Clinical Commissioning Policy
Glucarpidase for the urgent treatment of methotrexate - induced renal dysfunction

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Commissioning position

Summary

NHS England will commission glucarpidase for the urgent treatment of methotrexate-induced renal dysfunction in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

Plain language summary

About methotrexate-induced renal dysfunction

Methotrexate is an antifolate drug that is used alone or in combination with other drugs to treat a variety of cancers and autoimmune conditions (e.g. rheumatoid arthritis). It is administered over a wide dose range, which can be as low as 20 mg/m^2 (milligrams per square metre) for maintenance therapy or between 1gm^2 and 12g/m^2 (grams per square metre) when used as high dose therapy.

Acute renal dysfunction is a life-threatening complication that is caused by the precipitation of methotrexate, and its metabolites, in the renal tubules. Renal dysfunction delays the renal clearance of methotrexate, leading to elevated plasma concentrations of the drug and the potential for additional methotrexate toxicities including myelosuppression, mucositis, hepatitis, and dermatitis.

About current treatment

Patients receiving high-dose methotrexate therapy are treated with aggressive hydration and alkalinisation to improve the solubility of methotrexate, and with calcium folinate, a folate that can counteract the adverse effects of methotrexate. With this regimen, in combination with close patient monitoring, the incidence of methotrexate nephrotoxicity decreases from about 10% to approximately 1% to 2%. Despite the reduced incidence of methotrexate-induced toxicity, cases of severe and fatal nephrotoxicity still occur.

Glucarpidase is an orphan medicine, not licensed in the UK. It was licensed in the US in early 2012 for the treatment of patients with toxic levels of methotrexate in their blood due to kidney failure. Glucarpidase reduces methotrexate levels by >98% within 15 minutes of administration. It is a recombinant form of the bacterial enzyme carboxypeptidase G2 and works by rapidly hydrolysing methotrexate into inactive non cytotoxic metabolites. These are not eliminated by the kidney, providing an alternative clearance route in patients who have acute kidney injury and delayed renal elimination.

Glucarpidase is intended for use by paediatric and adult oncology and haematology consultants for treating children and adults receiving high-dose methotrexate chemotherapy who develop a significant deterioration in renal function after the start of the high dose methotrexate, have toxic plasma methotrexate levels and are at risk of life-threatening methotrexate-induced toxicities. It is very unlikely that in any given year glucarpidase will be used for more than 20 patients. However, when it is required, it is needed urgently without time to seek funding approval through the Individual Funding Request route. Determining a national commissioning position in advance of its use would allow clinicians to manage patients appropriately in full knowledge of funding streams

What we have decided

NHS England has carefully reviewed the evidence to treat methotrexate-induced renal dysfunction with Glucarpidase. We have concluded that there is enough evidence to make the treatment available at this time.

Epidemiology and needs assessment

Current usage data suggests demand for this product will be very low in the region of 5 to 10 patients a year (adults/paediatrics).

Glucarpidase is needed for use by paediatric and adult oncology / haematology patients who develop a significant deterioration in renal function after the start of high dose methotrexate, have toxic plasma methotrexate levels and are at risk of life-threatening methotrexate-induced toxicities.

Evidence summary

NHS England has concluded that there is sufficient evidence to support a proposition for the routine commissioning of this treatment for the indication.

A number of uncontrolled phase II single arm studies and case reports have been published previously (1-3). However, more recently a pooled analysis of efficacy data from four multicentre single-arm compassionate-use clinical trials using protocols from 1993 to 2007 was published (4).

Of 476 patients with renal toxicity and delayed methotrexate elimination who were treated with intravenous glucarpidase for rescue after high-dose methotrexate, 169 patients had at least one preglucarpidase (baseline) plasma methotrexate concentration greater than 1 micromol/L and one postglucarpidase methotrexate concentration measurement by high-performance liquid chromatography and were

included in the efficacy analysis; renal recovery was assessed in 436 patients who had at least one recorded preglucarpidase and postglucarpidase serum creatinine concentration measurement.

Efficacy was defined as rapid and sustained clinically important reduction (RSCIR) in plasma methotrexate concentration, with a concentration of 1 micromol/L or lower at all postglucarpidase determinations. Median age of efficacy-evaluable patients was 20 years (range 5 weeks-84 years). Osteosarcoma (36%), non-Hodgkin lymphoma (27%), and acute lymphoblastic leukaemia (20%) were the most frequent underlying diagnoses. Median preglucarpidase serum methotrexate was 11.7 micromol/L. At the first (median 15 minutes) through the last (median 40 hours) postglucarpidase measurement, plasma methotrexate concentrations demonstrated consistent 99% median reduction. RSCIR was achieved by 83 (59%) of 140 patients. A total of 64% of patients with renal impairment greater than or equal to Common Terminology Criteria for Adverse Events grade 2 recovered to grade 0 or 1 at a median of 12.5 days after glucarpidase administration.

The authors concluded that Glucarpidase caused a clinically important 99% or greater sustained reduction of serum methotrexate levels and provided noninvasive rescue from methotrexate toxicity in renally impaired patients.

