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RESEARCH ARTICLE

Prospective Collaborative Study for Pulse Dexamethasone and Lenalidomide in Relapsed/Refractory Langerhans Cell Histiocytosis (LENDEX-LCH Study): INPHOG-HIST-19-03 (CTRI/2020/07/026937)

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ABSTRACT

Background: The Indian Paediatric Haematology Oncology Group (INPHOG) multicentre study aimed to prospectively analyse the efficacy and safety of lenalidomide and dexamethasone (LENDEX) in children with refractory/relapsed Langerhans cell histiocytosis (LCH).

Procedure: The study was a prospective, multicentre study conducted through the INPHOG Histiocytosis Subcommittee. The Clinical Trials Registry of India registration was obtained, and the study was open to recruitment from June 2020 to June 2023.

Results: A total of 15 children were included from seven centres in India, median age being 4 years (Range 3–13 years). Thirteen children were diagnosed to have multisystem disease at relapse with involvement of skin, bone and liver; and one child each with multifocal bone disease and single site bone lesion. One child with refractory lung disease had progression after two cycles of LENDEX and was taken off protocol. Four (26%) children achieved CR after six cycles of LENDEX; while eight (53%) children had PR at three and six cycles, with CR at the end of nine cycles of LENDEX. The combination was well tolerated, the most common adverse effects being mild anaemia and myalgia. There were no deaths within the cohort, with a median follow-up of 24 months (Range 18–48 months). The overall response rate was 73%, with 26% responses at six cycles and 53% at nine cycles of LENDEX.

Conclusion: LENDEX is well tolerated and effective in 73% children with relapsed/refractory LCH. Future studies would include nine cycles of LENDEX followed by maintenance for 12 months with 6-mercaptopurine.

1 | Background

Langerhans cell histiocytosis (LCH) is a rare disorder with an incidence of approximately 1–3 cases per million children [1, 2]. Treatment principles of LCH include steroids as the backbone of all chemotherapy protocols. Children are risk-stratified as low-risk and high-risk disease based on involvement of risk organs, namely the liver, spleen and the haematopoietic system. Most

Abbreviations: CR, complete remission; CTRI, Clinical Trials Registry of India; INPHOG, Indian Paediatric Haematology Oncology Group; LCH, Langerhans cell histiocytosis; LENDEX, lenalidomide/dexamethasone; PR, partial response.

patients receive induction chemotherapy with steroids and vinblastine for 6–12 weeks. Based on response assessment, they are further given continuation treatment for a total of 12–24 months with steroids and vinblastine with or without 6-mercaptopurine.

Relapsed or refractory LCH has a guarded prognosis, with expensive salvage treatments available, particularly for high-risk disease. Treatment options include six cycles of salvage chemotherapy with cladribine and cytarabine and haematopoietic stem cell transplantation using a reduced intensity conditioning [3, 4]. Other treatment options documented include intralesional steroids, indomethacin, a combination of vincristine, cytarabine and prednisolone, and single-agent cladribine [5–7].

The pathophysiology of LCH is unique, as there is a combination of a reactive process and cellular proliferation. This results in extensive elaboration of several cytokines by dendritic cells and T-cells, resulting in cytokine storm. Immune dysfunction ensues through the creation of a permissive immunosurveillance system and expression of high serum levels of cytokines [8].

FIRST Trial for Refractory Multiple Myeloma [9]: The FIRST trial demonstrated a 28% reduction in progression or death with the use of low dose dexamethasone and lenalidomide in patients with refractory/relapsing multiple myeloma who were ineligible for transplant. We have extrapolated our protocol from this trial. A pilot study in four children with relapse/refractory LCH was performed with the protocol and was shown to result in durable remission in all four children [10].

2 | Patients and Methods

A prospective multicentre study was undertaken across India through the Indian Paediatric Haematology Oncology Group (INPHOG) with registration number INPHOG-HIST-19-03. The proposal was peer reviewed by two national and one international expert in the field of histiocytosis. The final approved protocol was registered with the Clinical Trials Registry of India (CTRI) with registration number CTRI/2020/07/026937. The trial was open for recruitment from July 2020 to June 2023. Written informed consent was obtained from guardians of all children before recruitment. In children above 7 years of age, assent was also obtained.

