

Research paper

Comparison between low-dose chemotherapy and surgery for the treatment of extremity-associated solitary bone lesions in children with Langerhans cell histiocytosis in South China: A case-control study

Hongyi Li¹, Xianbiao Xie¹, Junqiang Yin, Jian Tu, Xiaoshuai Wang, Weihai Liu, Jiajun Zhang, Hongbo Li, Changye Zou, Yongqian Wang, Jingnan Shen, Gang Huang*

Musculoskeletal Oncology Center, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

ARTICLE INFO

Keywords:

Langerhans cell histiocytosis
Solitary bone lesion
Extremity
Children
Chemotherapy

ABSTRACT

Background: The treatment algorithm for solitary bone lesions of Langerhans cell histiocytosis (SBL-LCH) in children extremities still remains controversial. We conducted a retrospective case-control study to compare the feasibility of low-dose chemotherapy (LDC) and surgery for SBL-LCH in children extremities.

Patients and methods: This study compares 43 pediatric patients starting LDC with a surgery control group ($n = 44$), matched for gender, age, follow-up time, and lesion sites and sizes, treated between 2001 and 2015 at our institution. Hospital stay (HS), time to symptom relief (TTSR), recovery time (RT), complications, relapse-free survival (RFS), health-related quality of life (HRQOL) and cost-effectiveness were analyzed for each strategy.

Results: HS, TTSR and RT in the LDC group were shorter than those in the surgery group ($p < 0.01$). Chemotherapy-related complications included nausea (16.30%), aminotransferase elevation (9.30%), slight hair loss (11.63%), decline in immune function (23.26%), growth retardation (16.30%), and moon face (9.30%). Chemotherapy-related side effects were mild and well tolerated. Pathologic fractures (6.81%), loosening of instrumentation (6.00%), surgical site infection (4.00%) and rejection of bone grafting (9.09%) developed in surgery patients. LDC treatment resulted in a longer RFS (87 months) than surgery alone (59 months) ($p = 0.011$). Furthermore, compared with surgery patients, patients in the LDC group had a better HRQOL at 3 months' follow-up for the physical, role, emotional and social function domains assessed ($p < 0.001$, $p = 0.001$, $p < 0.001$ and $p = 0.003$, respectively) according to the European Organisation for Research and Treatment of Cancer QLQ-C30® survey. However, HRQOL scores at 2 years' follow-up were similar between the two groups. The incremental cost-effectiveness ratio (ICER) was ¥-137,030/quality-adjusted life year (QALY) for LDC versus surgery.

Conclusions: Compared with surgery, LDC promotes more rapid recovery, is less invasive, is characterized by increased safety and a superior HRQOL, and is a more cost-effective treatment strategy for pediatric patients with SBL-LCH in the extremities.

1. Introduction

Langerhans cell histiocytosis (LCH) is a rare disease involving the clonal proliferation of pathological CD1a+ and CD207+ dendritic cells [1]. Children and adolescents are susceptible to LCH, with an estimated annual incidence of 4–8 cases per million [2]. LCH describes a broad spectrum of clinical presentations ranging from an isolated lytic bone lesion with a self-limiting tendency to disseminated multisystem life-threatening harm [3]. Unifocal bone lesions are the most common

presentation of LCH [4], and extremities are among the common sites in skeletal LCH [5]. Based on current studies, chemotherapy has become the mainstream treatment modality for multifocal bone-limited LCH or multisystem LCH (MS-LCH) [6]. However, MS-LCH has distinct clinical manifestations and prognoses, and the appropriate treatment for solitary bone lesions of LCH (SBL-LCH) remains debatable. Current treatment options include observation, immobilization, biopsy, surgery, intralesional methylprednisolone injection, chemotherapy and radiotherapy [7].

* Corresponding author.

E-mail address: drhuanggang@126.com (G. Huang).

¹ These authors have contributed equally to this work.

