalled specifically for this study; all data were obtained from medical records, histology, and radiographs. We had prior institutional review board approval.

Clinical and pathologic data were obtained from hospital records and paraffin-embedded specimens. All patients underwent routine peripheral blood tests, radiographs, and biopsy, which was positive for LCH in all cases. For this study, all 198 cases were reviewed by two pathologists (CRGCMO, RZF) with experience in musculoskeletal oncology, and LCH was confirmed in all of the lesions, with this final diagnosis registered in the databank. Data extracted from the charts included sex, age, number and location of the bone lesions, presence of extraskeletal lesions or systemic disease, clinical symptoms, treatment used, complications, and time lapse to complete remission.

The most frequent symptom was local pain (95%). One hundred thirteen patients (57.1%) had only skeletal involvement. Seventy (61.9%) of the 113 patients had

Table 1. Distribution of patients according to the Langerhans Cell Histiocyte Society clinical classification

Classification	Number of patients
Single-system LCH with bone involvement	113
Unifocal bone	70
Multifocal bone	43
Multisystem LCH with bone involvement	85
Total	198

LCH = Langerhans cell histiocytosis.

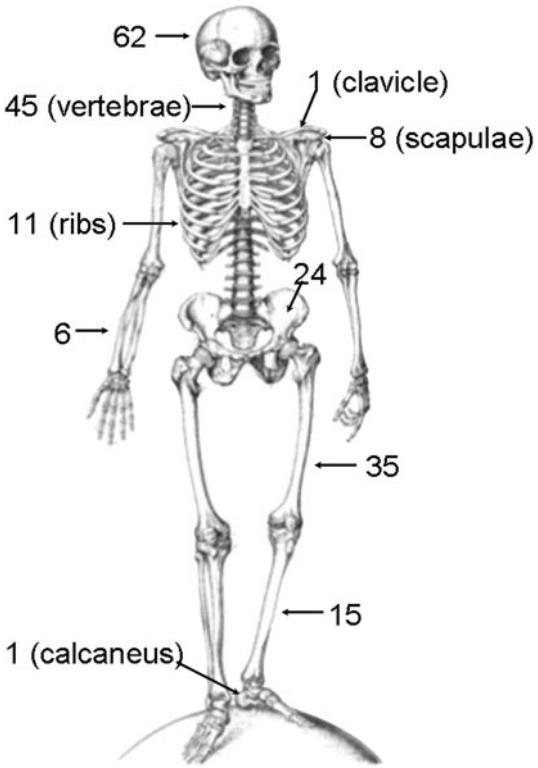

Fig. 1 The anatomic distribution of the 225 bone LCH lesions is shown.

unifocal bone involvement, whereas 43 (38.1%) had multifocal skeletal involvement (mean, 3.6 lesions; range, 2–11 lesions) (Table 1). The total number of skeletal lesions was 225 in the 113 patients. The most affected site was the skull (62 lesions, 27.6%), followed by the vertebrae (45 lesions, 20.0%) and the femur (35 lesions, 15.1%) (Fig. 1). Local injection of corticosteroids was the treatment of choice for the majority of the patients with unifocal bone involvement (52.9%) (Fig. 2), followed by oral corticosteroids (18.6%) (Fig. 3). The majority of the patients with multifocal bone involvement received chemotherapy and oral corticosteroids (69.8%), followed by oral corticosteroids only (13.9%) (Fig. 4).

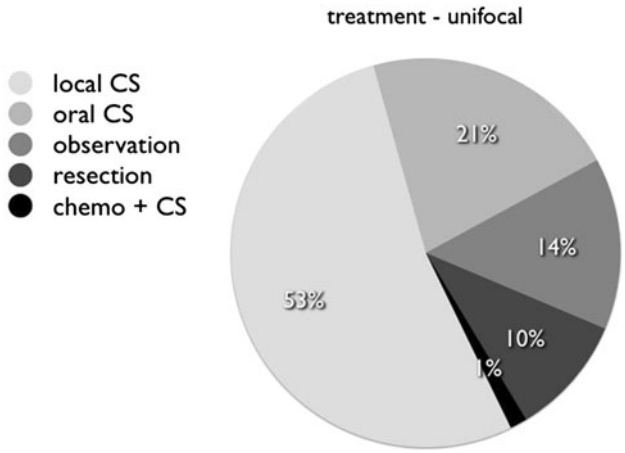

Fig. 2 A pie chart illustrates the treatment modalities applied to the 70 patients with unifocal bone involvement. CS = corticosteroids; chemo = chemotherapy.

