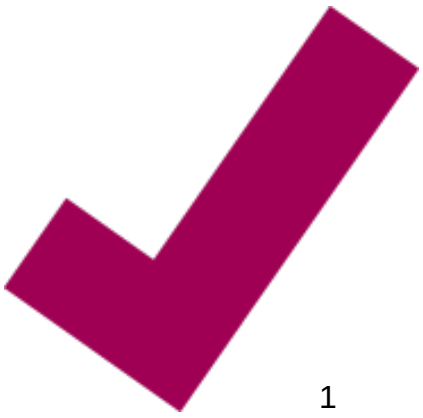
Clinical Commissioning Policy Proposition: Dexrazoxane for preventing cardiotoxicity in children and young people (< 25 years) receiving high-dose anthracyclines or related drugs for the treatment of cancer

Reference: NHS England 1825



Prepared by NHS England Specialised Services Clinical Reference Group for Children and Young People's Cancer

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1 Executive Summary

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

Plain Language Summary

About cancer in children and young people

Cancer in children and young people is rare. In the UK, approximately 1,600 children (up to the age of 15 years) and 2,200 teenagers and young adults (aged between 15 – 24 years of age) are diagnosed with cancer every year (Children's Cancer and Leukaemia Group, 2014).

The types of cancers affecting children and young people are different to those that affect adults; these cancers tend to occur in different parts of the body to adult cancers and respond differently to treatment. The most common cancers affecting children and young people are cancers of the blood, such as leukaemia, and lymphoma.

About current treatments

Treatment for children and young people with cancer depends on the type of cancer. Common treatments include surgery, chemotherapy and radiotherapy, which may be given in combination.

Treatment with chemotherapy is intensive and can include multiple medicines. Anthracyclines are a group of chemotherapy medicines that work by stopping cancer cells from replicating. This group of medicines are commonly used to treat children and young people with leukaemia or lymphoma.

Despite these medicines achieving high cure rates (almost 80%) they can cause long-term side effects including damage to the heart, known as cardiotoxicity. This damage means that the heart becomes weaker and is not as efficient at pumping blood around the body. These effects may not be seen for some time after treatment finishes.

About the new treatment

This policy proposition outlines the use of dexrazoxane to prevent cardiotoxicity in children and young people aged under 25 years where it is planned for them to receive high-dose anthracyclines for cancer. Dexrazoxane belongs to a group of medicines which protect the heart from damage. Dexrazoxane is a cytotoxic drug, i.e. it is toxic to living cells. It is unlicensed in the treatment of children and young people receiving anthracycline-based chemotherapy. This policy proposition for the use of dexrazoxane treatment, as outlined above, is not specific to a particular disease or tumour group.

What we have decided

NHS England has carefully reviewed the evidence to treat cardiotoxicity in children and young people where it is planned for them to receive high-dose anthracyclines or related drugs for the treatment of cancer with dexrazoxane, either as a front line-treatment or combined with other treatments**.** We have concluded that there is enough evidence to consider making the treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission dexrazoxane for preventing cardiotoxicity in children and young people (< 25 years) where it is planned for them to receive high-dose anthracyclines or related drugs for the treatment of cancer.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether dexrazoxane for preventing cardiotoxicity in children and young people (where it is planned for them to receive high-dose anthracyclines or related drugs for the treatment of cancer) will be routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

2 Proposed Intervention and Clinical Indication

Clinical indication

Anthracyclines (such as doxorubicin, daunorubicin, epirubicin and idarubicin) and related drugs (e.g. mitoxantrone and pixantrone) are chemotherapy agents used to treat cancer in adults and children. However, their use is limited because they can cause damage to the heart (cardiotoxicity), especially at higher doses. This damage to the heart may eventually lead to irreversible heart failure.

