Clinical Commissioning Urgent Policy Statement: Uridine triacetate for the treatment of patients exhibiting early-onset severe toxicities following 5-fluorouracil or capecitabine administration (all ages) [URN: 1929]

Commissioning Position

Summary

Uridine triacetate is recommended as a treatment option through routine commissioning for the treatment of patients exhibiting early-onset severe toxicities following 5-fluorouracil or capecitabine administration within the criteria set out in this document.

Information about Uridine Triacetate

The intervention

Uridine triacetate is an oral medicine used to treat people at risk of serious toxicity or overdose following administration of chemotherapy agents 5-fluorouracil and capecitabine. The medicine is usually given within 96 hours of treatment with either 5-fluorouracil or capecitabine and works by inhibiting cell death and damage caused by these chemotherapy medicines.

Uridine triacetate is approved by the Food and Drug Administration (FDA) authority in the United States of America (USA) for treatment of serious toxicity or overdose following administration of 5-fluorouracil or capecitabine. However, the treatment is not licensed in either the United Kingdom (UK) or the European Union. As of 2019, there is an agreed supply of the medicine into England intended for use in this indication.

Committee discussion

This was considered by the Clinical Panel as an urgent policy request. It was agreed that this did meet the criteria. The three evidence papers were considered and it was agreed to the policy would proceed based on these.

The condition

5-fluorouracil (also referred to as 5-FU) and capecitabine are a group of chemotherapy medicines, known as fluoropyrimidines, used as part of the treatment of various cancers including: (i) colorectal cancer; (ii) oesophago-gastric cancer; (iii) breast cancer; and (iv) cancers of the head and neck region. 5-Fluorouracil is administered intravenously (i.e. into the veins) and capecitabine is taken orally, however, both medicines work by stopping DNA replication which inhibits cancer cell growth.

It is common for people receiving these drugs to experience side effects (toxicity). Most people experience minor side effects (e.g. fatigue, diarrhoea, nausea, loss of appetite) and these can usually be managed at home with supportive medicines. However, some people receiving treatment with 5-fluorouracil or capecitabine will experience more severe side effects which require hospital admission and, in some situations, can be life threatening. The side effects include:

- Myelosuppression (Increased risk of infection and bleeding)
- Severe diarrhoea
- Severe mucositis (sore mouth meaning patients cannot swallow)
- Severe nausea or vomiting
- Severe skin reactions

It is estimated that between 10-30% of people receiving these drugs experience severe side effects (Henricks et al, 2018; Cancer Research UK, 2020), equating to approximately 2,000 patients per year, however, not all patients will require treatment with uridine triacetate. Although the exact number of patients is difficult to predict, clinical consensus estimates that around 50 patients per annum could be eligible for treatment with uridine triacetate as per the criteria set out in this document.

One of the main causes of severe toxicity following 5-fluorouracil or capecitabine administration is a genetic variation in the dihydropyrimidine dehydrogenase (DPYD) enzyme. The DPYD enzyme helps metabolise (break down) 5-fluorouracil/capecitabine in the body and without it, or at low levels, these chemotherapy medicines can build up in the body.

Tests for DPYD are available and a review is currently underway (January 2020) to determine whether all patients receiving NHS treatment should be tested routinely. However even with testing there will still be a very small group of patients who develop severe and life-threatening side effects due to other genetic enzyme variations.

Current treatments

For people experiencing severe side effects following 5-fluorouracil or capecitabine administration, current treatments are aimed at lessening or treating the side effects of these medicines, referred to as supportive care.

Treatment for severe toxicity may include but is not limited to:

- Intravenous hydration and intravenous administration of nutrition (parenteral nutrition);
- Antibiotic treatment;
- Blood or platelet transfusion; and
- Medication to increase white cell counts (growth factor treatment).

Comparators

Current standard treatment is supportive care.

Clinical trial evidence

NHS England considered the study by Ma et al (2017), submitted as part of the preliminary policy proposal, to establish the clinical commissioning policy statement. This is summarised below.

Ma et al (2017) reported the findings from two open-labelled clinical studies of patients treated with uridine triacetate who presented with a 5-FU/capecitabine overdose or an early onset of severe toxicities. The patients received uridine triacetate as soon as possible (most within the first 96 hours after 5-FU/capecitabine). Outcomes included survival, resumption of chemotherapy, and safety. Their survival was compared with the survival of a historical cohort of overdose patients who received only supportive care. These patients were identified from a review of the available literature, published medicolegal cases, the FDA's Manufacturer's and User Facility Device Experience database, the FDA's Adverse Event Databases, the FDA's Medical Product Safety Network and reports from the Institute of Safe Medication Practices.