One area of controversy is whether systemic chemotherapy is required for the first presentation of SBL-LCH, even in bones associated with central nervous system (CNS) risk (bone lesions in the mastoid, sphenoid, orbit, clivus, or temporal bone) [8]. Based on recent findings, particularly the discovery of the BRAF^{V600E} mutation in LCH lesions, somatic mutations in bone marrow myeloid progenitors drive the neoplastic process [9]. Although SBL-LCH encompasses only localized manifestations, these lesions should be considered as representing a potential systemic disease. Based on clinical findings and suspected pathogenesis, systemic chemotherapy, rather than local therapies, may be the appropriate strategy for the treatment of SBL-LCH in children. To attain optimal outcomes, the management of children diagnosed with SBL-LCH must consider the patient's age, degree of skeletal maturity, symptoms, stability, neurological function, sites and sizes of lesions. However, some cases of SBL-LCH in children, particularly in extremities that are amenable to curettage, may be primarily treated with surgery at the surgeon's discretion in China [10]. As the largest musculoskeletal oncology center in South China, our institution has substantial experience in treating skeletal LCH patients. Accordingly, we conducted a single-center retrospective case-control study aiming to comprehensively evaluate the feasibility of low-dose chemotherapy (LDC) and surgery in children diagnosed with SBL-LCH in the extremities.

2. Patients and methods

2.1. Study population

Data for our study were obtained from the database of the First Affiliated Hospital of Sun Yat-sen University. One hundred and ninety-eight consecutive pediatric patients who visited our institution for SBL-LCH in the extremities from January 2001 to June 2015 were administered chemotherapy or surgery. The inclusion criteria were as follows: a. patients (≤ 16 years old) who were diagnosed with SBL-LCH in the extremities; b. patients with positive histopathology examination for LCH; and c. patients who received surgery or low-dose chemotherapy alone. The exclusion criteria were: a. patients did not meet the inclusion criteria; b. patients without histopathology examination; c. multifocal bone lesions; d. MS-LCH; e. patients who did not undergo a screening examination for lesions at other sites or in other systems upon diagnosis; f. patients associated with other severe illnesses that might affect treatment or clinical outcome; g. patients who had previously been treated with intraskeletal methylprednisolone injection or radiotherapy; h. chemotherapy patients without a standard treatment course; and i. follow-up time of less than 2 years.

All patients underwent radiography, MRI, histopathology and a skeletal survey to make a definitive diagnosis of extremity-associated SBL-LCH. Age of disease onset, gender, site, clinical manifestations, biopsy and histopathology results, therapeutic strategy, duration of hospital stay (HS), time to symptom relief (TTSR), recovery time (RT), complications, relapse-free survival (RFS), health-related quality of life (HRQOL), and cost-effectiveness were recorded for all patients. Both LDC and surgeries were performed by two stable medical teams. All patients in the case cohort (LDC arm) and control cohort (surgery arm) were matched in terms of age of disease onset, gender, follow-up time, site, size and soft tissue lesion extension. Size and soft tissue lesion extension were assessed by performing radiography, CT or MRI at the time of diagnosis.

Informed consent was provided by each patient's parents. Ethics approval was obtained from the Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University.

2.2. LDC protocol

The LDC reagents in our study were prednisone, oncovin, methotrexate and 6-mercaptopurine (POMP). Based on the chemotherapy protocol [11], patients were administered 0.5–1 mg/m² vincristine (IV)

and 5–10 mg/m² methotrexate (IV) once per week for the first 3 months, every two weeks for the second 3 months and every four weeks for the last 3 months; 5 mg/m² prednisone (oral) per day for the entire 9-month period and 6-mercaptopurine (oral) at doses of 10 mg/m² per day for the first 6 months and 5 mg/m² per day for the remaining 3 months. We applied the Response Evaluation Criteria in Solid Tumors (RECIST) [12] rules to evaluate the response to chemotherapy after the first 6 weeks and then every three months. The standard duration of chemotherapy is 9 months. The average chemotherapeutic duration in our study was 11.93 months, with a median duration of 12 months (range: 9–19 months), depending on the response to initial treatment as well as lesion location and size.

2.3. Surgical procedures

Surgical procedures in the present study ranged from lesion curettage to resection with or without bone grafting. Plates and screws were placed in the bones of the extremities if they were at risk for pathologic fracture.

