Cyclophosphamide

EMLc | ATC codes: L01AA01

Indication	Anaplastic large cell lymphoma, ALK-positive ICD11 code: 2A90.A
INN	Cyclophosphamide
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 500 mg in vial powder for injection ; 1 g in vial powder for injection ; 2 g in vial powder for injection **Oral > Solid > dosage form:** 25 mg ; 50 mg
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	Cyclophosphamide
DrugBank	Cyclophosphamide

Expert Committee recommendation

The Expert Committee noted that ALCL is an important disease in paediatric oncology, accounting for 10–15% of cases of non-Hodgkin lymphoma in paediatric and adolescent patients. Despite limited evidence presented in the application, the Committee acknowledged that the ALCL99 treatment protocol, involving the use of cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide ifosfamide, methotrexate and prednisolone, is internationally recognized as the standard of care in the first-line treatment of ALCL. The Committee also acknowledged the accepted role of vinblastine in second-line treatment in relapsed/refractory disease. Based on the evidence available, the Committee noted that treatment is associated with clinically meaningful responses in a high proportion of patients. The benefits and harms of all medicines mentioned above were well established from their use in other indications in children and in adults. The Committee therefore recommended the extension of the current listings of these medicines of the complementary list of the EML and EMLc to include the indication of ALCL. However, because of insufficient evidence and important toxicity concerns for the use of crizotinib in the treatment of refractory/relapsed ALCL, the Committee did not recommended inclusion of crizotinib on the EML and EMLc. The Committee considered that the evidence on ALK-inhibitor therapies should continue to be monitored, since more potent and less toxic ALK-inhibitors than crizotinib are currently being tested in clinical trials.

Background

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

Public health relevance

Non-Hodgkin lymphoma is the fourth most common cancer in children and adolescents, with an annual incidence of 0.7–1.5 per 100 000 in Europe. Around 10–15% of these cases are ALCL (1). ALCL can be classified into four main types: anaplastic lymphoma kinase (ALK)-positive primary systemic ALCL; ALK-negative primary systemic ALCL; cutaneous ALCL; and breast implant-associated ALCL (2). ALK-positive ALCL is the most common type in children and adolescents, with almost all cases showing a translocation involving the ALK gene, leading to activation of the ALK kinase and tumour development (3). The incidence of ALCL varies, with about 1.2 cases per million in children younger than 15 years and around 2 cases per million in young adults aged 25–34 years (4). This results in about 80 newly diagnosed cases of ALCL in children each year in Europe. Many children with ALCL are diagnosed at an advanced stage. Although relapse occurs in about 30% of patients, the overall survival rate is high at 90% due to various second-line treatment approaches (3).