Paediatric patients

Experience with glucarpidase in children has been published in abstract (5). From November 1993 through June 2009, 232 paediatric patients experiencing renal toxicity and delayed elimination of methotrexate (methotrexate) were treated with glucarpidase (50 units/kg intravenously) in compassionate use trials conducted in the United States and Europe.

Of the 232 paediatric patients, 89 were < 12 years; the youngest was 5 weeks. Fifty-four percent were male. Forty-seven percent were treated for osteogenic sarcoma, 31% for ALL, 18% for non-Hodgkin lymphoma, and 4% for other malignancies. The median pre-glucarpidase methotrexate concentration was 34 micromol/L. Seventy percent of patients received a single dose of glucarpidase, 28% received 2 doses, and 2% received 3 doses.

Sixty-seven patients had methotrexate concentrations determined by central laboratory HPLC assay. At the first measurement (median 15 minutes postglucarpidase; range: 10 - 30 minutes) serum methotrexate concentration was reduced by ≥ 95% in 91% of patients. Eighty-four percent of patients had a ≥ 95% reduction at the last measurement (median 48 hours post-glucarpidase).

In the 201 patients with pre-glucarpidase renal impairment measured as NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or higher, 75% recovered to Grade 0 or 1 after a median of 10 days post-glucarpidase. Glucarpidase was well-tolerated overall, but side effects included paraesthesia (2.2%), flushing (1.7%), headache (1.3%), burning sensation (1.3%), and feeling hot (1.3%). Thirteen patients died during the follow-up period of causes unrelated to glucarpidase, as judged by the treating physician.

Glucarpidase is the treatment recommendation within the UKALL2011 (trial for acute lymphoblastic leukaemia and lymphoma (EudraCT no. 2010-020924-22)) when a child has: raised Methotrexate levels at specified time points post high dose Methotrexate infusion, serum creatinine rises >100% within 24 hours of infusion, delayed excretion when plasma methotrexate levels plateau.

Alternative treatments

There are no other drugs currently used for the same indication. Haemodialysis is a possible option if renal failure occurs. However, this must be repeated continuously

or daily, in order to reduce the methotrexate level to non-toxic concentrations.

The use and efficacy of dialysis-based methods of methotrexate removal in patients with HD- methotrexate-induced renal dysfunction has been reviewed (6). The review included 49 patients from 30 publications. The most frequently used single methods reviewed were haemodialysis (n=10), high-flux haemodialysis (n=9) and charcoal haemoperfusion or charcoal haemofiltration (n = 7) with 16 patients treated with multiple modalities. Dialysis-based methods were used for up to 14 days. Peritoneal dialysis alone resulted in only a minimal decrease in plasma methotrexate concentrations. The use of other single-modality methods of methotrexate removal resulted in a median decrease in plasma methotrexate concentration of 52% (range, 26 - 82%). High-flux haemodialysis resulted in the greatest decrease in plasma methotrexate concentrations (median 75.5%; range 42 - 94%) within the shortest period of time (median 4 hours; range 4 - 12 hours). Only 3 patients had a > 90% decrease in methotrexate concentration with the use of single method in one dialysis session. However a major limitation on the use of dialysis-based methods is the marked rebound in plasma methotrexate concentrations that can occur when the dialysis is stopped. Rebound increases in the post-dialysis plasma methotrexate concentration were in the range of 10 - 221% of the post-procedure methotrexate level and 90 - 100% of the pre-procedure methotrexate level.

Implementation Criteria

Before patients receive high-dose methotrexate, there should be formal checks to ensure the patient has normal renal function and there is good hydration / alkalinisation of urine. Before using glucarpidase, all other supportive measures must have been optimised, such as use of fluids and calcium folinate.

Glucarpidase will be routinely funded for the treatment of adults and children receiving high-dose methotrexate chemotherapy (doses > 1g/m^2) who develop a significant deterioration in renal function after the start of the high dose methotrexate, have toxic plasma methotrexate levels and, despite rescue measures, are at risk of life-threatening methotrexate induced toxicities.

A significant deterioration in renal function is regarded as a serum creatinine that is at least 1.5 times baseline and rising, or the presence of oliguria.

Defining a toxic methotrexate level is complicated by the regimen used and the time at which the level is tested. However, patients must have a dangerously high blood methotrexate level that is elevated relative to the expected level at that time point despite all standard rescue measures or renal function is decreasing. For children refer to paediatric specific chemotherapy protocol.

Dose

The recommended dose and schedule for glucarpidase is as a single intravenous injection of 50 units/kg. Multiple doses are not permitted under this policy.

Patient pathway

Glucarpidase has been used in NHS England to urgently treat toxic methotrexate levels that have occurred during cancer chemotherapy. It may be used in any patient receiving high-dose methotrexate therapy who develops significant renal dysfunction, has a toxic level of methotrexate and who is at risk of life-threatening complications.

Governance arrangements

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is

prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Methotrexate chemotherapy is funded by NHS England.

Glucarpidase for the urgent treatment of methotrexate-induced renal dysfunction is commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of specialised services in line with this Clinical Commissioning Policy

Audit requirements

Collation of patient details and outcome by Acute Trust and reported to the NHS England Area Team.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

References

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