2.4. TTSR and RT

TTSR and RT were determined to assess the efficacy and invasiveness of chemotherapy and surgery. TTSR was defined as the time from treatment initiation to symptom relief, and RT was the time from treatment initiation to the recovery of a normal life.

2.5. Health-related quality of life

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life (QLQ-C30[®]) survey (version 3) was selected to assess HRQOL. The scale contains 5 functional subscales, 3 symptomatic subscales, 1 quality of life subscale, several individual symptomatic items and perceived financial impact of the disease. The items from both measures were scaled and scored according to the scoring manual method, and then raw scores were aggregated and transformed into a linear scale of 0–100 points. A higher score represents a higher degree of functioning (function scales) or a higher level of symptoms (symptom scales). The results were analyzed in accordance with the 2001 guidelines for reporting HRQOL [13]. To test the HRQOL baseline, each patient in our study received a QLQ-C30 questionnaire upon their initial diagnosis of extremity-associated SBL-LCH. At 3 months and 2 years after diagnosis, each eligible patient received the second and third questionnaires, respectively, to assess post-treatment HRQOL.

2.6. Cost-effectiveness analysis

Our economic analysis compared the cumulative costs of each therapeutic strategy during the 5-year follow-up period. The resources analyzed included: a. the standard cost of chemotherapy and surgery; b. in-patient complications of treatment procedures; c. outpatient visits; d. medications; e. radiography, ultrasonic, CT, MRI, histopathology and skeletal surveys; and f. routine tests and blood biochemistry. Costs are expressed in RMB (Yuan, ¥). To further analyze cost-effectiveness, QLQ-C30 scores were transformed into EQ-5D [14], and then quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were calculated based on the data [15].

2.7. Statistical analysis

Data were analyzed using SPSS version 20.0 (IBM Co., Armonk, NY, USA). χ^2 tests and *t*-tests were used to compare differences between groups and means. Cohorts were checked for statistical homogeneity at baseline. RFS was defined as the time from diagnosis to relapse or the last follow-up visit. A Kaplan–Meier survival analysis was performed to estimate RFS, and the log rank test was used to compare rates between

Table 1
Baseline demographic characteristics of the two study groups.

Characteristics	Chemotherapy (%) n = 43	Surgery (%) n = 44	TOTAL (%) n = 87	p value
Age of onset				0.506
< 6 years	20 (46.51)	18 (40.91)	38 (43.68)	
6–16 years	23 (53.49)	26 (59.09)	49 (46.32)	
Gender				0.078
Male	33 (76.74)	26 (59.09)	59 (67.82)	
Female	10 (23.26)	18 (40.91)	28 (32.18)	
Follow-up time (months, mean ± SD)	94.23 ± 44.89	78.50 ± 41.98	86.28 ± 43.91	0.109
Sites of involvement				0.645 ^a
Ilium	3 (3.49)	4 (3.03)	7 (7.89)	
Scapula	5 (5.81)	5 (3.03)	10 (11.84)	
Clavicle	2 (2.33)	3 (3.03)	5 (5.26)	
Humerus	9 (12.79)	7 (6.06)	16 (18.42)	
Ulna	3 (3.49)	0 (0.00)	3 (2.63)	
Radius	2 (2.33)	1 (0.00)	3 (2.63)	
Femur	14 (18.60)	18 (18.18)	32 (36.84)	
Tibia	4 (4.65)	5 (6.06)	9 (10.53)	
Fibula	0 (0.00)	1 (3.03)	1 (1.32)	
Calcaneus	1 (1.16)	0 (1.32)	1 (1.32)	
Lesion size				0.590
Maximum diameter of lesions (cm, mean ± SD)	3.82 ± 1.93	4.19 ± 1.81		
Soft tissue extension (n, %)	25 (48.08)	22 (44.00)		0.446
Pathological fracture	2 (4.65)	4 (9.09)	6 (6.90)	
Surgical method (n, %)				
Curettage		10 (22.73)		
Resection		2 (4.54)		
Curettage and bone grafting		24 (54.55)		
Curettage and internal fixation ^b		8 (18.18)		

^a Denotes no statistically significant presence of bone lesions in the extremities among the two groups ($p = 0.796$).