Benefits

The standard treatment for paediatric ALCL in Europe is the ALCL99-protocol, which consists of a prephase of dexamethasone, cyclophosphamide and intrathecal treatment (with cytarabine, methotrexate and prednisone), followed by three to six cycles of alternating multiagent chemotherapy (course A: cytarabine, dexamethasone, etoposide, ifosfamide, methotrexate, and intrathecal treatment; course B: cyclophosphamide, dexamethasone, doxorubicin methotrexate, and intrathecal treatment), depending on the stage of the disease (5). For some patients with completely resected stage I disease, three cycles of chemotherapy are given. The treatment duration is 10 weeks. For patients in the standard risk and high-risk group, six cycles of chemotherapy are administered over 4–5 months. With this treatment approach, the 2-year event-free survival rate has been reported to range from 70% to 75% (3,6). Most children and adolescents with recurrence can be cured with second-line therapy, which may involve vinblastine monotherapy for late relapse, reinduction chemotherapy or targeted therapy (such as crizotinib) followed by allogeneic haematopoietic stem-cell transplantation for early relapse. The ALCL99 protocol is based on the non-Hodgkin lymphoma-Berlin-Frankfurt-Münster (NHL-BFM) treatment strategy (7). The NHL-BFM 83 and 86 trials used a prephase followed by two alternating courses of treatment. The medicines used in these trials included cyclophosphamide, cytarabine, doxorubicin, ifosfamide, methotrexate, prednisone, and teniposide. In the NHL-BFM 90 protocol, teniposide was replaced with etoposide, both of which are topoisomerase II inhibitors. The NHL-BFM 90 trial demonstrated a favourable event-free survival rate of 76%. The ALCL99 trial built upon the previous NHL-BFM protocols and showed that the 24-hour infusion of methotrexate with additional intrathecal methotrexate can be safely replaced by a schedule of 3 g/m2 intravenous methotrexate administered over 3 hours; this was associated with 2-year overall survival of 94.9% (3). After 10 years of follow up, progression-free survival was 70% and overall survival was 90% in the ALCL99 trial (8). Vinblastine has a role in the second-line treatment of paediatric ALCL. A retrospective analysis of 41 patients with relapsed ALCL included 12 patients who received weekly vinblastine for 6 to 18 months for relapsed disease. Ten patients achieved complete remission, defined as the complete disappearance of all lesions for at least 4 weeks (9). In a prospective ALCL relapse trial, vinblastine monotherapy was effective for patients experiencing a relapse after the first year of initial diagnosis, with an observed long-term remission rate of 81% reported in patients who received vinblastine monotherapy (10). Crizotinib, an ALK-specific tyrosine kinase inhibitor, has been effective in treating relapsed ALK-positive ALCL in both adults and children (11–14). Retrospective and prospective studies have shown an unfavourable prognosis for patients who experience progression during first-line treatment, with a high risk of treatment failure during conventional re-induction chemotherapy (15). Treatment strategies for re-induction therapy often involve the use of ALK inhibitors, either alone or in combination with other treatments. A phase I/II trial evaluated the efficacy of crizotinib in 26 paediatric patients with relapsed or refractory ALK-positive ALCL and 14 paediatric patients with metastatic or inoperable ALK-positive inflammatory myofibroblastic tumour. The children with ALCL received crizotinib at doses of either 165 mg/m2 or 280 mg/m2. The overall

response rates were 83% (5/6 patients achieving a complete response) for the lower-dose group and 90% (16/20 patients achieving a complete response and two with a partial response) for the higher-dose group (14). Another phase II trial evaluated the efficacy of crizotinib in 17 paediatric and adult patients with ALCL (15 who could be evaluated, 13 with progression and two front-line). Children and adults received crizotinib 165 mg/m2 twice daily and 250 mg/m2 twice daily, respectively. The overall response rate for the 15 patients was 67% (95% confidence interval (CI), 42% to 85%) – 10 patients achieved an objective response, of whom nine achieved a complete response and one achieved a partial response. Response rates were similar in children and adults (13).

Harms

In the ALCL99 protocol, the most frequently reported adverse reaction was haematological toxicity, including with grade 4 neutropenia occurring after 70% of treatment courses. Other frequent adverse reactions reported were infections (after 41% of courses), elevated liver transaminase and stomatitis (both after 39% of courses). Significant weight gain was reported in 20% of patients (16). The most frequently reported adverse event for crizotinib, regardless of grade, in the ALCL groups was neutropenia, occurring in 33% of patients receiving the lower dose and 70% of patients receiving the higher dose (14). Other reported adverse events associated with crizotinib include thromboembolic events, elevated liver transaminases,, visual disorders, nausea and vomiting, and bradycardia (13).

Cost / cost effectiveness

Comparative cost–effectiveness data were not presented in the application. Based on vial prices from the Kingdom of the Netherlands, for a child with a body surface area of 1 m2 receiving one course of induction and three (or six) courses of consolidation according to the ALCL99 protocol, the estimated cost of chemotherapy would be about €1126 (or €3292). The costs per dose for vinblastine and crizotinib were reported in the application as about €76 and €86, respectively.

WHO guidelines

WHO guidelines for the treatment of ALCL are not available.

