Temozolomide

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

EMLc | ATC codes: L01AX03

Indication	Ewing sarcoma of bone and articular cartilage of unspecified sites — ICD11 code: 2C22.Z
INN	Temozolomide
Medicine type	Chemical agent
List type	Complementary (EML) (EMLc)
Formulations	Parenteral > General injections > IV: 100 mg in vial powder for injection Oral > Solid > capsule: 5 mg ; 20 mg ; 100 mg ; 140 mg ; 180 mg ; 250 mg
EML status history	Application rejected in 2025 (TRS 1064)
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.
Wikipedia	Temozolomide
DrugBank	Temozolomide

Expert Committee recommendation

The Expert Committee recognized the public health relevance of effective treatments for childhood cancers and acknowledged the goal of the WHO global initiative for childhood cancer to increase the survival rate of children with cancer globally to at least 60% by 2030, while reducing their suffering and improving their quality of life. The Committee noted that temozolomide was identified as a priority paediatric cancer medicine during the WHO paediatric drug optimization exercise for cancer medicines for which development of a more age-appropriate oral formulation than currently available capsules was recommended. For high-grade glioma, the Committee noted limited evidence of an overall survival benefit associated with temozolomide radiochemotherapy compared with cisplatinum-based radiochemotherapy in patients with non-pontine tumours. However, the magnitude of the survival gain was below the EML threshold of 4-6 months. In neuroblastoma, the Committee noted evidence from phase II studies that objective response rates for temozolomide plus irinotecan and temozolomide plus topotecan were below 20%. In Ewing sarcoma, data from retrospective studies showed modest benefit for temozolomide plus irinotecan in objective response rates. Temozolomide has not been demonstrated to improve survival in patients with neuroblastoma or Ewing sarcoma. In other refractory solid tumour types, evidence for benefit was even more limited. In terms of safety, the Committee noted that the main concerns with temozolomide involve haematological toxicities, which may be severe and require inpatient monitoring and management. Overall, the Committee considered that the balance of benefits to harm for temozolomide was not favourable. Based on these considerations, the Expert Committee did not recommend the inclusion of temozolomide on the EML and EMLc for the treatment of high-grade glioma (as monotherapy), relapsed or refractory high-risk neuroblastoma (in combination with irinotecan or topotecan), relapsed Ewing sarcoma (in combination with irinotecan), or as monotherapy for treatment of other relapsed or refractory paediatric solid tumours as palliative treatment.

Background

Medicines for the treatment of high-grade glioma and neuroblastoma have not previously been evaluated for inclusion in the Model Lists. Medicines for the treatment of Ewing sarcoma were evaluated by the Expert Committee in 2015. Based on the evidence presented in the application, the Committee recommended the inclusion of cyclophosphamide, doxorubicin, etoposide, ifosfamide, mesna and vincristine on the complementary list of the EML and EMLc for the treatment of Ewing sarcoma (1). In 2021, the Expert Committee also recommended the inclusion of dactinomycin on the complementary list of the EML and EMLc for this indication (2). Irinotecan is currently included on the Model Lists for other indications, that is, metastatic colorectal cancer, nephroblastoma and rhabdomyosarcoma.

Public health relevance

The application included data from the International Agency for Research on Cancer published in 2017 (3), which reported the following age-specific incidence rates among children 0 to 14 years for the indications being proposed for listing: • central nervous system and miscellaneous intracranial and intraspinal neoplasms – from 3.4 per million in Uganda to 49.7 per million in Italy; • neuroblastoma and ganglioneuroblastoma – from 0.4 per million in Cameroon to 21.5 per million in Italy; • Ewing tumour and related sarcomas of bone – from 0.2 per million in Ecuador, Kuwait, and Uganda to 7.5 per million in New Zealand. Data from the United States reported annual average number of cases in children 0 to 14 years was 32 and 78 for anaplastic astrocytoma and glioblastoma, respectively. The 5- and 10-year relative survival rates among children aged 0 to 14 years with anaplastic astrocytoma were 25.5% and 20.4%, respectively, and with glioblastoma were 20.7% and 17.1%, respectively. Median survival of 21 months and 9 months were reported for anaplastic astrocytoma and glioblastoma, respectively (4). The application reported that survival data from low- and middle-income countries were not available.

