Rasburicase

Essential medicine status

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.5. Supportive medicines

EMLc | ATC codes: V03AF07

Indication	Tumour lysis syndrome ICD11 code: 5C70
INN	Rasburicase
Medicine type	Biological agent
List type	Complementary (EML) (EMLc)
Formulations	Parenteral > General injections > IV: 1.5 mg in vial powder and solvent for solution ; 7.5 mg in vial powder and solvent for solution
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 supportive care
Wikipedia	Rasburicase
DrugBank	Rasburicase

Expert Committee recommendation

The Expert Committee acknowledged that tumour lysis syndrome is an oncological emergency for which prevention and treatment are critical to avoid severe acute kidney injury, which is resource-intensive to treat and may be fatal. The Committee noted that only allopurinol is currently included on the Model Lists for tumour lysis syndrome. Allopurinol, while inexpensive and administered orally, is only effective for the prevention of tumour lysis syndrome by inhibiting the formation of new uric acid; it does not eliminate already formed uric acid. It therefore takes several days to have an effect on uric acid levels. The Committee noted that allopurinol is associated with xanthinuria (deposition of xanthine crystals in the renal tubules and associated acute kidney injury), and can interact with several medicines, including chemotherapeutic agents, antibiotics and diuretics. The Committee noted that rasburicase, which is a recombinant version of urate oxidase, works by metabolizing uric acid to a more water-soluble metabolite. Rasburicase can markedly and rapidly decrease uric acid levels and prevent other complications of tumour lysis syndrome (such as end-stage renal failure and need for life-long dialysis). It therefore offers a significant advantage for the management of paediatric and adult patients at high risk of tumour lysis syndrome, especially those with impaired renal or cardiac function, and for patients with pre-existing hyperuricaemia. From the meta-analysis presented in the application, the Committee noted that rasburicase may halve the risk of laboratory tumour lysis syndrome compared with allopurinol. The Committee noted that rasburicase is well tolerated. However, it should not be given to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency because hydrogen peroxide, a by-product of uric acid breakdown, can cause severe haemolysis in these patients. Patients at risk of G6PD deficiency (e.g. prior medicine-induced haemolytic anaemia, ethnic background associated with high prevalence of G6PD deficiency) should be tested for G6PD deficiency, preferably before administration of rasburicase. The Committee noted that rasburicase is expensive, especially when used according to the dosage approved by the United States Food and Drug Administration and the European Medicines Agency, which is 0.2 mg/kg a day for up to 5 days. The Committee acknowledged

numerous experimental studies showing that a single dose of rasburicase is as effective in lowering uric acid levels as approved daily dosing of rasburicase for 5 days, and this dosing is associated with considerable cost savings. The Committee considered that the high cost of rasburicase could be reduced by using single-dose administration and using it only in selected high-risk patients. The Expert Committee therefore recommended inclusion of rasburicase on the complementary list of the EML and EMLc for the prevention and treatment of tumour lysis syndrome in high-risk patients. However, noting the high price of rasburicase, the Committee considered that the single-dose administration strategy for rasburicase is the preferred dosing option, based on evidence of similar response rates and greatly reduced costs.

Background

Rasburicase had not previously been considered for inclusion on the Model Lists. Allopurinol is currently included on the EMLc for the prevention and treatment of tumour lysis syndrome in children. It has not been considered for inclusion on the EML for treatment of adults for this indication.