Damage to the heart associated with anthracycline therapy can be classified as early or late cardiotoxicity. Early cardiotoxicity develops during anthracycline therapy or in the first year after finishing treatment. Late cardiotoxicity only becomes apparent at least 1 year after finishing anthracycline therapy. The risk of

developing heart failure remains a lifelong threat, especially to children who have a long life-expectancy after successful treatment for cancer (van Dalen et al. 2011).

Most paediatric cancer treatment protocols avoid high cumulative doses of anthracyclines. However, a small number of children with cancer do require high cumulative doses of anthracycline. These children have poor survival outcomes, high-risk disease and are at high-risk of acute anthracycline cardiotoxicity.

Around 1 in 10 childhood cancer survivors who receive an anthracycline develop a symptomatic cardiac event over time. People treated with a cumulative anthracycline dose of 300 mg/m^2 doxorubicin or equivalent are 23 times more likely to develop cardiac dysfunction (abnormality or impairment of the heart) compared to people who are not treated. Cardiovascular disease is the leading cause of non-cancer-related morbidity and mortality in people who survive childhood cancer (Shaikh et al. 2016).

<u>Proposed intervention</u>

Dexrazoxane belongs to a group of medicines which protect the heart from damage. It is administered by a short intravenous infusion (15 minutes), approximately 30 minutes prior to anthracycline administration.

Dexrazoxane is unlicensed in the treatment of children and young people aged under 25 years where it is planned for them to receive high-dose anthracyclines or related drugs (doxorubicin 300 mg/m^2 or more or an equivalent dose of another anthracycline) for children and young people with cancer. Dexrazoxane is not contraindicated in this population.

Dexrazoxane is contraindicated in children and young people aged 18 years and under who expect to receive a cumulative dose of less than 300 mg/m^2 of doxorubicin (or the equivalent cumulative dose of another anthracycline).

It is important to note that there is a dexrazoxane preparation licensed for the treatment of extravasation (leakage from a vein into surrounding tissue): this treatment is excluded from this policy.

3 Definitions

Anthracycline	A type of chemotherapy used to treat cancer.
Cardiotoxicity	Damage to the heart.
Second malignant neoplasm	A histologically distinct second cancer that develops after the first.
Sub-clinical cardiotoxicity	Asymptomatic changes in echocardiographic measures beyond specified thresholds (for example, a decline in ejection fraction to <50% shortening fraction to <28%, or a decrease of ≥10% from baseline). [definition used in Shaikh et al. 2016]
Troponin-T	A protein released when cardiac muscle is damaged which is a marker of cardiac damage.

4 Aims and Objectives

This policy proposition considered: Dexrazoxane to treat cardiotoxicity in children and young people where it is planned for them to receive high-dose anthracyclines or related drugs for the treatment of cancer.

The objectives were to: establish, via an evidence review, the following information:

- Safety and effectiveness of the treatment;
- Cost effectiveness of treatment; and
- Identification of sub-groups and clinical criteria.

5 Epidemiology and Needs Assessment

Cancer in children and young people is rare. In the UK, approximately 1,600 children (up to the age of 15 years) and 2,200 teenagers and young adults (aged

between 15 – 24 years of age) are diagnosed with cancer every year (Children's Cancer and Leukaemia Group, 2014). The spectrum of cancers affecting children and young people is vast, however, the most common cancers are cancers of the blood such as leukaemia and lymphoma.

Children and young people with either acute myeloid leukaemia (AML) or bone sarcomas are most likely to be in the cohort of patients that would receive dexrazoxane. A 2012 National Cancer Intelligence Network (NCIN) report on childhood tumours registered with children's cancer and leukaemia groups between 1977-2011 (for children aged under 15) showed an average (mean) of 88 AMLs a year, and an average (mean) of 20 bone cancers each year. Both AML and bone cancers are more numerous in teenagers and young adults aged 16-24 years than those aged less than 15 years (Office of National Statistics, 2017, as cited by Cancer Research UK).

