Indomethacin is an effective treatment in adults and children with bone Langerhans cell histiocytosis (LCH)

Langerhans cell histiocytosis (LCH) is a rare disease due to a clonal proliferation of myeloid precursors that differentiate in $CD1a^+/CD207^+$ in lesions. More frequent in children than in adults, it can occur at any age with various degrees of systemic involvement. Among the large landscape of clinical manifestations, bone involvement represents the commonest single organ involved in LCH. Many different therapeutic strategies have been used for bone LCH.[1,2] Among less toxic and more effective regimens, indomethacin was found to be an effective analgesic and, subsequently, its effectiveness in reversing the disease process in children with symptomatic bone LCH, at diagnosis, or after reactivation, was demonstrated.[3–5] The rationale of its use is based on the mechanism of action of indomethacin, a non-steroidal anti-inflammatory drug that inhibits the cyclooxygenase 1 and 2 enzymes, involved in the arachidonic acid–prostaglandin pathway. Prostaglandins (PGs), the hormone-like molecules derived from arachidonic acid, have been implicated in the pathogenesis of LCH.[6,7] In our centre, we first successfully employed indomethacin as salvage therapy in LCH patients with multiple bone reactivations, including those with other organ or tissue involvement.[8] We then used indomethacin as first-line treatment in patients with unifocal or multifocal bone LCH, trying to avoid the potential toxicity of traditional therapy.[9]

We hereby report the results of treatment with indomethacin in 63 unselected patients with a confirmed diagnosis of LCH ($CD1a^+$, $S100^+$, $CD207^+$/$Langerin^+$) and bone involvement, managed at the Haematology Section, Sapienza University of Rome over a 20-year period. Fifty-four of the 63 patients (86%) were adults (age at diagnosis ≥18 years) and nine (14%) were children. Clinical and instrumental evaluations were performed before starting treatment and, thereafter, at planned intervals, during and after treatment discontinuation, or when symptoms appeared. Patients with a single-site lesion, and those with multiple lesions were grouped as unifocal and multifocal bone LCH, respectively, independently of other organ or tissue involvement.

Indomethacin was given, at a dose ranging from 1 to 2 mg/kg/day, in 46 patients as first-line treatment, and in 17 patients after multiple disease reactivations. It was given as a single agent in 58 patients (92%), in five of them (8·5%) as consolidation after surgical curettage, or local infiltration, and combined with vinblastine and prednisone in five adults with recurrent multisystem disease. The duration of indomethacin therapy was not prospectively defined, but it was longer in patients who received a low dose of indomethacin, and shorter in those treated after local therapy, or in combination with other drugs. Treatment responses and disease progression were evaluated according to the Histiocyte Society (HS) criteria.[10] The minimum follow-up (FU) was six months from beginning treatment with indomethacin. Reactivation-free survival (RFS) was calculated from the time of disease response to the time of disease reactivation, or to the last follow-up. This study was conducted in accordance with the Helsinki Declaration.

Features, response to treatment and outcome of patients are summarized in Table I, detailed in Fig 1A,B, and in the supplemental files (Table SI, Figures S1 and S2). The median duration of treatment was 11 months (range, 3–81). Overall response to indomethacin was achieved in 62/63 (98%) patients, in 32 of them (52%) it was complete (CR). All but one patient, 52/53 (98%) treated only with indomethacin, and all 10 patients who received indomethacin combined with other therapy, showed a response that was complete in 26 (50%) and six (60%) respectively. The median time to response was nine months (range, 3–25), with no differences between adults and children. All nine children and 53/54 adults (98%) achieved a response, that was complete in seven (78%) and in 25 (47%) of them respectively. Considering the disease phase, all 46 untreated patients achieved a response that was complete in 26 (56·5%), of whom 19/32 (59%) and 7/14 (50%) were with unifocal and multifocal disease respectively. All but one of the 17 patients who received indomethacin after reactivation obtained a response, that was complete in 1/6 (16·5%) and 5/11 (45·5%) patients with unifocal and multifocal disease respectively. Regarding the disease extension, all 38 patients with unifocal bone disease, and 24/25 (96%) patients with multifocal bone disease, achieved a response, that was complete in 20 (53%) and in 12 (50%) patients respectively. Reactivations of the disease, that were recorded in 10/62 (16%) responders, were late (median time, 42·5 months; range, 17·5–110) and occurred after treatment discontinuation. Failures (progression disease or reactivation) were observed in 11 (17%) pretreated patients, most of them adults with multisystem, or multifocal bone disease. Indomethacin treatment was tolerated well. The side effects, observed in 17 (27%) patients, most of them adults, were limited, and this led to reducing the dose in all 17 patients, and discontinuing indomethacin in one adult (Table SII).