^b Internal fixation denotes implantation of plates and screws.

the two groups.

3. Results

3.1. Demographic characteristics

Patients with multifocal osseous LCH ($n = 8$), diabetes insipidus (DI) ($n = 4$), skeletal LCH at other sites ($n = 35$), or other MS-LCH ($n = 3$) were excluded from the 198 cases, 26 patients were lost to follow-up or did not complete a minimum of two years of follow-up, and 34 patients failed to match the baseline demographic characteristics. Thus, our statistical analysis comprised 87 consecutive patients, of whom 43 patients received LDC and 44 underwent surgery. There were 59 males and 28 females with a median age of 7 years (range, 1–16 years). The mean follow-up time after diagnosis in the LDC and surgery arms was 94 months (range: 24–169 months) and 79 months (range: 24–173 months), respectively. The two cohorts had similar baseline characteristics, as showed by the p values in Table 1.

3.2. A shorter HS length and rapid effects and recovery were observed in chemotherapy patients

Given to the satisfactory safety of LDC, the chemotherapy regimen was administered both in the clinic and at patients' homes. Thus, the average HS of patients in the LDC group (5.77 ± 5.92 days) was substantially lower than that in the surgery group (12.32 ± 11.76 days) ($p = 0.002$) (Fig. 1A). The TTSRs of the LDC group and surgery group were 3.07 weeks (SD: 1.61 weeks) and 4.82 weeks (SD: 3.57 weeks), respectively ($p = 0.003$) (Fig. 1 B). The average RT length was also shorter in the LDC group (3.42 months, SD: 1.38 months) than in the surgery group (4.66 months, SD: 2.51 months) ($p = 0.019$) (Fig. 1C).

3.3. LDC side effects were mild and well tolerated

The following chemotherapy-related adverse events were observed

in the LDC group: nausea (16.30%, 7/43), aminotransferase elevation (9.30%, 4/43), slight hair loss (11.63%, 5/43), decline in immune function (23.26%, 10/43), growth retardation (16.30%, 7/43) and moon face (9.30%, 4/43). Most of these adverse events were mild, well tolerated and transient. Children who experienced growth retardation in our study received blood tests to evaluate their growth hormone levels and pituitary MRI to exclude anterior pituitary dysfunction. Pathologic fractures occurred in 2.32% (1/43) of the chemotherapy patients and 6.81% (3/44) of surgery patients. Other complications, such as loosening of instrumentation (4.55%, 2/44), surgical site infection (2.27%, 1/44) and rejection of bone grafting (9.09%, 4/44), occurred in surgery patients. None of the patients died from treatment-related complications. Notably, chemotherapy-related side effects were mild and well tolerated. Furthermore, no impact or sequelae were observed during long-term follow-up (Table 2).

3.4. Longer RFS was detected in LDC patients

According to our statistical analysis, the rate of relapse in patients who received LDC and surgery was 9.30% (4/43) and 29.55% (13/44), respectively. Statistically significant differences in RFS were observed between the surgery group and the LDC group ($p = 0.011$). No patients died as a result of disease progression (Fig. 2).

3.5. LDC patients had superior HRQOL during short-term follow-up

Surveys were sent to all 87 patients. The guardians of 3 pediatric patients refused to participate in HRQOL assessments upon the initiation of treatment, while 5 patients discontinued after treatment. A total of 79 patients (90.80%) responded to the survey, resulting in the collection of 39 surveys from the chemotherapy group and 40 surveys from the surgery group. The median follow-up time for HRQOL was 88 months (range: 24–173 months). Demographics, treatment strategies and clinical outcomes between the respondents and the non-respondents were not significantly different. Based on the results of the