Benefits

High-grade glioma The HIT-HGG 2007 trial was a multicentre, prospective phase II clinical trial that aimed to demonstrate therapeutic non-inferiority between temozolomide radiochemotherapy versus cisplatinum-based radiochemotherapy in paediatric patients aged 3 to 18 years with high-grade gliomas (5). Between 2009 and 2016, 438 participants were enrolled to receive temozolomide combined with craniospinal irradiation, and 438 participants from the HIT-GMB-C/-D trial of cisplatinum-based radiochemotherapy served as historical controls. The results for 6-months event-free survival and overall survival indicated that the primary objective of non-inferiority was achieved. Subgroup analyses showed longer event-free survival in temozolomide-treated patients with pontine (8.2 months versus 6.2 months; $P = 0.008$) and non-pontine tumours (10.7 months versus 7.4 months; $P < 0.0001$). Overall survival was improved in temozolomide-treated patients with non-pontine tumours (median overall survival 19.3 months versus 16.2 months; $P = 0.018$), but not in those with pontine tumours (median overall survival 11.4 months versus 11.3 months; $P = 0.402$). The HIT-HGG 2013 trial is a multicentre, prospective, phase III trial that is investigating the effect of adding valproic acid to standard treatment with temozolomide radiochemotherapy in 198 paediatric patients aged 3 to 18 years with high-grade glioma (6). Results are not yet reported. Neuroblastoma A 2006 study described the antitumour effects of a 5-day course of irinotecan 50 mg/m2 per day (intravenous) plus temozolomide 150 mg/m2 per day (oral) every 3–4 weeks in 49 patients aged between 2 and 26 years with relapsed or refractory neuroblastoma (7). Nineteen patients were assessable for response of refractory disease. Of these, nine showed evidence of disease regression, including two complete responses and seven objective responses. Of 17 patients treated for progressive disease, three showed evidence of disease regression, including one partial response and two objective responses. A phase II study evaluated the response rate of irinotecan plus temozolomide in 55 children aged younger than 3 months to 18.5 years with relapsed or refractory neuroblastoma (8). Participants received irinotecan 10 mg/m2 per dose (intravenous) 5 days a week for 2 weeks plus temozolomide 100 mg/m2 per dose (oral) for 5 days every 3 weeks. Two strata of patients were defined, one that could be evaluated for response by cross-sectional imaging (stratum 1, $n = 28$) and the other that could be assessed by bone marrow aspirate/biopsy or metaiodobenzylguanidine scan only (stratum 2, $n = 27$). Participants who received at least two courses of treatment were considered suitable for evaluation of response. An objective response (complete response or partial response) was reported in 8/55 (14.5%) participants overall, 3/28 in stratum 1 (10.7%) and 5/27 (18.5%) in stratum 2. Stable disease was reported in 14/28 (50.0%) and 15/27 (55.5%) participants in stratums 1 and 2, respectively. A phase II study evaluated the objective response rate following two cycles of temozolomide in combination with topotecan (TOTEM regimen) in 38 children aged between 6 months and ≤ 20 years with relapsed or refractory neuroblastoma (9).

