Cisplatin

Essential medicine status

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

EMLc | ATC codes: L01XA01

Indication	Other specified gliomas of brain ICD11 code: 2A00.0Y
INN	Cisplatin
Medicine type	Chemical agent
List type	Complementary (EML) (EMLc)
Formulations	Parenteral > General injections > IV: 50 mg per 50 mL ; 100 mg per 100 mL ; 10 mg per 10 mL ; 20 mg per 20 mL
EML status history	First added in 2021 (TRS 1035)
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	Cisplatin
DrugBank	Cisplatin

Expert Committee recommendation

The Expert Committee noted that low-grade glioma is the most common type of paediatric brain tumour and is one of the priority paediatric cancers in WHO Global Initiative for Childhood Cancer. Despite the limitation in the evidence presented in the application, treatment protocols including carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine in low-grade glioma are recognized as the standard of care and are associated with some benefits. Therefore, the Committee recommended the extension of current listings on the complementary list of the EML and EMLc for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine to include the indication low-grade gliomas. The Committee also recommended the inclusion of additional formulations and strengths of cisplatin, cyclophosphamide, vinblastine and vincristine as proposed in the application.

Background

Chemotherapy for the treatment of low-grade glioma has not previously been considered by the Expert Committee. All the proposed medicines (carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine) are currently included on the EML and EMLc for other cancer indications.

Public health relevance

Brain tumours are the largest group of solid tumours in children and account for about one quarter of all cancers in children younger than 15 years. Low-grade gliomas are the most common paediatric brain tumours, estimated to account for around 40% of all central nervous system tumours in children younger than 18 years (1). The annual incidence of paediatric low-grade glioma is 10 per 1 million in high-income countries. Incidence rates vary among high-, middle- and low-income countries; data are not available

for some regions where imaging methods required for diagnosis or centralized cancer registries are not available (2). The median age at diagnosis is 6 to 8 years (3). Low-grade gliomas are WHO grade I and II tumours (4) of glial origin; they are rather slow-growing tumours. Low-grade gliomas can occur anywhere in the brain and spinal cord, but most appear in the cerebral and cerebellar hemispheres. Dissemination develops in only a very small proportion of patients (5–10%). Low-grade gliomas can be associated with cancer predisposition syndromes, such as neurofibromatosis type 1 and tuberous sclerosis complex. The clinical course of low-grade glioma is very varied and not always predictable at diagnosis. Age at diagnosis, histological subtype and biological tumour characteristics all affect the clinical course. Some low-grade gliomas do not need treatment but are monitored to follow the clinical course, other types need neurosurgery or chemotherapy only, and other types need a combination of chemotherapy and radiotherapy. In general, low-grade gliomas have a 10-year overall survival rate of 90–95% and 10-year progression-free survival rate of around 44% (3,5). However, these rates might differ for some subtypes or if additional risk factors are present, such as BRAF V600E mutation. Low-grade glioma is considered a chronic disease with periods of stable disease, followed by progressive tumour growth needing treatment, followed by a stable period again. The effectiveness and feasibility of repeated chemotherapy in progressive low-grade glioma has been shown in a small trial (38 patients) to result in 5-year overall survival and progression-free survival rates of 86% and 37%, respectively (6).