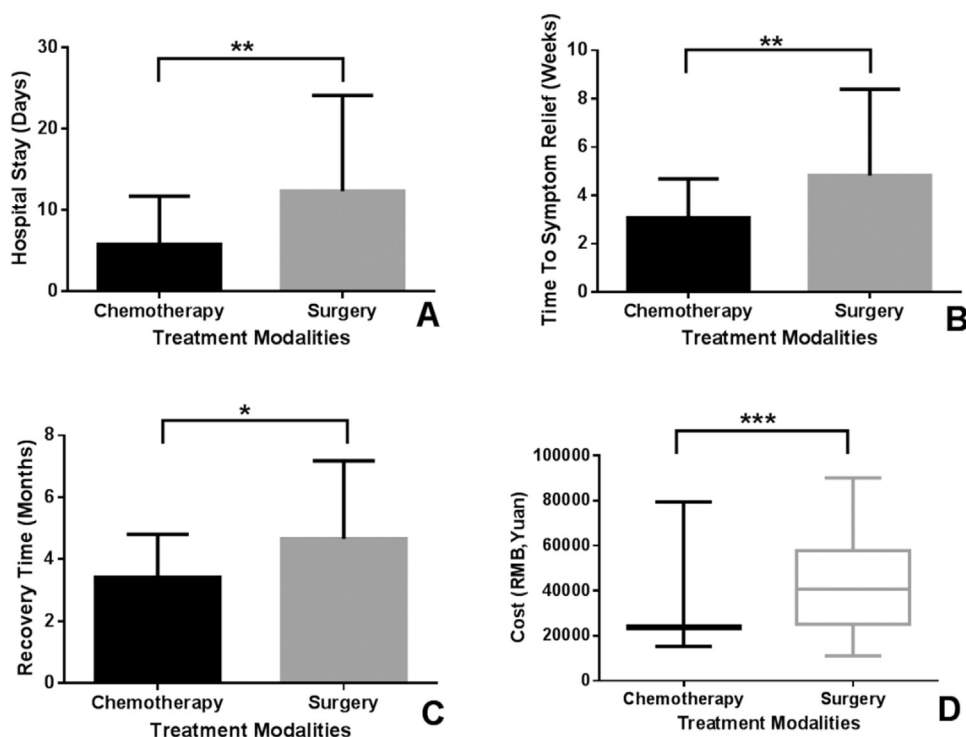


Fig. 1. The mean values for HS, TTSR, RT and five-year costs between the chemotherapy and surgery groups. 1A: HS: hospital stay ($p = 0.002$). 1B: TTSR: the time from treatment initiation to symptom relief, ($p = 0.003$). 1C: RT: the time from treatment initiation to recovery of a normal daily life ($p = 0.019$). 1D: Box plot showing five-year costs ($p < 0.0001$). ***: $p < 0.001$; **: $p < 0.01$, *: $p < 0.05$.

Table 2
Complications of the two treatment modalities.

Complications	Chemotherapy (%) N = 43	Surgery (%) N = 44
Pathologic fracture	1 (2.32)	3 (6.81)
Loosening of instrumentation	0	2 (4.55)
Surgical site infection	0	1 (2.27)
Bone graft rejection	0	4 (9.09)
Chemotherapy-related adverse events		
Aminotransferase elevation	4 (9.30)	0
Nausea	7 (16.30)	0
Slight hair loss	5 (11.63)	0
Decline in immunity function	10 (23.26)	0
Growth retardation	7 (16.30)	0
Moon face	4 (9.30)	0

3.6. Increased cost-effectiveness for chemotherapy patients

Total health care costs at 5 years were lower for the chemotherapy group (¥27,787, SD: ¥15,428) than the surgery group (¥42,689, SD: ¥19,004) (Fig. 1D) ($p < 0.001$). According to the EQ-5D transformed data from the QLQ-C30 surveys (Table 3), QALY at 5 years was also higher for the chemotherapy group (4.94 QALYs) than for the surgery group (4.83 QALYs). Moreover, the ICER was ¥-137,030/QALY for the LDC group versus the surgery group, suggesting LDC was much more cost-effective than surgery (Table 4).