Public health relevance

Tumour lysis syndrome is an oncological emergency characterized by a group of metabolic disturbances including hyperkalaemia, hyperphosphataemia, hypocalcaemia and hyperuricaemia. In particular, hyperuricaemia may lead to renal damage and end-stage renal failure. The exact incidence of tumour lysis syndrome is unknown since its frequency varies with the underlying malignancy and the specific definition used. Some definitions include only laboratory abnormalities such as plasma levels of potassium, phosphate, calcium or uric acid. Under these definitions, the incidence of laboratory abnormalities can be as high as 45% of patients as it has been observed in small cohorts of children with acute lymphoblastic leukaemia (1,2). In broader populations, however, the incidence of a laboratory tumour lysis syndrome has been estimated in around 10–15% of patients (3,4). Only a small proportion of patients with laboratory abnormalities ultimately develop clinical symptoms, such as nausea, muscle cramps, weakness or fatigue. The reported incidence of clinical tumour lysis syndrome is around 4–6% (3,5,6). Tumour lysis syndrome is far more frequent in haematological malignancies, although it has also been reported in solid tumours, especially in gastrointestinal and lung cancers (7). In general, the risk of tumour lysis syndrome is higher in cancers with a high proliferative rate and rapid response to therapy. Treating the complications of tumour lysis syndrome is very resource intensive, particularly for hyperuricaemia, which may lead to renal complications and the need for renal-replacement therapies. Therefore, in low- and middle-income settings, the use of rasburicase might result in net savings, especially with shortened regimens (8–10).

Benefits

The applicants conducted a literature search for randomized trials and systematic reviews of rasburicase and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool and judgements about the certainty of the evidence were made following the GRADE approach. Three systematic reviews (11–13) and two randomized trials were identified (14,15). One trial included 280 adults with leukaemia or lymphoma. Participants were randomized to rasburicase, allopurinol or a combination of rasburicase plus allopurinol. All the interventions were given for 5 days after receiving chemotherapy (15). The other trial included 52 children with leukaemia or lymphoma, who were randomized to rasburicase or allopurinol for 5 to 7 days, also after receiving chemotherapy (14). Both trials focused on uric acid levels and were not powered to detect differences in patient-relevant outcomes. In both trials, plasma uric acid levels decreased faster with rasburicase: 4 hours after the first dose, uric acid decreased by 86–88% with rasburicase compared with 12–14% with allopurinol. This finding reflects the mechanism of action of the drugs: rasburicase can effectively reduce uric acid levels, while allopurinol can only prevent the formation of new uric acid. Only one trial reported data to estimate the effect of rasburicase on the incidence of tumour lysis syndrome and patient-relevant outcomes (15). Compared with allopurinol, rasburicase may reduce the incidence of laboratory tumour lysis syndrome (risk ratio (RR) 0.51, 95% confidence interval (CI) 0.33 to 0.79; in absolute terms, 222 fewer events per 1000 patients, 95% CI 94 fewer to 301 fewer; very-low-certainty evidence). However, evidence of the effect of rasburicase on clinical tumour lysis syndrome or renal failure was less clear (RR 0.74, 95% CI 0.17 to 3.22 and RR 0.98, 95% CI 0.14 to 6.87, respectively; both very-low-certainty evidence).

Harms

Compared with allopurinol, rasburicase might increase the risk of adverse events (RR 3.96, 95% CI 0.45 to 34.7; in absolute terms,

33 more events per 1000, 95% CI 6 fewer to 371 more; very-low-certainty evidence). The events observed with rasburicase were mainly hypersensitivity reactions such as rash, arthralgia or injection-site irritation. They were generally mild and lead to a discontinuation of the drug in only one out of 92 participants (15).