Participants received oral temozolomide 150 mg/m2 followed by intravenous topotecan 0.75 mg/m2 for 5 consecutive days every 28 days. The study endpoint was objective response rate defined as complete or partial response after two cycles of treatment. After two cycles, the estimated objective response rate was 18% (seven participants achieved a partial response, and no participants achieved a complete response). For the outcome of best response at any time of evaluation, the objective response rate was 24% (six participants achieved a partial response and three participants achieved a complete response). The estimated tumour control rate (combining complete, partial and mixed response and stable disease) was 79% (95% confidence interval (CI) 63% to 90%). With median follow-up of 28.5 months, median progression-free survival was 10.3 months (95% CI 6.4 to 17.8 months) and the 12-month progression-free survival rate was 45%. Median overall survival was 25.8 months (95% CI 11.3 to not estimated) and the 12-month overall survival rate was 58%. The application also described further studies in which temozolomide-based chemotherapy was used in combination with other therapies, e.g. temsirolimus, anti-GD2 monoclonal antibodies and bevacizumab (10–13). Ewing sarcoma A retrospective study reviewed efficacy and toxicity outcomes of irinotecan and temozolomide in adult and paediatric patients with relapsed Ewing sarcoma from electronic medical records in two institutions in Australia and Jordan (14). Records for 53 eligible patients were identified (16 paediatric and 37 adult), all of whom received temozolomide 100 mg/m2/day on days 1 to 5 of each treatment cycle. Additionally, 29 patients received irinotecan < 250 mg/m2/cycle and 24 patients received ≥ 250 mg/m2/cycle. Of 43 patients assessable for response, 12 (28%) achieved an objective response (one complete response, 11 partial responses), 19 (44%) had disease progression and 12 (28%) had stable disease. No significant differences were noted between age cohorts in the overall response rate (36% versus 25% for paediatric patients and adults, respectively; P = 0.47). For progression-free survival, 52 patients were assessable. Median progression-free survival was 3.8 months and the 6-month progression-free survival rate was 39%. Median progression-free survival was significantly longer in paediatric patients than in adults (7.4 months versus 2.2 months; P = 0.039). Another multicentre retrospective study analysed efficacy outcomes of irinotecan and temozolomide in adult (n = 34) and paediatric (n = 17) patients with recurrent Ewing sarcoma in Italy and the United Kingdom (15). Administered doses were temozolomide 100 mg/m2/day and irinotecan 40 mg/m2/day, on days 1–5 of each 21-day treatment cycle. An objective response was achieved by 17/51 (33%) patients (5 with complete response, 12 with partial response). No significant difference was seen in the objective response rate by age cohort. Median progression-free survival was 3.9 months and the 6-month progression-free survival rate was 49%, significantly influenced by Eastern Cooperative Oncology Group (ECOG) performance status and lactate dehydrogenase levels. The 1-year overall survival rate was 55%, with response to treatment and ECOG score being independent predictors of outcome. Another retrospective study evaluated the use of irinotecan and temozolomide in 20 patients with recurrent or progressive Ewing sarcoma at Memorial Sloan-Kettering Cancer Center in the United States of America (16). Of the 19 patients who could be evaluated, the objective response rate was 63% (five complete responses and seven partial responses). Progressive disease was reported in seven patients. After a median follow-up of 25.7 months, the median time to progression was 8.3 months overall and 16.2 months for patients with recurrent disease. Time to progression was better in patients with a sustained 2-year first remission and those with localized, rather than metastatic, disease. Other resistant or relapsed solid tumours An off-label, compassionate-use study in Italy evaluated the therapeutic activity and toxicity of temozolomide in 52 children with relapsed solid tumours 17 with neuroblastoma, eight with medulloblastoma, eight with brain stem glioma, six with neuroectodermal tumours, four with Ewing sarcoma, three with anaplastic astrocytoma, two with rhabdomyosarcoma, two with ependymoma, one with hepatocarcinoma and one with osteosarcoma (17). Temozolomide was administered at a dose of 180 mg/m²/day or 215 mg/m²/day 5 days, repeated every 21–28 days, in patients with prior craniospinal irradiation or who had relapsed after bone marrow transplantation and in patients without prior craniospinal irradiation, respectively. Twenty-seven patients were eligible for response evaluation after two courses. The objective response rate was 13.4% (one complete response, two partial responses and four minor responses). Stable disease was reported in 38.4% of patients, and 48.1% of patients had progressive disease. Median survival was 7.8 months and time to progression was 3.4 months. A multicentre retrospective review study investigated response rate and progression-free survival with temozolomide in combination with irinotecan and vincristine in the treatment of 19 patients aged 2–17 years with relapsed rhabdomyosarcoma (18). Administered doses were vincristine 1.5 mg/m2 intravenous on day 1, irinotecan 50 mg/m2 intravenous or 70−100 mg/m2 orally on days 1–5, and temozolomide 100–150 mg/m2 orally on days 1–5 every 21 days. Fifteen patients were evaluable for response. Four patients achieved stable disease, and 11 patients had progressive disease. No complete or partial responses were reported. The objective response rate was 26.7%. Progression-free survival at 3 months was 23%. Toxicity data were not collected.