Local injections of corticosteroids were done under anesthesia and the usual antisepsis in the operating room. The most used drug and dose was 500 mg methylprednisolone. The most frequent chemotherapy scheme was vinblastine plus etoposide associated with prednisone; methotrexate was used as second-line treatment, according to the Langerhans Cell Histiocytosis Society Guidelines adopted for the occasion [24]. Cyclophosphamide, alone or in association with etoposide or methotrexate, was also used. All 85 patients with systemic disease were treated with chemotherapy and oral corticosteroids.

After starting treatment or after surgery, the patients were seen weekly during the first month, then once in the second and third months, once in each following trimester for the first year, twice in the second year, and then once a year. At each visit, the patients were assessed for site pain, ROM, and functional limitations of the affected location. Radiographs of the affected bone (AP and lateral views) were taken at each visit. Two of us (AMB, AFFC) independently evaluated all radiographs for signs of healing or progression of the lesion. We considered decreasing size with increasing mineralization of the lesion as signs of healing. Signs of progression were increasing size of the lesion or appearance of new foci.

Results

The overall survival rate in our study was 89.9% (178 of 198) at a median followup of 5 years (range, 1–20 years). The survival rate of the systemic disease group was 76.5% (65 of 85) while the survival rate in the unifocal and multifocal bone involvement groups was 100% at a median 5-year followup.

At last followup, we found complete remission in 100% (70 of 70) of the patients with unifocal bone involvement

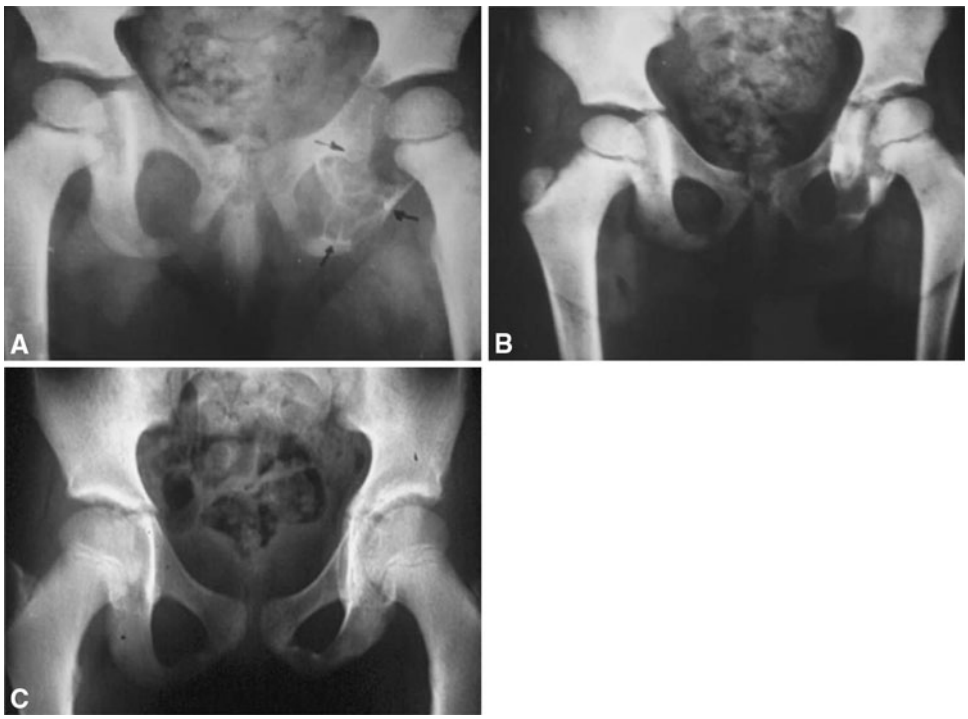

Fig. 3A–C Healing of a unifocal left ischium lesion after oral corticosteroids for 3 months is shown (**A**) before treatment (arrows), (**B**) after 6 weeks, and (**C**) after 12 weeks.