The overall RFS at 36 and 60 months was 85·4% and 71·4%, respectively, with no differences between adults and

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Table I. Patient features, response and reactivation-free survival (RFS).

	All patients (n = 63)	Adults (n = 54)	Children (n = 9)
Gender (%)			
M	28 (44·4)	21 (38·9)	7 (77·7)
F	35 (55·6)	33 (61·1)	2 (22·3)
Age at diagnosis, median [range]	34 [1–66]	37 [20–66]	10 [1–18]
Age at start of indomethacin, median [range]	36 [2–66]	39 [20–66]	15 [2–18]
Bone lesion			
Unifocal bone LCH	38 (60)	30 (56)	8 (89)
Isolated	17 (45)	11 (37)	6 (75)
Combined	21 (55)	19 (63)	2 (25)
Multifocal bone LCH	25 (40)	24 (44)	1 (11)
Isolated	14 (56)	13 (54)	1 (100)
Combined	11 (44)	11(46)	/
Symptoms at start of indomethacin			
Yes	44 (70%)	38 (70%)	6 (67%)
No	19 (30%)	16 (30%)	3 (33%)
Status at start of indomethacin			
Untreated (first-line) (%)	46 (73)	39 (72)	7 (78)
Pretreated (further lines) (%)	17 (27)	15(28)*	2 (22)†
$BRAF^{V600E}$ mutation	26	21	5
Positive (%)	10 (34·5)	9 (37·5)	1 (20)
Negative (%)	16 (65·5)	15 (62·5)	4 (80)
Response (%)			
CR	32 (50·8)	25 (46·3)	7 (77·8)
IR	30 (47·6)	28 (51·8)	2 (22·2)
PD	1 (1·6)	1 (1·9)	–
Time to response, median (months) [range]	9 [1–25]	9 [1–23]	8 [4–25]
Reactivation (%)	10 (16)	9 (16)	1 (11·1)
Time to reactivation (months) median [range]	42·5 [17·5–110]	36 [17·5–65.7]	110

Reactivation-free survival	36 months	60 months	P value
All patients (n = 62)	85·4% (CI 95% 84·3–86·5)	71·4% (CI 95% 69·6–73·2)	
Adults (n = 54)	81·9% (CI 95% 80·6–83·2)	72% (CI 95% 70·3–73·7)	=0·34
Children (n = 9)	100%	100%	
Untreated (n = 46)	89·9% (CI 95% 88·5–91·3)	81·7% (CI 95% 79·7–83·7)	=0·01
Pretreated (n = 17)	63% (CI 95% 60·4–65·6)	52·5% (CI 95% 46·6–55·4)	
Indomethacin alone (n = 53)	88·5% (CI 95% 87·4–89·6)	80·5% (CI 95% 78·7–82·3)	=0·005
Indomethacin in combination (n = 10)	72·9% (CI 95% 69·7–76·1)	36·5% (CI 95% 32·6–40·4)	
Unifocal bone (n = 38)	100%	90·9% (CI 95% 89·2–92·6)	=0·003
Multifocal bone (n = 25)	68·7% (CI 95% 66·6–70·8)	48·1% (CI 95% 45·2–50·9)	

RFS was calculated according to the Kaplan–Meier product-limit method. CI, confidence interval; CR, complete response; IR, intermediate response; LCH, Langerhans cell histiocytosis; PD, progressive disease.

*Previous treatments in 15 adults: Vinblastine (VBL) + Prednisone (PDN) in 10 patients; VBL + PDN and interferon in two patients; VBL + PDN, local steroid infiltration, and surgical curettage in two patients.

†Previous treatments in two children: VBL + PDN in one child; VBL + PDN, local steroid infiltration, and surgical curettage in one child.

children. The five-year RFS was significantly higher: (i) in patients treated with indomethacin as first line (81·7% vs. 52·5%; P = 0·01); (ii) in those who received indomethacin as single agent (80·5% vs. 36·5%, P = 0·005); and (iii) in those with unifocal bone disease (90·9% vs. 48·1%, P = 0·003).

A $BRAF^{V600E}$ mutation was found in 10/29 (35%) evaluable cases. No differences in treatment results and outcome were found in $BRAF^{V600E}$-mutated patients compared to those with wild type (Figures S3 and S4). All patients are alive after a median time from the beginning of indomethacin of 44·9 months (range, 6–243).

