Rituximab

Statut de médicament essentiel ✓

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

EMLc | Codes ATC: L01FA01

Indication	Burkitt lymphoma including Burkitt leukaemia — Code ICD11: 2A85.6
INN	Rituximab
Type de médicament	Biological agent
Type de liste	Liste complémentaire (EML) (EMLc)
Additional notes	Including quality-assured biosimilars
Formulations	Parenteral > General injections > IV: 100 mg per 10 mL in 10 mL vial ; 500 mg per 50 mL in 50 mL vial
Historique des statuts LME	Ajouté pour la première fois en 2023 (TRS 1049)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Balises	Cancer, Biological
Wikipédia	Rituximab
DrugBank	Rituximab

Recommandation du comité d'experts

The Expert Committee noted that Burkitt lymphoma is the most frequent type of non-Hodgkin lymphoma in children, the majority of children diagnosed lived in low- and middle-income countries and there was a need for safe, effective and affordable treatments. Despite limitations in the evidence presented in the application, the Committee noted that rituximab, added to standard chemotherapy, was associated with prolonged event-free and overall survival in children and adolescents with high-grade, high-risk mature B-cell non-Hodgkin lymphoma, including Burkitt lymphoma. The Committee considered that the safety profile of rituximab was well established. The most common adverse events were febrile neutropenia, infections, hypogammaglobulinaemia and anaphylactic reactions, and these required careful monitoring and management. The Committee noted that rituximab was available globally as originator and biosimilar brands, both of which were prequalified by WHO to facilitate greater access and affordability of quality-assured products. The Expert Committee therefore recommended that the listing for rituximab on the complementary list of the EML and EMLc be extended to include the new indication of Burkitt lymphoma.

Contexte

Rituximab has not previously been evaluated for inclusion on the Model Lists for the treatment of Burkitt lymphoma. It is listed on the EML and/or EMLc for follicular lymphoma, chronic lymphocytic leukaemia and diffuse large B-cell lymphomas. There are a variety of chemotherapies listed on the EML and EMLc for use in the treatment of Burkitt lymphoma.

Pertinence pour la santé publique

Non-Hodgkin lymphomas are the fourth most common group of malignancies in children and adolescents. In 2019, the global incidence of non-Hodgkin lymphoma in people younger than 20 years was 0.98 (range 0.82 to 1.18) per 100 000 (1). Among non-Hodgkin lymphomas, the three main subtypes are mature aggressive B-cell lymphoma (58%), lymphoblastic lymphoma (21%), and anaplastic large cell lymphoma (13%) (2,3). Burkitt lymphoma (and leukaemia) is the most common subtype of mature aggressive B-cell lymphoma and accounts for 80% of cases (4). It is estimated that 90% of children diagnosed with non-Hodgkin lymphoma live in low- and middle-income countries (5). Burkitt lymphoma is endemic in the area known as the Burkitt belt in sub-Saharan Africa, where it represents more than 50% of childhood cancers.

