Journal of Bone Oncology 12 (2018) 1–6

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

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

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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].

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https://doi.org/10.1016/j.jbo.2018.02.003
Received 18 August 2017; Accepted 12 February 2018
Available online 15 February 2018

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 ($\leq$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 intralesional 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/m^2 vincristine (IV) and 5–10 mg/m^2 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/m^2 prednisone (oral) per day for the entire 9-month period and 6-mercaptopurine (oral) at doses of 10 mg/m^2 per day for the first 6 months and 5 mg/m^2 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