The Policy Working Group estimate that, based on this information, at least 108 children and young people a year may be eligible for dexrazoxane. However, because this policy proposition for the use of dexrazoxane treatment is not specific to a particular disease or tumour group, the actual number of eligible children and young people who may receive high-dose anthracyclines for all diseases and tumour groups may be higher.

6 Evidence Base

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

This review considers the evidence for using dexrazoxane to prevent cardiotoxicity in people aged under 25 years where it is planned for them to receive anthracyclines (cumulative dose of doxorubicin 300 mg/m^2 or more or an equivalent dose of another anthracycline) for cancer.

Anthracyclines (for example, doxorubicin and daunorubicin) are effective chemotherapy medicines for cancer in adults and children and young people. However, their use is limited because they can damage the heart, especially at higher doses. Most paediatric cancer treatment protocols avoid high cumulative doses of anthracyclines; however, a small number of children and young people do need high doses of anthracycline and are therefore at increased risk of cardiotoxicity. Over time, around 1 in 10 childhood cancer survivors who received an anthracycline have a symptomatic cardiac event (Shaikh et al. 2016).

It is unclear how anthracyclines damage the heart, and how dexrazoxane might prevent this damage. Anthracyclines form complexes with heavy metals, particularly iron, producing free radicals that can damage heart cells. Dexrazoxane also bonds with metals, which can prevent the formation of anthracycline and heavy metal complexes and harmful free radicals. This may be how it prevents the heart being damaged.

Using dexrazoxane to prevent cardiotoxicity in people aged under 25 years is controversial. In 2011, the European Medicines Agency (EMA) reviewed dexrazoxane (EMA: dexrazoxane 2011), noting the limited efficacy data in children, and the results of 2 studies that reported an increased risk of second malignant neoplasms (a new primary cancer in a person who has had cancer in the past) in children treated with the medicine. Following this review, dexrazoxane was contraindicated in children and young people aged under 18 years. The EMA reviewed dexrazoxane again in 2017 (EMA: dexrazoxane 2017). This new review concluded that dexrazoxane can improve surrogate cardiac markers (scan results or laboratory measures suggesting how well the heart is working, which may or may not be related to actual clinical outcomes, such as heart attacks or heart failure) and did not appear to affect survival in children with second malignant neoplasms. Following this review, the contraindication was removed for people aged under 18 years who were receiving a cumulative dose of doxorubicin of 300 mg/m2 or more (or equivalent anthracycline).

This evidence review includes a systematic review and meta-analysis of five randomised controlled trials (RCTs) and 12 non-randomised trials (Shaikh et al. 2016). One of the RCTs was only available in abstract form at the time of the Shaikh systematic review; therefore, extra outcomes from the fully published study (Asselin et al. 2016) are also included, as are longer-term mortality data from a follow-up study of three of the RCTs in the Shaikh systematic review (Chow et al. 2015).

Dexrazoxane did not reduce the rates of clinical cardiotoxicity (for example, heart failure, heart transplant or death because of a heart problem) in children and young people compared with no dexrazoxane in the five RCTs included in the systematic review. However, it should be noted that the rates of clinical cardiotoxicity were low across the RCTs, with only three cases reported. Heart failure develops over a much longer time in children and young people compared with adults receiving cancer treatment, meaning a very long follow-up would be needed to see a clinically significant difference in symptomatic heart failure.

The systematic review and additional RCT assessed surrogate markers for cardiac damage, as well as actual clinical outcomes such as heart failure. For example, troponin release after anthracycline-based chemotherapy has a correlation with statistically significant decrease in left ventricular function (Cardinale et al, 2000; Cardinale et al., 2006). Children and young people treated with dexrazoxane were significantly less likely to have raised troponin-T (a surrogate marker, high levels of which suggest the heart muscle is damaged). They also had less reduction in left ventricular fractional shortening and a better left ventricular thickness-to-dimension ratio (measures of the heart's ability to pump blood around the body). While fractional shortening is a direct measure of heart function, troponin release and left ventricular thickness-to-dimension ratio are surrogate cardiac markers and it is unclear whether they predict either long-term cardiac dysfunction (abnormality or impairment of the heart) or heart failure; therefore, these results cannot reliably be used to determine the long-term cardioprotective effect of dexrazoxane.