2.1 | Objectives of the Study

Primary: 1. To study prospectively the efficacy of LENDEX in attaining remission in children diagnosed with refractory/relapsed LCH. 2. To evaluate the safety profile of the combination in children.

Secondary: To improve access to cost-effective and outpatient-based salvage chemotherapy.

2.2 | Protocol

1. Six cycles of oral pulse dexamethasone and lenalidomide, with each cycle being for 28 days.
2. Lenalidomide to be given continuously for 21 days at a dose of 2.5 mg daily in children weighing less than 15 kg and 5 mg daily in children weighing more than 15 kg.
3. Dexamethasone to be given at 0.8 mg/kg on Days 1, 8, 15 and 21 of each cycle.
4. All children to be monitored for neuropathy, convulsions, tremors, constipation, headache, myalgia and cytopenia.

2.3 | Outcome Measures to be Evaluated

1. Response to six cycles of chemotherapy.
2. Adverse effects of the drugs were noted during and post-treatment.

Imaging modality for evaluation—whole body PET CT scan to be preferred. In case of non-availability, an MRI of the whole body.

2.4 | Eligibility

2.4.1 | Inclusion Criteria

1. Patients from 1 year of age to 18 years of age with biopsy-proven LCH.
2. Relapsed or refractory disease after having received 6–12 weeks of induction chemotherapy with vinblastine plus prednisolone as per LCH II or III protocol.
3. Relapsed or refractory disease after receiving salvage chemotherapy with cladribine ± cytarabine can also be included.

2.4.2 | Exclusion Criteria

1. Pregnancy or lactation.
2. Patients with renal impairment are defined as having a serum creatinine level> 1 mg/dL.
3. Patients with liver impairment (excluding those due to disease), defined as alanine aminotransferase (ALT) and/or prothrombin time (PT) more than five times the upper limit of normal.
4. Patients with pre-existing peripheral neuropathy.

2.5 | Biopsy at the Time of Relapse

All patients were planned for a repeat biopsy, excision biopsy, or core needle biopsy prior to entering the study. For children with definitive biopsy LCH who have progressive disease during treatment, biopsy may be deferred.

2.6 | Criteria to Come Off the Protocol

The treating physician could decide to take the patient off protocol prior to completion of the six cycles of LENDEX if there is

progressive disease at any point in time or in case of intolerable adverse effects.

2.7 | Definitions

1. Response:
   a. Complete response (CR): complete resolution of all lesions on repeat imaging with no evidence of active disease and resolution of signs and symptoms.
   b. Partial response (PR): 50%–75% resolution of all lesions on repeat imaging with no evidence of active disease and resolution of signs and symptoms.
   c. Incomplete response: less than 50% resolution of lesions on repeat imaging and/or evidence of active disease and/or persistence of signs and symptoms.
2. Relapsed LCH: Disease detection > 3 months after completion of therapy.
3. Refractory LCH: Persistent disease that has failed to achieve complete remission on frontline therapy and/or post-salvage chemotherapy or progression at any point during therapy.
4. Progression of disease: increase in clinical symptoms or increase in lesions as evaluated by imaging, or appearance of new lesions which were not noted at the time of diagnosis.

3 | Results

The study was open to recruitment from July 2020 and was closed for recruitment in July 2023. A total of 15 children were included in the study from seven centres in India, with a median age of 4 years (range 3–13 years) and a male:female ratio of 0.8:1. Fourteen children had multisystem LCH at diagnosis, while one child had a single-site bone lesion. Thirteen children were treated upfront using the LCH III protocol [11], one child using the LCH IV [12] and one child using the TMH high risk protocol [13]. Eight children achieved complete remission at 6 weeks of induction, four achieved CR at 12 weeks of induction and three children had refractory disease.

Relapse was noted on an average of 9 months following the end of treatment, with 13 children diagnosed to have multisystem disease at relapse with involvement of skin, bone and liver; and one child each with multifocal bone disease and single-site bone lesion. LENDEX was administered at first relapse in twelve children, while the combination was administered in second relapse following six cycles of cytarabine/cladribine in three children in view of persistent and refractory disease.

