Mercaptopurine

Essential medicine status

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.1. Cytotoxic medicines

EMLc | ATC codes: L01BB02

Indication	Langerhans cell histiocytosis ICD11 code: 2B31.2
INN	Mercaptopurine
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Liquid:** 20 mg per mL (EMLc) **Oral > Solid:** 50 mg tablet
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Cancer
Wikipedia	Mercaptopurine
DrugBank	Mercaptopurine

Expert Committee recommendation

The Expert Committee noted that while LCH is a relatively rare condition, affecting 4.6 per 1 million children each year, treatment of single-system disease has an excellent prognosis, with survival rates close to 100%. Prognosis for multisystem disease is variable, but treatment is generally associated with high survival rates. Despite limited evidence presented in the application, the Committee acknowledged that the treatment for LCH involving cytarabine, intravenous immunoglobulin, 6-mercaptopurine, methotrexate, prednisone, vinblastine and vincristine is recognized as the current standard of care and is associated with meaningful survival benefits. The benefits and harms were accepted as well established from use in other indications in children and in adults. The Committee therefore recommended the extension of the current listings of these medicines on the complementary list of the EML and EMLc to include the indication of LCH. However, the Committee expressed concern about the use of cladribine in the treatment of refractory high-risk LCH, noting important haematological toxicities that would limit its safe use to tertiary care centres with capacity to deliver supportive treatment to manage toxicities. The Committee therefore did not recommend the inclusion of cladribine on the EML and EMLc for treatment of LCH.

Background

Chemotherapy for the treatment of LCH has not previously been considered by the Expert Committee. With the exception of cladribine, all the other medicines proposed in the application are already included in the EML and EMLc for other oncological indications.

Public health relevance

LCH is a rare clonal disease of the immune system with a myeloid origin. It can affect single or multiple organ systems and hence the range of clinical symptoms is wide. It has an annual incidence of 4.6 cases per 1 million children younger than 15 years. It can affect people of any age group but is most common in children aged 1–3 years. Single-system disease, where only

one organ is involved, has a survival rate of nearly 100% with (or without) treatment. In multisystem disease, the outcome is more variable but overall survival is still relatively high. Historically, patients with multisystem disease involving so-called risk organs such as the liver, spleen and haematopoietic system and who did not respond to induction therapy had a poorer prognosis. However, the use of intensive therapy or inhibitors targeting the mitogen-activated protein kinase pathway has improved outcomes (1, 2). About 30–40% of patients with LCH experience permanent sequelae, depending on the organ(s) affected and treatment required. This includes patients who undergo haematopoietic stem cell transplantation. The long-term survival and late effects in LCH depend on the initial location and extent of the disease. For example, single-site and single-system disease involving the bone carries a low risk of late effects and impact on quality of life. However, involvement of the pituitary gland can lead to a lifelong need for hormone substitution.