4. Discussion

The cause of LCH remains elusive, but BRAF^{V600E} mutations have been found in approximately 60% of LCH lesions [16]. Additionally, BRAF^{V600E} mutations have been associated with an increased risk of recurrence and a greater chance of organ and skin involvement [9,17]. BRAF is a serine/threonine-protein kinase that transduces signals through the mitogen-activated protein kinase (MAPK) signaling pathway [18]. Daniel et al. [19] speculated that MAPK-activating mutations in precursor myeloid cells may be integral to the pathophysiology of LCH, and experimental findings support this concept of LCH pathogenesis, suggesting the classification of LCH as a myeloid neoplasia [20]. Furthermore, the coincidence of LCH with myelodysplastic syndrome and other hematological malignancies [21], as well as evidence indicating LCH cells are clonal, supports a neoplastic origin for LCH [22].

Some reports suggest local therapy may not be a curative strategy if LCH is truly driven by hematopoietic myeloid precursors [19]. Patients with SBL-LCH achieve satisfactory local control with local therapy, but new lesions will likely develop at other skeletal sites or even in other systems. Accordingly, 14 out of 17 relapse patients (82.35%) in our study had new lesions at other sites although their primary lesions had been eliminated after treatment. These findings further support the neoplastic characteristics of LCH. As such, systemic chemotherapy rather than local surgery might be curative for SBL-LCH. Consistent with this hypothesis, the rate of occurrence of new lesions in patients who received systemic chemotherapy (2/43, 4.65%) in our study was

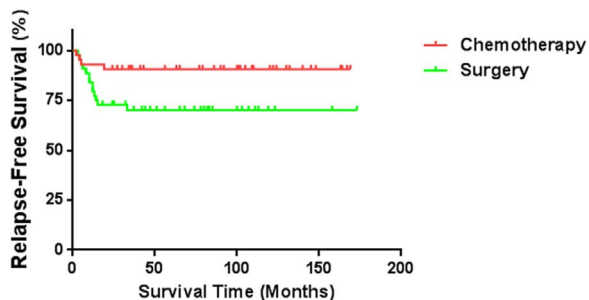


Fig. 2. Kaplan-Meier curves for RFS in patients treated with chemotherapy and surgery ($p = 0.011$).

QLQ-C30 surveys, HRQOLs at the 3-month follow-up time point for the LDC group were better than for patients who received surgery, particularly for the physical, role, emotional and social function domains ($p < 0.01$). However, HRQOLs at 2 years' follow-up were similar between the two groups (Table 3)

Table 3
Comparative QLQ-C30 scores for the two treatment modalities.