Harms

In the HIT-HGG 2007 trial, the toxicity profile of temozolomide radiochemotherapy was considered favourable, with less toxicity observed in comparison with cisplatinum- or methotrexate-based radiochemotherapy protocols for high-grade glioma (5). Most adverse events ≥ grade 3 were haematological toxicity, hepatotoxicity and neurotoxicity. In the phase II study of temozolomide plus irinotecan in the treatment of relapsed or refractory neuroblastoma, grade 3 or 4 adverse events included haematological toxicity (neutropenia, thrombocytopenia and anaemia) reported in almost 50% of patients. Less than 10% of patients developed evidence of infection while neutropenic. Grades 3 or 4 fever and infection were reported in about 20% of all patients, while grade 3 or 4 diarrhoea were reported in about 5% of all patients (8). In the phase II study of temozolomide plus topotecan in the treatment of relapsed or refractory neuroblastoma, the most commonly reported adverse events were haematological toxicities, including grade 3 or 4 neutropenia and thrombocytopenia. Less than 10% of patients experienced febrile neutropenia (9). In studies of temozolomide plus irinotecan in the treatment of Ewing sarcoma, toxicities were similar to those seen in studies for neuroblastoma (14–16). In studies of temozolomide in other resistant or relapsed solid tumours, the most frequently reported toxicities were neutropenia and thrombocytopenia. Non-haematological adverse events were infrequent (17, 19).

Cost / cost effectiveness

No information on cost–effectiveness was presented in the application. The application presented limited information on the cost of temozolomide, irinotecan and topotecan in different settings.

WHO guidelines

WHO guidelines for the treatment of high-grade glioma, neuroblastoma, or Ewing sarcoma are not currently available.

Availability

Approved indications for temozolomide vary depending on jurisdiction. For example, in Europe, temozolomide has regulatory approval for use in children from the age of 3 years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy. In the United States, temozolomide is approved only for use in adults. Temozolomide is used off-label for the treatment of neuroblastoma, Ewing sarcoma and other paediatric solid tumours. Irinotecan and topotecan are used off-label for the indications proposed in the application. Temozolomide, irinotecan and topotecan are widely available as innovator and generic brands.

Other considerations

As part of the WHO paediatric drug optimization exercise for cancer medicines, temozolomide was included as one of six paediatric cancer medicines prioritized for development of an age-appropriate formulation for children. The exercise noted that paediatric dosages of temozolomide are typically achievable with the available range of capsule sizes without imposing a significant pill burden. However, it was noted that use could be limited by the inability of some children to swallow capsules whole. The recommendation of the paediatric drug optimization exercise was to investigate and develop a more age-appropriate formulation in a non-liquid oral dosage form, predominantly for use in the treatment of relapsed or refractory disease (20). The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of temozolomide on the EMLc for the proposed indications. It highlighted that overall survival data were only available from two studies in high-grade glioma, and thus the data are limited. Furthermore, the group judged that the benefits associated with oral administration of temozolomide in terms of feasibility and equity, including patient compliance and quality of life, would be likely to be offset by the increased risk of severe haematological toxicity and the need for monitoring of adverse events in the hospital. The technical team in cancer in the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed the application. The team commented that evidence supporting the efficacy of temozolomide as a single agent in proposed relapsed paediatric cancers was limited and that for newly diagnosed high-grade gliomas, inconsistencies in outcomes in different studies have been reported. Additionally, in heavily treated patients with refractory or relapsed solid tumours, treatment is associated with haematological toxicity requiring continuous laboratory monitoring of white blood cells which may not be feasible in resource-constrained settings. The technical team did not support the inclusion of temozolomide on the Model Lists at this time, suggesting that a decision could be deferred until more mature data become available.

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