Additional evidence

As regards dosage, a meta-analysis of 10 studies compared efficacy and cost-savings of a single-dose regimen of rasburicase (at doses ranging from 3 mg to 7.5 mg (fixed dose) or 0.05 mg/kg to 0.20 mg/kg (weight-based dose) versus the daily dosing of 0.2 mg/kg for 5 days approved by the United States Food and Drug Administration in adult patients with hyperuricaemia or at high risk of tumour lysis syndrome (16). There was no significant difference in response rates between the pooled single-dose rasburicase arm and the daily dose rasburicase arm (88.2% versus 90.2%; odds ratio (OR) 0.81, 95% CI 0.41 to 1.60). When only studies using single-dose rasburicase at standard doses (6–7.5 mg fixed dose or 0.15–0.20 mg/kg weight-based dose) were considered, the pooled response rate was 91.8%. Moreover, single dose administration of standard-dose rasburicase was associated with important cost savings. Wholesale drug acquisition prices for the different treatment regimens were about US$ 4500 for single standard-dose rasburicase versus about US$ 36 000 for daily-dose rasburicase. The use of rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to observations of severe haemolysis during clinical trials (17). Haemolytic anaemia is likely to occur in G6PD-deficient patients because of their inability to break down hydrogen peroxide, a by-product of the oxidation of uric acid. Testing to identify patients with G6PD deficiency is recommended before treatment with rasburicase. In emergency settings where G6PD deficiency cannot be determined, monitoring for signs and symptoms of haemolytic anaemia is recommended and supportive care (e.g. haemodialysis) must be available.

Cost / cost effectiveness

The applicants identified four studies: one cost–benefit analysis (18), two cost–effectiveness analyses (19,20) and one cost–consequence study (21). Three of the four studies identified were considered to have serious limitations and their results were judged unreliable (18,20,21). These studies did not use an appropriate mathematical model nor a probabilistic sensitivity analysis. In addition, they had several errors or omissions and some assumptions were not shown or were incorrect. Only one study, a cost–effectiveness study in China, had acceptable quality. It used a decision tree as the model method, from a perspective of the Chinese health care system (19). The study considered the use of rasburicase in the prevention and treatment paediatric patients with acute myeloid leukaemia, acute lymphoid leukaemia or non-Hodgkin lymphoma. The results suggested that rasburicase was cost-effective in most of the scenarios, with an incremental cos–effectiveness ratio between US$ 991 and US$ 2031 per quality-adjusted life year (QALY) as treatment and US$ 5391 and US$ 17 580 per QALY as prophylaxis.

WHO guidelines

WHO guidelines for the management of tumour lysis syndrome are not available.

Availability

Rasburicase has wide global marketing and regulatory approval.

Other considerations

The EML Cancer Medicines Working Group advised that it supported the inclusion of rasburicase on the EML and EMLc for the treatment and prevention of tumour lysis syndrome. The available evidence shows rasburicase to be more effective than allopurinol in reducing plasma uric acid levels, and it can be used for treatment as well as prevention of tumour lysis syndrome (allopurinol is used only for prevention). Evidence for benefit for clinical outcomes (e.g. mortality, renal failure) is less clear, but in this context the benefit of rasburicase is undisputed for reducing uric acid (e.g. a surrogate outcome considered reasonably likely based on therapeutic and pathophysiological evidence); to predict clinical benefit; and to avoid clinical sequalae. Treating tumour lysis syndrome once it occurs is very resource intensive so effective preventative measures are desirable. In terms of safety, of particular concern is the risk of severe haemolysis, and rasburicase should not be given to patients with G6PD deficiency. Thus, testing to identify patients with G6PD is required. In emergency settings, where G6PD deficiency cannot be determined, rasburicase should only be used when haemodialysis is available. Careful patient selection to limit the use of rasburicase to

patients most likely to benefit (e.g. at high risk of tumour lysis syndrome) and less likely to experience adverse effects (e.g. G6PD deficiency) will also be important at the country level. The Working Group acknowledged the high cost rasburicase, and also noted the potential for cost savings by using single-dose administration rather than daily dose administration over several days, without significantly compromising benefit. Comments were received from the WHO Department of Noncommunicable Diseases, which supported the inclusion of rasburicase on the Model Lists as it offers significant clinical value in all settings, has broad population value (about 5% of cancer patients) and has been well validated. The use of rasburicase is particularly relevant in countries where late diagnosis and greater tumour burden might increase the likelihood of tumour lysis syndrome. It will be necessary to consider issues related to safety (capacity to manage toxicities of rasburicase) and strategies to improve accessibility (e.g. dosing frequency).

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