One child with refractory disease with lung involvement was noted to have disease progression after two cycles of LENDEX and was taken off protocol. Four (26%) children had documented CR after six cycles of LENDEX; while eight (53%) children had PR at three and six cycles, with CR at the end of nine cycles of LENDEX. Three children were continued on maintenance chemotherapy with 6-mercaptopurine for a maximum of 12 months following CR after LENDEX. One child with a single-site bone lesion who had received six cycles of LENDEX had a recurrence in the same site 1 year after stopping treatment, which was treated with intralesional steroids.

The combination was well tolerated, with the most common adverse effects reported as mild anaemia with haemoglobin up to 8 g/dL in six (40%) children and myalgia in eight (53%) children. There were no deaths within the cohort, with a median follow-up of those in remission of 24 months (range 18 months – 48 months). The overall response rate was 73%, with 26% responses at six cycles and 53% at nine cycles of LENDEX.

3.1 | Cost of Therapy

The combination was well tolerated on an outpatient basis, and none of the children required inpatient care during the treatment. Each 5-mg tablet of lenalidomide costs ₹32 ($0.37), and the cost for a dexamethasone tablet at a strength of 2 mg was ₹1 ($0.011). The average overall expense for six cycles of treatment for a 20-kg child was ₹792 ($9) and for nine cycles was ₹1188 ($13).

4 | Discussion

The prospective, multicentre, collaborative trial in India highlights the feasibility and cost-effectiveness of pulse dexamethasone and lenalidomide in relapsed/refractory LCH in children, with an overall response rate of 73%. The combination was well tolerated with no significant adverse effects. The outcome was superior at the end of nine versus six cycles with no increase in potential toxicity.

4.1 | Basis for the Trial

Glucocorticoids are one of the most important anti-inflammatory drugs available. They exert their effects through direct genomic and indirect membrane and mitochondrial pathways. They attach to the glucocorticoid receptors in the cytoplasm and result in genomic inhibition of second messengers, namely NF-kappa B, c-fos and c-jun, and increase expression of negative glucocorticoid response elements [8].

Lenalidomide has several effects through various mechanisms. It has potent anti-inflammatory effects by decreasing pro-inflammatory cytokines such as TNF- alpha, IL1 and IL6. It exerts anti-angiogenic effects by decreasing production of VEGF, pro-apoptotic properties through increased expression of tumour suppressor gene p21, and cell cycle arrest in G0 phase and immunomodulation by increasing Th1 expression, thereby augmenting NK cell activity [8].

Thalidomide has been used successfully in refractory bone and/or mucocutaneous LCH [14, 15]. However, it can cause sedation and neurological adverse effects and is known to be teratogenic and carcinogenic. Lenalidomide is an analogue of Thalidomide with improved potency and a better safety profile. It has been licensed for use in adults with multiple myeloma and myelodysplastic syndrome [9]. There are a few case reports published in adults using lenalidomide in LCH. Ibrahim et al. have reported remission in a patient with recurrent LCH of the vulva with lenalidomide

[16]. Adam et al. have also reported the efficacy of this drug in rare disorders such as LCH and Castleman disease [17]. In 2012, Szturz et al. published a case report highlighting the effects of lenalidomide in multisystem LCH [18].

Limitations of the study include small sample size and duration of 3 years. Lenalidomide in the trial was used on a compassionate basis, and ethics approval was obtained by each of the individual participating centres.

Studies in LCH have demonstrated the need for prolonged treatment to reduce the risks of reactivation. The INPHOG Histiocytosis Subcommittee plans to conduct further studies with a larger sample size and longer follow-up. We plan to conduct the above trial through INPHOG as a prospective multicentre study in India, with particular focus on children from the lower socioeconomic strata.

Author Contributions

R.U. and R.R. conceptualised the study, planned the study protocol and conducted the multicentre study. M.K., S.K., V.G., C.D., S.S. and N.R. helped with data collection, data entry and analysis.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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