Bénéfices

A randomized, open-label, international, phase III trial evaluated rituximab in 328 patients younger than 18 years with high-risk, mature B-cell non-Hodgkin lymphoma, 85.7% of whom had Burkitt lymphoma (6). After median follow-up of 39.9 months, event-free survival at 3 years was 93.9% the rituximab-chemotherapy group and 82.3% in the chemotherapy group (hazard ratio (HR) for primary refractory disease or first occurrence of progression, relapse after response, death from any cause, or second cancer: 0.32, 95% confidence interval (CI) 0.15 to 0.66). Overall survival at 3 years was 95.1% and 87.3% in the rituximab + chemotherapy and chemotherapy groups, respectively (HR for death 0.36, 95% CI 0.16 to 0.82). A phase II window of opportunity study evaluated the activity of rituximab in 136 patients younger than 19 years with newly diagnosed paediatric mature B-cell non-Hodgkin lymphoma (7). The study design allowed evaluation of the activity of a single dose of rituximab (375 mg/m2) as monotherapy in a 5-day upfront window before starting chemotherapy. Response criterion was defined as the product of the two largest perpendicular diameters of one to three lesions and/or the percentage of blasts in bone marrow or peripheral blood within 24 hours before rituximab and on day 5. In view of a possible subsequent phase III trial testing whether rituximab can be a substitute for chemotherapy drugs, a high response rate for favourable activity was set at 65%. A total of 87 participants could be evaluated, giving a response rate of 41% (95% CI 31% to 52%), including 27 (of 67) participants with Burkitt lymphoma. The study found that single-agent rituximab was active in newly diagnosed paediatric mature B-cell non-Hodgkin lymphoma, despite the response rate being lower than set in the trial plan. The authors considered that the short window of 5 days may not have allowed the full effect of rituximab to be measured, and their findings might be an underestimate of the true response rate. The Children's Oncology Group ANHL01P1 trial evaluated the efficacy and safety of rituximab in combination with standard chemotherapy in 45 children and young adults (younger than 30 years) with intermediate-risk mature B-cell lymphoma, of whom 56% had Burkitt lymphoma (8). The 3-year event-free survival for all 45 eligible patients was 93% (95% CI 79% to 98%). For 38 patients who received six doses of rituximab, the 3-year event-free survival was 95% (95% CI 80% to 99%) and 3-year overall survival was 95% (95% CI 83% to 99%).

Torts

In the randomized, open-label, phase III trial of rituximab plus standard chemotherapy versus standard chemotherapy alone, acute adverse events of grade 4 or higher were reported in 33% and 24% of participants in the rituximab + chemotherapy and chemotherapy groups, respectively. Grade 4 or higher febrile neutropenia was reported in 11.7% and 6.5% of participants in the rituximab + chemotherapy and chemotherapy groups, respectively. The incidence of grade 4 or higher infection was 18.5% and 11.1%, respectively. Low immunoglobulin G levels were significantly higher in the patients treated with rituximab both at the end of therapy (70.3% versus 46.8%, P = 0.002) and 1 year after inclusion (55.9% versus 25.4%, P < 0.001) (6).

Rapport coût/efficacité

No information on comparative cost–effectiveness of rituximab in Burkitt lymphoma was provided in the application. The application reported the price of rituximab in the Netherlands as €213.74 for the 10 mL vial and €1068.74 for the 50 mL vial. Prices in other countries were not reported.

Directives de l'OMS

WHO guidelines for Burkitt Lymphoma (and/or leukaemia) are not available.

Disponibilité

Rituximab intravenous injection is already included on the Model Lists and has regulatory approval and market availability in more than 60 countries globally. Innovator and biosimilar brands of rituximab were prequalified by WHO in 2020.

Autres considérations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department commented that there was strong merit to extend the listed indications for rituximab to include the treatment of Burkitt lymphoma based on its clinical effect in decreasing early death and improving survival for advanced disease. It also highlighted that feasibility must also be considered in terms of diagnostic capacity, management of side-effects and affordability. The Global Platform for Access to Childhood Cancer Medicines, established by WHO and St Jude Children's Research Hospital in Memphis, Tennessee, will play an important role in increasing access to rituximab in low- and middle-income settings. In this context, the technical unit advised that it generally favoured the inclusion of rituximab on the Model Lists for treatment of Burkitt lymphoma. The EML Cancer Medicines Working Group reviewed the application and advised that it supported the inclusion of rituximab on the EML and EMLc for use in the treatment of Burkitt lymphoma. The Working Group acknowledged the limited availability of clinical evidence but agreed that efficacy and safety could be accepted based on the limited evidence, together with extrapolation of well known benefits and harms from the use of this medicine in adults, and for other indications in children, as part of standard cancer care. The Working Group acknowledged that expanding the indications for rituximab would support the goals of the WHO Global Paediatric Cancer Initiative and contribute to achieving the best possible cancer care for children.

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