Our results confirmed the efficacy of indomethacin in treating bone LCH, not only in children, but also in adults, with unifocal, or multifocal disease, especially as first-line medical treatment, with minimal side effects. Indeed, all but two failures occurred in pretreated patients with widespread disease. Most patients showed a sustained and favourable clinical outcome, probably due to a tailored treatment based

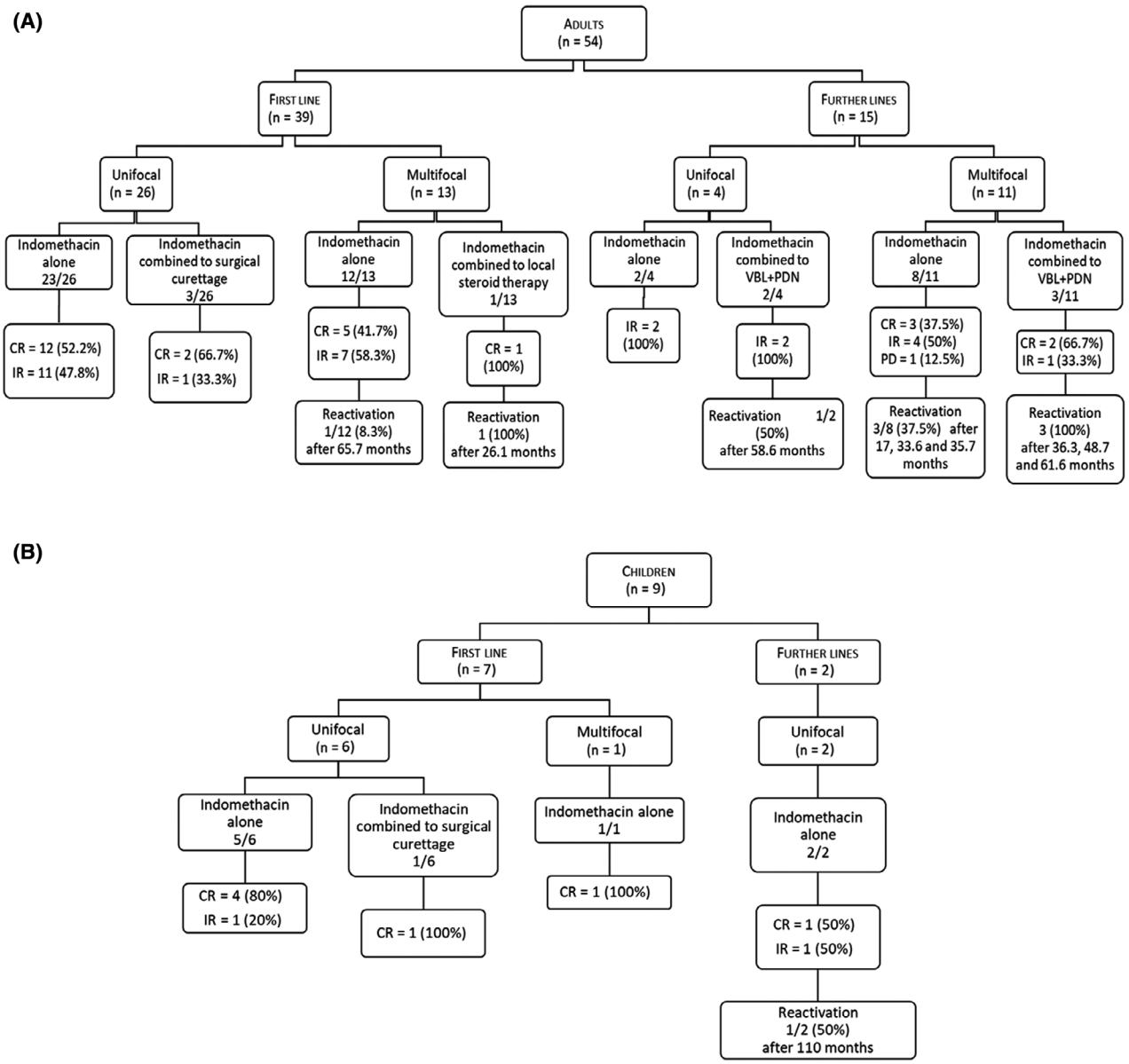

Fig 1. Response to indomethacin (alone, or in combination), and outcome, according to the status and extension of the disease in adults (A) and in children (B). Adults: patients with age ≥18 years at diagnosis. Children: patients with age <18 years at diagnosis. Complete Response (CR): complete resolution, or regression ≥50% of all measurable lesions; Intermediate Response (IR): stable disease, or regression <50% of lesions; Progressive Disease (PD): occurrence of new disease-related lesions. VBL: vinblastine 6 mg/m^2 weekly for six courses. PDN: prednisone 40 mg/m^2 weekly for six courses.