Benefits

The International Society of Paediatric Oncology–Low Grade Glioma trial (SIOP-LGG-2004 trial) is a cooperative multicentre randomized controlled trial for children and adolescents with low-grade glioma, without neurofibromatosis type 1-associated visual pathway glioma at high risk of progression (7). Paediatric oncology societies from 11 European countries participated in this trial, which consisted of two arms: (i) standard chemotherapy induction (vincristine, carboplatin), or (ii) intensified chemotherapy induction (vincristine, carboplatin, etoposide). Both treatments were followed by a consolidation phase with vincristine and carboplatin, or, in case of allergy or early progression, with vincristine, cisplatin and cyclophosphamide. Standard induction consisted of 10 weekly doses of vincristine 1.5 mg/m2 by intravenous (IV) bolus and four doses of carboplatin 550 mg/m2 by IV infusion at 3-week intervals followed by three cycles of simultaneous vincristine and carboplatin at 4-week intervals. Intensification with etoposide 100 mg/m2 by IV infusion was added on days 1–3 in weeks 1, 4, 7 and 10. For consolidation, patients in both arms received 10 6-week cycles of vincristine 1.5 mg/m2 IV on days 1, 8 and 15 and carboplatin 550 mg/m2 IV on day 1. The total duration of chemotherapy was 18 months. Dose modifications were advised for children weighing less than 10 kg and for children younger than 6 months. Dose reductions were prescribed in case of haematological or organ toxicity. Grade I hypersensitivity reactions to carboplatin permitted the repeated administration under close surveillance, premedication and slowed infusion rate. In cases of Grade II or higher hypersensitivity reactions, replacement of carboplatin with cycles of cisplatin (30 mg/m2, day 1 and 2) and cyclophosphamide (1500 mg/m2, day 1) was recommended (7). One of the aims of the SIOP-LGG-2004 trial was to determine if etoposide added to standard induction with vincristine and carboplatin increased progression-free survival. The trial found no difference in terms of survival and radiological response between the two arms. The 5-year progression-free survival and overall survival were 46% and 89%, respectively, in the vincristine/carboplatin arm and 45% and 89%, respectively in the vincristine/carboplatin/etoposide arm. If the same progression-free survival and overall survival can be reached with a two-drug regimen, this is preferred over a three-drug regimen, especially because etoposide is also known to cause considerable late effects, such as secondary haematological malignancies. These results support the role of vincristine and carboplatin as the standard of care for induction chemotherapy for low-grade glioma. Subgroup analyses of the SIOP-LGG-2004 trial also show the benefit of vincristine plus carboplatin in terms of overall survival in patients with low-grade glioma of the brainstem (8), tectal plate (9) and thalamus (10). Vinblastine monotherapy is used in first- and second-line treatment of low-grade glioma. A phase II study evaluated the efficacy of vinblastine 6 mg/m2 administered once a week for 70 weeks in 54 paediatric patients who had not received prior chemotherapy for progressive low-grade glioma. The time to best response was 52 weeks. The total response rate was 25.9%: one complete response, nine partial responses and four minor responses. Thirty-four patients had stable disease and six patients had progressive disease. After median follow-up of 5 years, the 5-year overall survival was 94.4% and 5-year progression-free survival was 53.2%. Two thirds of participants required a reduction in vinblastine dose, mainly due to haematological toxicity (neutropenia) (11). Another phase II study evaluated the efficacy of vinblastine 6 mg/m2 administered once a week for 1 year in 50 paediatric patients with recurrent or refractory low-grade glioma. The median time to best response was 12 months. The total response rate was 36%: one complete response, 10 partial responses and seven minor responses. Nineteen patients had stable disease and 13 patients had progressive disease. After median follow-up of 67 months, the 5-year overall survival rate was 93.2% and the estimated 5-year event-free survival was 42.3% (12).

Harms

The most commonly reported grade 3 and 4 toxicities associated with the vincristine plus carboplatin regimen in the SIOP-LGG-400 trial were haematological events, infection and nausea/vomiting. Thirty-one patients experienced at least one allergic event to carboplatin (7). In the phase II studies of vinblastine monotherapy, overall, treatment was well tolerated. The most frequently reported adverse events were haematological events (neutropenia), infection and fever (11,12).

Cost / cost effectiveness

Based on vial prices from the Netherlands, a single treatment course of induction and consolidation chemotherapy with vincristine and carboplatin for a child with body surface area of 1 m2 is estimated to cost about € 4172. A single treatment course of vinblastine monotherapy for a child with body surface area of 1 m2 is estimated to cost about € 1983. The total duration of treatment (number of treatment courses) can vary largely between patients, due to the heterogeneous nature of the clinical course of low-grade glioma.

WHO guidelines

WHO guidelines for the treatment of low-grade glioma are not available. However, low-grade glioma is one of the six tracer cancers in the WHO Global Initiative for Childhood Cancer. This initiative seeks to increase countries' capacity to provide quality services for children with cancer, and increase prioritization of childhood cancer at national, regional and global levels. The goal of the initiative is to achieve a 60% survival rate for children with cancer by 2030 and reduce suffering from childhood cancer globally.