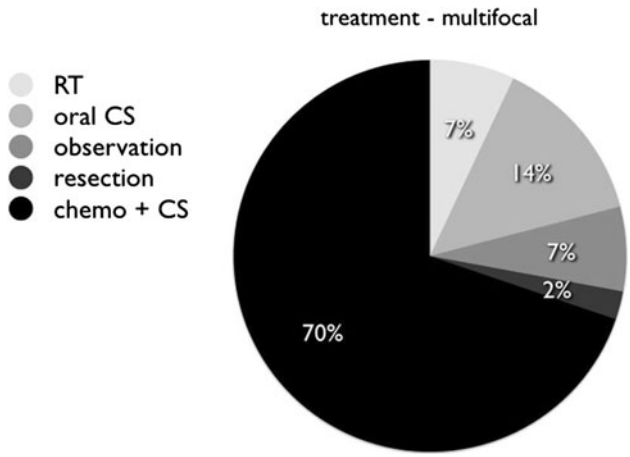

Fig. 4 A pie chart illustrates the treatment modalities applied to the 43 patients with multifocal bone involvement. RT = radiotherapy; CS = corticosteroids; chemo = chemotherapy.

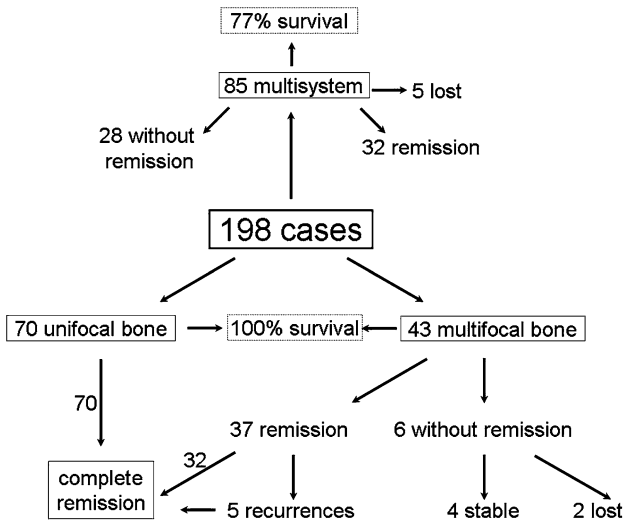

Fig. 5 A flowchart shows the clinical evolution of the 198 patients with LCH.

within a mean 3.1 months (range, 1–12 months) (Fig. 5). There was complete remission in 86% (37 of 43) of the patients with multifocal bone involvement within a mean 3.1 months (range, 1–7 months) (Table 2). Among the 30 patients with multifocal bone involvement treated with chemotherapy and oral corticosteroids, only one patient did not reach remission (3.3%) whereas, among the six patients receiving only corticosteroids, two did not reach remission (33.3%). There was no remission in six patients with multifocal bone involvement. One 10-year-old boy was initially treated with chemotherapy and corticosteroids and was being observed without remission when he was lost to followup after 8 months. Another 3-year-old boy was initially treated with oral corticosteroids for 3 months and then the treatment was changed to chemotherapy, but there was still no remission. The patient had only mild occasional pain during exercise and received no further treatment at last followup (3 years). The third patient without remission was a 2-year-old boy who received oral corticosteroids for 3 months. Although the patient became asymptomatic, the lesions (skull, jaw, rib, and humerus) did not disappear but were stable and the patient received no further treatment (6-year followup). Another three

patients did not go into remission. One was a 6-year-old girl treated with radiotherapy whose lesion did not disappear after 1 year and was lost to followup. Two patients became asymptomatic although the lesions did not resolve: a 7-year-old girl and a 4-year-old boy who had only minor discomfort at the affected location and received no further treatment after biopsy.

Among the patients with multifocal bone involvement who had complete remission, five had recurrence of at least one lesion. One was a 5-year-old boy with a lesion in the skull and another lesion in the femur. He was treated by surgical resection of the skull lesion. Spontaneous remission of the femoral lesion occurred after 6 months, but this lesion recurred after 2 years. Since the patient had only mild occasional pain, he received no further treatment and was followed by observation only and the lesion spontaneously remitted after 1 year (5-year followup). Another patient was a 6-year-old girl who was initially treated with chemotherapy and corticosteroids with remission after 4 months. The lesions recurred after 1 year but were stable and the patient received no further treatment. Her lesions spontaneously remitted after 10 months (4-year followup). The other three children (4-year-old boy, 6-year-old boy, and 7-year-old girl) were treated with chemotherapy and corticosteroids. The lesions disappeared after a mean interval of 4 months but recurred after a mean interval of 8 months. These children were additionally treated with local radiotherapy, with complete remission after a mean interval of 3 months.