Treatment Scores	Chemotherapy (m ± s)			Surgery (m ± s)			p value for C versus S		
	Time 0	Time 1	Time 2	Time 0	Time 1	Time 2	Time 0	Time 1	Time 2
Global Health Status	60.68 ± 18.92	93.60 ± 7.27*	96.59 ± 5.64	64.37 ± 16.55	85.85 ± 12.83*	94.79 ± 6.73†	0.437	0.003	0.244
Physical Functioning	77.78 ± 14.13	98.12 ± 3.73*	99.14 ± 2.73	79.50 ± 12.58	92.00 ± 9.56*	98.17 ± 3.99†	0.920	0.000	0.220
Role Functioning	69.67 ± 15.23	91.45 ± 12.60*	97.86 ± 5.66†	62.51 ± 21.61	76.68 ± 22.58*	97.50 ± 6.04†	0.122	0.001	0.781
Emotional Functioning	89.32 ± 14.56	96.37 ± 8.07*	98.93 ± 3.41	88.54 ± 17.06	86.04 ± 14.67	96.88 ± 5.23†	0.869	0.000	0.031
Cognitive Functioning	95.72 ± 11.92	97.01 ± 7.53	99.14 ± 3.73	96.25 ± 12.23	95.42 ± 10.66	95.00 ± 9.40	0.726	0.704	0.013
Social Functioning	68.40 ± 10.67	77.79 ± 13.41*	95.29 ± 8.51†	64.61 ± 13.18	67.10 ± 17.49	93.74 ± 12.91†	0.134	0.003	0.804
Fatigue	7.12 ± 19.83	4.27 ± 7.48	3.98 ± 7.84	5.55 ± 10.66	8.05 ± 11.79	3.33 ± 10.12†	0.551	0.188	0.202
Nausea and Vomiting	2.57 ± 7.20	5.13 ± 10.23	3.42 ± 16.30	0.84 ± 3.69	9.17 ± 12.48*	0.00 ± 0.00†	0.217	0.106	0.076
Pain	37.58 ± 16.55	1.71 ± 5.13†	1.28 ± 4.51	33.31 ± 16.01	6.68 ± 9.85*	0.00 ± 0.00†	0.111	0.008	0.076
Dyspnea	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.83 ± 5.27	0.00 ± 0.00	1.000	0.323	1.000
Insomnia	7.69 ± 20.89	5.13 ± 14.38	0.85 ± 5.33	4.17 ± 13.48	5.83 ± 12.81	4.16 ± 11.15	0.460	0.603	0.098
Appetite Loss	7.69 ± 23.53	5.12 ± 12.17	17.08 ± 20.04†	0.83 ± 5.27	12.49 ± 17.99*	9.99 ± 17.20	0.146	0.043	0.086
Constipation	4.27 ± 15.64	5.13 ± 14.38	2.56 ± 8.99	2.50 ± 11.67	11.66 ± 22.07*	2.50 ± 8.88	0.617	0.108	0.974
Diarrhea	1.71 ± 7.44	3.42 ± 10.23	1.71 ± 7.44	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.149	0.039	0.149
Financial Difficulties	22.21 ± 22.07	19.65 ± 22.58	6.83 ± 15.63†	31.65 ± 22.58	38.32 ± 28.80	7.49 ± 14.08†	0.061	0.003	0.663

Time 0: baseline; Time 1: 3 months after diagnosis; Time 2: 2 years after diagnosis. Due to the heterogeneity of variance among the three groups, the Kruskal-Wallis Test was employed; the significance level for the Bonferroni paired comparison was adjusted to 0.0167.

Bold type p value denotes a significantly different attribute between the two treatment strategies at the same time point (p < 0.05). Abbreviations: m ± s, mean ± standard deviation; C, chemotherapy; S, surgery.

* Denotes a significantly different attribute between the paired comparisons at Time 0 and Time 1.

† Denotes a significantly different attribute between the paired comparisons at Time 1 and Time 2 (p < 0.0167).

significantly lower (p = 0.003) than the rate in those patients who received local surgery 12/44, 27.27%). Moreover, based on the RECIST results, the outcomes of chemotherapy in our study included complete response (CR, n = 34), partial response (PR, n = 3), stable disease (SD, n = 2) and progressive disease (PD, n = 4). The overall response rate (CR + PR + SD) was 90.70% (39/43), indicating chemotherapy also results in a high rate of local control.

Optimal management of SBL-LCH patients remains elusive. Although researches indicate that bone-limited LCH has self-resolving tendency, the time to symptom relief in observational patients might last several months, which would impede patients' daily life. Moreover, patients with SBL-LCH have a 10% chance of progress and reactivation [1]. In our study, patients with intact bone cortex could receive an observational period upon diagnosis, after 4–6 weeks of wait and watch, the patients were started on LDC or surgery if unsatisfactory remission or even progress developed. Systemic therapy may be indicated in isolated bone lesions involving functionally critical anatomical sites, such as bones associated with CNS risk and the vertebral column, which also involve adjacent soft tissues [4]. Guidelines from the Histiocyte Society suggest that simple curettage during diagnostic biopsy will result in SBL-LCH healing [23]. However, even simple curettage may enhance invasiveness in pediatric patients, and damage to the epiphysis may result in sequelae affecting skeletal development.