A total of 137 of 142 overdose patients (96%) treated with uridine triacetate survived and had a rapid reversal of severe acute cardiotoxicity and neurotoxicity; in addition, mucositis and leukopenia were prevented, or the patients recovered from them. In the historical

cohort, 21 of 25 patients (84%) died. Among the 141 uridine triacetate treated overdose patients with a diagnosis of cancer (the noncancer patients included 6 intentional or accidental paediatric overdoses), 53 resumed chemotherapy in<30 days (median time after 5-FU, 19.6 days), and this indicated a rapid recovery from toxicity.

Adverse events

Adverse reactions in patients receiving uridine triacetate included vomiting (8.1%), nausea (4.6%), and diarrhoea (3.5%).

Implementation

Inclusion Criteria

The following criteria must be met for patients exhibiting early onset, severe or life-threatening adverse events:

1. Severe or life-threatening adverse events must occur following the end of fluorouracil infusion or last administration of capecitabine;
2. Patients must be on their first cycle of treatment with either fluorouracil or capecitabine; and
3. Adverse events must be deemed severe/life threatening by a clinician experienced in fluoropyrimidine prescribing.

Adverse events indicating treatment with uridine triacetate should be graded Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 and occur in combination. These include, but are not limited to:

- Grade 3 mucositis
- Grade 3 palmar-plantar erythema
- Grade 3 diarrhoea
- Grade 3 myelosuppression.

In rare cases, uridine triacetate may be prescribed in the event of a known overdose or pump malfunction where severe or life-threatening adverse events are likely.

Exclusion Criteria

1. Non-emergency treatment of adverse reactions associated with fluoropyrimidine chemotherapy
2. Treatment should not commence any earlier than 3 hours after administration of the dose of the fluoropyrimidine chemotherapy
3. Severe or life-threatening adverse events occurring >96 hours following the end of fluorouracil infusion or last administration of capecitabine
4. Patients not on their first cycle of treatment with either fluorouracil or capecitabine.

Dose

Adults

- 10g orally every 6 hours for 20 doses.

Children

- 6.2g/m^2 of body surface (not to exceed 10g per dose) orally every 6 hours for 20 doses.

Treatment with uridine triacetate must be given within 96 hours of development of toxicity or within 96 hours of known overdose as defined above.

Effective from

This policy is effective from March 2020.

Recommendations for data collection

Registry to record rates of severe toxicity and numbers of patients accessing treatment.

Mechanism for funding

Treatment will be funded by Regional Commissioning Teams through established funding processes.

Policy review date

This is an urgent policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. 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.

Links to other Policies

Not applicable.

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

Definitions

Term	Definition
Common Terminology Criteria for Adverse Events (CTCAE)	A grading system use to group adverse effects (side effects) by severity – beginning at 1, mild/minimal symptoms not impacting on activities of daily living, up to 5 which is death resulting from treatment
Mucositis	A condition in which your mouth or gut is sore and inflamed. It's a common side effect of chemotherapy and radiotherapy for cancer. It can cause mouth ulcers (known as oral mucositis) which makes chewing and swallowing painful, or the condition can manifest itself in the digestive gut which can cause diarrhoea.
Myelosuppression	Decrease in the production of cells responsible for providing immunity, carrying oxygen, and those responsible for normal blood clotting
Palmar-plantar erythema	A skin reaction that occurs when a small amount of the medication leaks out of capillaries (small blood vessels),

	usually on the palms of the hands and soles of the feet. When the medication leaks out of the capillaries, it can damage the surrounding tissues. It is also referred to as hand-foot syndrome (HFS).
Parenteral nutrition	Artificial nutrition given through a vein. This is used when a patient in unlikely to absorb nutrition taken orally or through a feeding tube

References

CancerResearchUk.org. (2020). *DPD deficiency. Cancer Research UK*. [online] Available at: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/chemotherapy/side-effects/dpd-deficiency [Accessed January 2020].

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Ma W, Saif M, El-Rayes B, Fakih M, Cartwright T, Posey J, King T, von Borstel R and Bamat M. (2017). Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. Cancer, 123(2), pp.345-356.