Benefits

Chemotherapy is the mainstay of LCH treatment, and the intensity and duration of treatment depend on the site and extent of the disease. In the 1980s, the l'Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) Group and the DAL-HX group conducted the largest prospective clinical trials for LCH (3,4). These trials used systemic chemotherapy immediately after diagnosis. In the AIEOP-CNR-HX 83 trial, various chemotherapeutic agents were used based on the patient's prognosis. Vinblastine was used as monotherapy for patients with a good prognosis, while doxorubicin + etoposide was used for non-responders, and doxorubicin + vincristine + cyclophosphamide + prednisone was used for patients with a poor prognosis. Most of these medicines are still used in LCH treatment today. The overall mortality in both trial series was low, at 8% (3) and 9% (4), respectively. The current standard treatment protocol for LCH is the LCH-IV protocol (5), based on the findings of previous protocol versions (6). The LCH-IV protocol assigns patients to seven strata, with each stratum having specific treatment dependent on features at presentation and on response to treatment. Medicines included in this protocol include vinblastine, prednisone, 6-mercaptopurine, methotrexate, vincristine, cytarabine, cladribine and intravenous immunoglobulin. These medications have demonstrated effectiveness in LCH treatment, and their combinations have been refined over time. Even for relapsed disease, the second-line treatment is relatively mild and has a relatively good prognosis (7). Due to the extensive experience with these drug combinations, individual studies examining the efficacy of each medication specifically for LCH treatment have not been conducted. Two studies investigated the use of cladribine as monotherapy for salvage therapy for refractory high-risk LCH patients. The first was a retrospective multicentre study in which data were collected from a survey among members of the Histiocyte Society and a literature review. The authors reported on 23 paediatric and adult patients who received treatment with cladribine. The results showed that 57% (13/23) of the patients achieved complete response, 13% (3/23) had a partial response, 26% (6/23) showed no response and one early death occurred (8). The subsequent LCH-S-98 prospective multicentre clinical trial registered 92 children with refractory LCH who were treated with cladribine monotherapy, 83 of whom were included in the analysis. The primary outcome measure was early response. The study found that 38% (17/45) of high-risk patients and 62% (23/37) of low-risk patients achieved an early response. The 2-year overall survival rates were 48% for high-risk patients and 97% for low-risk patients (9). Another retrospective study focused on granulomatous type of central nervous system LCH, where 12 paediatric and adult patients were treated with cladribine monotherapy. In this study, 67% (8/12) of patients achieved complete response and 33% (4/12) had a partial response based on radiological evaluation (10). Two studies investigated the use of cladribine in combination with cytarabine for the treatment of LCH. A multicentre prospective pilot study evaluated efficacy and safety of cladribine and cytarabine in 10 children with refractory multisystem LCH and haematological dysfunction (11). The primary outcome measure was early response. The study reported three deaths, with six of the remaining seven children showing a partial response. A subsequent international open-label, prospective, non-randomized phase II study (LCH-S-2005), evaluated cladribine and cytarabine in 27 paediatric patients with high-risk refractory LCH (1). The primary endpoint was the response after two cycles of chemotherapy. The results showed that 7% (2/27) of patients achieved complete response, 85% (23/27) had a partial response, and 7% (2/27) had stable disease. Overall 5-year survival was 85.0% (95% confidence interval 65.2% to 94.2%).

Harms

No evidence on the harms and toxicity of the medicines proposed was presented in the application. The application states that as the medicines proposed are considered part of standard care protocols for LCH, their benefits are therefore deemed to outweigh potential harms and toxicity associated with their use. With the exception of cladribine, all of the proposed medicines are already included in the EML and EMLc. Their safety profiles are well known as a result of long-standing experience with their use. Cladribine is associated with myelotoxicity. In the LCH-S-2005 study, all patients experienced prolonged pancytopenia along with infectious complications, including septicaemia and invasive aspergillosis (11).

Cost / cost effectiveness

Comparative cost–effectiveness data were not presented in the application. LCH has different clinical presentations and courses. Overall, the treatment approach is characterized by relatively low intensity but requires several months of treatment. The LCH-IV protocol assigns patients into seven strata. Different stages and strata may have varying treatment durations according to the protocol. Based on vial prices from the Kingdom of the Netherlands, the estimated costs of chemotherapy for a child with body surface area of 1 m2, weighing 15 kg, and with LCH treated according to different strata in the LCH IV protocol ranged from €1410 to €80 932. The costs of cladribine depend on the strata and were estimated to range from €1554 to €9324.

WHO guidelines

WHO guidelines for the treatment of LCH are not available.

Availability

Cytarabine, IV immunoglobulin, 6-mercaptopurine, methotrexate, prednisone, vinblastine and vincristine are already included on the EML and EMLc for other indications and are available globally in branded and generic versions. Cladribine has regulatory approval for use in the treatment of patients with hairy cell leukaemia and patients with B-cell chronic lymphocytic leukaemia. No information on the availability of intravenous cladribine in low- and middle-income settings was presented in the application.

Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department advised that it supported extending the listings of the currently included medicines to include the new indication of LCH, given that systemic chemotherapy according to international protocols had demonstrated high response rates and overall survival > 80% in patients with LCH with high-risk characteristics. The technical department advised that it did not support the inclusion of cladribine on the EML and EMLc for LCH for feasibility and safety reasons, namely capacity for histopathological diagnosis, and identification and management of immune-related toxicity. The EML Cancer Medicines Working Group reviewed the application and advised that it supported expansion of the listing of existing medicines for the new indication of LCH but did not support the inclusion of cladribine. The Working Group highlighted the severe toxicity associated with cladribine and the difficulty of managing these in resource-constrained settings because its use would be limited to tertiary care centres. Cladribine, as a salvage treatment, is associated with high rates of cure in high-risk patients. However, it is also associated with prolonged hospitalization and increased risk of treatment-related death. The Working Group noted that an international, multicentre, prospective clinical study for paediatric LCH is ongoing (NCT02205762) (5). This study plans to recruit 1400 patients and might provide data to guide the clinical care of children and young adults.

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