As shown in our study, systemic chemotherapy is applicable not only to CNS-risk lesions [24] and the axial skeleton [1] but also to extremity-associated SBL-LCH. The most common first-line systemic chemotherapy protocol for MS-LCH is DAL-HX89/90 [23]. Unlike DAL-

HX89/90, LDC reagents for low-risk SBL-LCH encompass POMP, and the doses in our protocol were substantially lower than those for DAL-HX89/90 [11,25]. Vincristine and steroid were established as a treatment backbone in randomized international clinical trials undertaken by the Histiocyte Society [26], and 6-mercaptopurine was added to the continuation phase of the protocol. The LCH-III study revealed no added benefit of methotrexate in the MS-LCH chemotherapy protocol, with or without risk organ [27]. However, low-dose methotrexate is effective and safe for low-risk disease (such as single-system or skin-limited LCH) [28], demonstrating minimal toxicity. Low-dose reagents likely halt clonal proliferation by killing the offending cells or modifying the cytokine expression that drives Langerhans cell proliferation in LCH confined to the bone. By stopping the proliferation of these cells, bone lesions usually heal completely, and other skeletal lesions or organ involvement generally do not develop [29]. Thus, combination low-dose POMP may be a rational protocol for SBL-LCH. The inclusion criteria for LDC include patients diagnosed with SBL-LCH and multifocal bone-limited LCH, while the exclusion criterion is MS-LCH with or without risk organ.

In our study, positive clinical outcomes were seen in patients diagnosed with extremity-associated SBL-LCH treated with LDC alone. LDC resulted in a substantially shorter TTSR and a lower rate of relapse and was less invasive and more cost-effective than surgery. Safety assessments in the LDC group indicated that chemotherapy-related adverse events were mild, well tolerated and transient. Furthermore, our long-term follow-up revealed no significant differences in the growth and development of LDC patients compared with average growth rates.

Table 4
EQ-5D values and cost-effectiveness data for the two therapeutic strategies.

Therapeutic strategies		Chemotherapy	Surgery	Chemotherapy Versus Surgery
Mean value of EQ-5D QALYs (m ± s)	Time 0	0.75 ± 0.16	0.75 ± 0.15	
	Time 1	0.97 ± 0.07	0.87 ± 0.12	
	Time 2	1.02 ± 0.04	1.01 ± 0.04	
QALYs (5 years)		4.94	4.83	0.11
COST (¥, 5 years)		27,787	42,689	-14,902
IC (¥)				-14,902
ICER (¥/QALY)				-137,030

Time 0: baseline; Time 1: 3 months after diagnosis; Time 2: 2 years after diagnosis.

Abbreviations: m ± s, mean ± standard deviation; IC: incremental cost; ICER: incremental cost-effectiveness ratio.

LCH had no significant impact on patient HRQOL during long-term follow-up (2 years) in either group. However, the invasiveness of surgical intervention impacted quality of life at 3 months follow-up in the surgery arm. The physical, role, emotional and social function domains were among those most affected.

5. Conclusions

In conclusion, our comparative case-control study investigating LDC and surgery suggests that systemic LDC is a less invasive, safer, and more cost-effective therapeutic option that promotes more rapid recovery, superior HRQOL, and a complete cure for extremity-associated SBL-LCH in children. The contraindications for chemotherapy include severe liver damage and renal dysfunction, drug allergies, and intolerance to adverse events or severe comorbidities. In cases of imminent pathological fracture, neurological deficits, unacceptable deformity and functional disability, surgical intervention is recommended. To the best of our knowledge, this is the first study to compare the feasibility of LDC and surgical intervention for extremity-associated SBL-LCH in pediatric patients. Our study therefore provides a new point of reference for the management of extremity-associated SBL-LCH in pediatric patients.

Unfortunately, the rarity of LCH makes it difficult to perform large controlled clinical trials to evaluate different treatment options. The absence of an observational group and its retrospective nature may have introduced bias into this comparative study. Consequently, further studies utilizing observational groups and well-conducted prospective clinical trials are required to confirm our conclusions.

Acknowledgements

There was no grant support or institutional/corporate affiliation associated with this study.

Conflict of interest statement

The authors have disclosed no relevant financial relationship.

Supported by

The National Natural Science Foundation of China (81572638 and 81772864, to Xianbiao Xie and 81772860, to Gang Huang) ; and the Fundamental Research Funds for the Central Universities (17ykzd16 , to Xianbiao Xie).

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