on closed clinical and instrumental evaluations. In addition, the use of indomethacin, a non-chemotherapeutic drug, had a favourable impact on the patients and/or their parents, with positive influence on the compliance to treatment. Based on these considerations, indomethacin treatment is currently included in the GIMEMA 2001 guidelines, for adults with unifocal or multifocal bone LCH.

Conflicts of interest

The authors declare no competing financial interests.

Author contributions

DDB, SM and LR analyzed and interpreted data and wrote part of the manuscript; MS enrolled and monitored patients and recorded data; GP and LC enrolled patients; MR monitored patients by performing instrumental evaluations; FG contributed to the study design, enrolled and monitored patients, and critically reviewed the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Sites of bone involvement (unifocal or multifocal) in all patients, and according to age (adults and children).

Table SII. Incidence of side effects in adults and children, during treatment with indomethacin.

Figure S1. Treatment response to indomethacin and outcome, according to age (adults and children).

Figure S2. Treatment response to indomethacin and outcome, according to extent of disease (unifocal and multifocal disease).

Figure S3. Treatment response to indomethacin and outcome in 10 $BRAF^{V600E}$-mutated patients.

Figure S4. Treatment response to indomethacin and outcome in 19 BRAF wild-type patients.

References

1. Morimoto A, Shioda Y, Imamura T, Kudo K, Kitoh T, Kawaguchi H, et al. Japan LCH Study Group. Intensification of induction therapy and prolongation of maintenance therapy did not improve the outcome of pediatric Langerhans cell histiocytosis with single-system multifocal bone lesions: results of the Japan Langerhans Cell Histiocytosis Study Group-02 Protocol Study. *Int J Hematol*. 2018;**108**(2):192–8.
2. Cantu MA, Lupo PJ, Bilgi M, Hicks MJ, Allen CE, McClain KL. Optimal therapy for adults with Langerhans cell histiocytosis bone lesions. *PLoS One*. 2012;**7**(8):e43257.
3. Munn SE, Olliver L, Broadbent V, Pritchard J. Use of indomethacin in Langerhans cell histiocytosis. *Med Pediatr Oncol*. 1999;**32**(4):247–9.
4. Han I, Suh ES, Lee SH, Cho HS, Oh JH, Kim HS. Management of eosinophilic granuloma occurring in the appendicular skeleton in children. *Clin Orthop Surg*. 2009;**1**(2):63–7.
5. Braier J, Rosso D, Pollono D, Rey G, Lagomarsino E, Latella A, et al. Symptomatic bone Langerhans cell histiocytosis treated at diagnosis or after reactivation with indomethacin alone. *J Pediatr Hematol Oncol*. 2014;**36**(5):280–4.
6. Gonzales-Crussi F, Hsueh W, Wiederhold MD. Prostaglandins in histiocytosis-X: PG synthesis by histiocytosis-X cells. *Am J Clin Pathol*. 1981;**75**(2):243–53.
7. Arenzana-Seisdedos F, Barbey S, Virelizier JL, Kornprobst M, Nezelof C, Histiocytosis X. Purified (T6+) cells from bone granuloma produce interleukin 1 and prostaglandin E2 in culture. *J Clin Invest*. 1986;**77**(1):326–9.
8. Rizzo L, Santopietro M, Palumbo G, Cardarelli L, Moleti ML, Malaspina F, et al. Efficacy of Indomethacin as salvage therapy in children and adults with Langerhans Cell Histiocytosis with bone involvement. *Pediatr Blood Cancer*. 2019;**66**(Suppl 1):38.
9. Rizzo L, Santopietro M, Palumbo G, Cardarelli L, Moleti ML, Malaspina F, et al. Indomethacin as first-line treatment of Langerhans Cell Histiocytosis (LCH). A 20-year experience of a single centre. *Pediatr Blood Cancer*. 2019;**66**(Suppl 1):38.
10. Haupt R, Minkov M, Astigarraga I, Shafer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years Histiocyte Society. *Pediatr Blood Cancer*. 2013;**60**(2):175–84.