Table 2. Treatment and outcomes of patients with multifocal bone involvement

Treatment	Number of patients	No remission	Remission/ recurrence
Chemotherapy + oral corticosteroids	30	1 (asymptomatic)	29/4
Oral corticosteroids	6	2 (oligosymptomatic, 1 asymptomatic)	4/0
Radiotherapy	3	1 (lost)	2/0
Observation	3	2 (both asymptomatic)	1/1
Resection	1	0	1/0
Total	43	6	37/5

Discussion

LCH is a rare disorder that can affect almost any organ. Possible treatment modalities include local corticosteroid infiltration in isolated bone lesions and oral corticosteroids and chemotherapy in multifocal bone lesions. We question whether chemotherapy is necessary in bone LCH since it has been shown local injection of corticosteroids in unifocal bone lesions achieves greater than 75% of complete healing with a low incidence of side effects [7]. We therefore compared patients with LCH with bone involvement treated with chemotherapy and corticosteroids or corticosteroids alone in terms of overall survival, remission rate, and recurrence rate.

We recognize limitations to our study. First, because the study spanned six decades, chemotherapy regimens varied substantially and details on these regimens were not available for some patients. This was particularly true for multifocal disease, where five different regimens were used. Second, because of many different treatment modalities, there was not a large number of patients in each group, precluding any multivariate analysis that would control for potentially confounding variables.

Concerning only the patients with multifocal bone involvement, our survival data are similar to those of other studies (Table 3). Overall survival ranged from 90% [1, 13] to 100%, which confirms the good outcome for patients without systemic involvement [7, 22, 28].

Our remission rate for multifocal bone involvement (86%) was also similar to that of other studies (89%–96.6%), demonstrating the success of the available treatments used (Table 3). Although the outcome of LCH ranges from spontaneous remission to death, the prognosis is generally good. We found an overall survival rate of 89.9%. All 20 deaths occurred in patients with Letterer-Siwe disease. This finding confirms the number of organs involved is a key factor affecting the prognosis of LCH [11]. Among the patients with single-system bone LCH,

Table 3. Comparison of our data with those in the literature concerning Langerhans cell histiocytosis with multifocal bone involvement

Study	Year	Overall survival	Remission rate	Recurrence rate
Gadner et al. [13]	1994	90%	89%	12%
Kilpatrick et al. [17]	1995	94.7%	96.3%	27.3%
The French Langerhans' Cell Study Group [1]	1996	90%	96.3%	27.3%
Current study	2011	100%	86%	13.5%

unifocal bone LCH had an excellent prognosis, with a 100% (70 of 70) resolution rate in this study. Multifocal bone disease also carried a good prognosis, with 93% (40 of 43) of resolution in this series.

The recurrence rate for multifocal bone involvement in the literature ranges from 12% [13] to 27.3% [1]. In our study, even with the different kinds of treatment used, our results were similar (13.5%) (Table 3).

We used five treatment modalities for multifocal single-system bone involvement. Nevertheless, when we compared the two most frequently applied modalities, we observed, among the 30 patients treated with chemotherapy and oral corticosteroids, only one patient did not reach remission (3.3%). On the other hand, among the six patients receiving only corticosteroids, two did not reach remission (33.3%).

In conclusion, we found the typical clinicopathologic features of LCH: the disease was more frequent in boys, at a mean age of 5 years, and in most cases, the patients presented with an isolated lytic bone lesion. In multifocal bone LCH, a remission rate of more than 65% was obtained with both corticosteroids and corticosteroids associated with chemotherapy. However, our observations and those of other studies [1, 5–7, 9, 17, 25, 26] and the Langerhans Cell Histiocytosis Society Guidelines [24] suggest, although intralesional corticosteroid injection may achieve a 100% remission rate in unifocal bone LCH (as in our study), corticosteroid treatment alone may be not as effective in multifocal single-system bone involvement as chemotherapy with corticosteroids (remission rates of 66.7% versus 96.7%, respectively).

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