Availability

Carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine are already included on the EML and EMLc and are available globally in branded and generic versions.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the expansion of the listings on the EMLc for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine to include the indication of low-grade glioma. The Working Group recognized that the evidence presented is not always from large randomized controlled trials, but that the treatment protocols are associated with relevant benefits and are recognized as the standard of care for treatment of paediatric low-grade glioma and this supports the inclusion of these medicines on the EMLc. The Working Group acknowledged that the availability of clinical evidence in paediatrics was limited but considered that obtaining the usual level of evidence required for EML listings was unlikely. In this case, efficacy and safety could be accepted based on extrapolation of the well known benefits and harms from use of these medicines in adults, for other indications in children and as part of standard cancer care in children. Noting that the EMLc lists medicines for the treatment of children up to 12 years of age, and that low-grade glioma also affects older children and adolescents, the Working Group also supports inclusion of these medicines on the EML for this indication. Expanding the EMLc indications for these medicines would also support the goals of WHO's Global Initiative for Childhood Cancer and contribute towards the achievement of the best possible cancer care for children. Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that, in line with the recommendation from the EML Cancer Medicines Working Group, the inclusion of the indication of low-grade glioma for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine on EMLc is appropriate. These medicines and accompanying treatment protocols are well established, recognized as the standard of care and associated with clinical benefits, including improved survival and reduction in the long-term sequelae from alternate treatments. The extension of the indication for these medicines also supports the effort the WHO Global Initiative for Childhood Cancer, which has low-grade glioma as one of the six priority cancers.

1. Udaka YT, Packer RJ. Pediatric brain tumors. Neurol Clin. 2018;36(3):533–56.
2. Hessissen L, Parkes J, Amayiri N, Mushtaq N, Sirachainan N, Anacak Y, et al. SIOP PODC adapted treatment guidelines for low gra de gliomas in low and middle income settings. Pediatr Blood Cancer. 2017;64(Suppl 5).
3. Gnekow AK, Kandels D, Tilburg CV, Azizi AA, Opocher E, Stokland T, et al. SIOP-E-BTG and GPOH guidelines for diagnosis and trea tment of children and adolescents with low grade glioma. Klin Padiatr. 2019;231(3):107–35.
4. WHO classification of tumours of the central nervous system. WHO classification of tumours, revised 4th edition. Lyon: Internatio nal Agency for Research on Cancer; 2016.

5. Scheinemann K, Bouffet E, editors. Pediatric neuro-oncology. First edition. New York: Springer-Verlag; 2015.
6. Scheinemann K, Bartels U, Tsangaris E, Hawkins C, Huang A, Dirks P, et al. Feasibility and efficacy of repeated chemotherapy for progressive pediatric low-grade gliomas. Pediatr Blood Cancer. 2011;57(1):84–8.
7. Gnekow AK, Walker DA, Kandels D, Picton S, Giorgio P, Grill J, et al. A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤ 16 years) low grade glioma – a final report. Eur J Cancer. 2017;81:206–25.
8. Holzapfel J, Kandels D, Schmidt R, Pietsch T, Warmuth-Metz M, Bison B, et al. Favorable prognosis in pediatric brainstem low-grade glioma: report from the German SIOP-LGG 2004 cohort. Int J Cancer. 2020;146(12):3385–96.
9. Kaufmann A, Gerber NU, Kandels D, Azizi AA, Schmidt R, Warmuth-Metz M, et al. Management of primary tectal plate low-grade glioma in pediatric patients: results of the multicenter treatment study SIOP-LGG 2004. Neuropediatrics. 2018;49(5):314–23.
10. Boesten T, Gerber NU, Kandels D, Azizi AA, Schmidt R, Warmuth-Metz M, et al. Management of primary thalamic low-grade glioma in pediatric patients: results of the multicenter treatment studies HIT-LGG 1996 and SIOP-LGG 2004. Neurooncol Pract. 2017;4(1):29–39.
11. Lassaletta A, Scheinemann K, Zelcer SM, Hukin J, Wilson BA, Jabado N, et al. Phase II weekly vinblastine for chemotherapy-naïve children with progressive low-grade glioma: a Canadian Pediatric Brain Tumor Consortium study. J Clin Oncol. 2016;34(29):3537–43.
12. Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol. 2012;30(12):1358–63.