Availability

Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, and prednisolone and vinblastine are already included on the EML and EMLc for other indications and are available globally in branded and generic versions. Crizotinib has regulatory approval for use in ALCL from the United States Food and Drug Administration and the European Medicines Agency. No information on the availability of crizotinib 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 for the new indication of ALCL, given that it is a highly curable disease, and that EMLc listing can contribute to improving access and quality of care for children and adolescents diagnosed with ALCL, in alignment with the objectives of WHO’s global initiative for childhood cancer. The technical department did not support the addition of crizotinib at this time, and preferred to prioritize access to first-line chemotherapy. The EML Cancer Medicines Working Group reviewed the application and advised that it supported expansion of the listings of existing medicines for the new indication of ALCL but did not unanimously support inclusion of crizotinib. The Working Group noted that crizotinib is associated with benefits as other first-line chemotherapies, and it is considered a therapeutic option for relapsed or refractory ALK-positive disease. However, crizotinib is associated with potentially severe toxicities. The Working Group commented that brentuximab-based chemotherapy was a new standard of care in adults with ALCL. Brentuximab-based chemotherapy is now studied also in children as it may be a favourable first-line option based on its benefit to harm ratio. The application did not cover brentuximab-

based chemotherapy.

1. Turner SD, Lamant L, Kenner L, Brugières L. Anaplastic large cell lymphoma in paediatric and young adult patients. Br J Haematol. 2016;173(4):560–72.
2. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
3. Brugières L, Le Deley MC, Rosolen A, Williams D, Horibe K, Wrobel G, et al. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group. J Clin Oncol. 2009;27(6):897–903.
4. Prokoph N, Larose H, Lim MS, Burke GAA, Turner SD. Treatment options for paediatric anaplastic large cell lymphoma (ALCL): current standard and beyond. Cancers (Basel). 2018;10(4):99.
5. Combination chemotherapy in treating children with anaplastic large cell lymphoma (ALCL 99). Bethseda, MD: U.S. National Library of Medicine (ClinicalTrials.gov Identifier: NCT00006455; https://www.clinicaltrials.gov/study/NCT00006455, accessed 6 October 2023).
6. Le Deley MC, Rosolen A, Williams DM, Horibe K, Wrobel G, Attarbaschi A, et al. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. J Clin Oncol. 2010;28(25):3987–93.
7. Reiter A, Schrappe M, Tiemann M, Parwaresch R, Zimmermann M, Yakisan E, et al. Successful treatment strategy for Ki-1 anaplastic large-cell lymphoma of childhood: a prospective analysis of 62 patients enrolled in three consecutive Berlin-Frankfurt-Munster group studies. J Clin Oncol. 1994;12(5):899–908.
8. Mussolin L, Le Deley MC, Carraro E, Damm-Welk C, Attarbaschi A, Williams D, et al. Prognostic factors in childhood anaplastic large cell lymphoma: long term results of the International ALCL99 Trial. Cancers (Basel). 2020;12(10):2747.
9. Brugières L, Quartier P, Le Deley MC, Pacquement H, Perel Y, Bergeron C, et al. Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children -- a report from the French Society of Pediatric Oncology. Ann Oncol. 2000;11(1):53–8.
10. Knörr F, Brugières L, Pillon M, Zimmermann M, Ruf S, Attarbaschi A, et al. Stem cell transplantation and vinblastine monotherapy for relapsed pediatric anaplastic large cell lymphoma: results of the International, prospective ALCL-relapse trial. J Clin Oncol. 2020;38(34):3999–4009.
11. Mossé YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol. 2013;14(6):472–80.
12. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med. 2011;364(8):775–6.
13. Brugières L, Houot R, Cozic N, De La Fouchardière C, Morschhauser F, Brice P, et al. Crizotinib in advanced ALK + anaplastic large cell lymphoma in children and adults: results of the Acs© Phase II Trial. Blood (Abstract). 2017;130:2831.
14. Mossé YP, Voss SD, Lim MS, Rolland D, Minard CG, Fox E, et al. Targeting ALK With crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a children's oncology group study. J Clin Oncol. 2017;35(28):3215–21.
15. Rigaud C, Abbas R, Grand D, Minard-Colin V, Aladjidi N, Buchbinder N, et al. Should treatment of ALK-positive anaplastic large cell lymphoma be stratified according to minimal residual disease? Pediatr Blood Cancer. 2021;68(6):e28982.
16. Wrobel G, Mauguen A, Rosolen A, Reiter A, Williams D, Horibe K, et al. Safety assessment of intensive induction therapy in childhood anaplastic large cell lymphoma: report of the ALCL99 randomised trial. Pediatr Blood Cancer. 2011;56(7):1071–7.