There was no statistically significant increase in the rate of second malignant neoplasms up to around 10 years after treatment with dexrazoxane in the systematic review. Higher rates of second malignant neoplasms seen in children treated with dexrazoxane in individual RCTs may be because of an increased risk of second malignant neoplasms when dexrazoxane is used in combination with other cancer treatments. The long-term risk of second malignant neoplasms in children treated with dexrazoxane is not currently known.

Up to a 12-year follow-up, dexrazoxane did not have a detrimental impact on overall survival, event-free survival or disease progression in children and young people receiving anthracycline-based chemotherapy in the studies included in this review. However, the impact of dexrazoxane on these outcomes in the longer-term is not currently known.

Adverse events were reported in one RCT included in this review. Grade 3 and 4 toxicities (severe, life-threatening or disabling adverse events) reported in people treated with dexrazoxane included infection, haematological effects (conditions affecting the blood), mucositis (painful inflammation and ulceration of the mucous membranes lining the digestive tract) and central nervous system (brain and spinal cord) events. Other adverse events listed in the SmPC as being very common (occurring in 1/10 people or more) for dexrazoxane include nausea, vomiting and alopecia.

7 Proposed Criteria for Commissioning

NHS England will commission dexrazoxane to prevent cardiotoxicity in children and young people in accordance with the criteria outlined in this document.

Inclusion criteria

Dexrazoxane to prevent cardiotoxicity must be considered in all children and young people aged under 25 years where it is planned for them to receive anthracyclines with a cumulative dose of doxorubicin 300 mg/m^2 or more or an

equivalent dose of another anthracycline for cancer either as a front line-treatment or combined with other treatments. The cumulative dose refers to when it is planned that the doxorubicin dose will meet or exceed 300 mg/m^2 over the entire lifetime of current or primary treatment regime.

The use of dexrazoxane is not specific to a particular disease or tumour group.

Starting criteria

Approval for use of dexrazoxane for each patient will require a multi-disciplinary team (MDT) discussion. Equivalence and conversion of related drugs (such as mitoxantrone and pixantrone) should be considered as part of the treatment planning process.

Dexrazoxane dose should be that equal to 10 times the doxorubicin-equivalent dose. The Medicines and Healthcare products Regulatory Agency (MHRA) summary of product characteristics (SmPC) contains advice on dosing in renal impairment and further information.

When deciding whether to use dexrazoxane prescribers should consider the short- and long-term risks associated with this product (e.g. myelosuppression – bone marrow suppression), alongside possible benefits in relation to protection of the heart. At higher doses of chemotherapy, where the dexrazoxane dose exceeds 1000 mg/m2, myelosuppression may increase significantly as outlined in the SmPC. The consent for treatment must include any proposed dexrazoxane and its associated side effects.

Treatment pathways and decision-making will adhere to guidance in the relevant children and young people's NHS England cancer service specification(s) and NHS England policy on Commissioning Medicines for Children in Specialised Services.

Duration of anthracycline infusion

Due to the short half-life of dexrazoxane, the anthracycline must be given alongside dexrazoxane over a period of one hour or less.

Stopping criteria

There are no specific criteria relating to treatment cessation for dexrazoxane in this population group. See MHRA SmPC for further details on adverse events.

Exclusion criteria

Use of dexrazoxane is unsuitable in children and young people (please refer to the MHRA SmPC for latest guidance):

- Where it is planned for them to receive a cumulative dose of doxorubicin < 300 mg/m^2 or an equivalent dose of another anthracycline.
- With hypersensitivity to dexrazoxane.
- Where the child or young person is breastfeeding their own child.
- Receiving concomitant vaccination with yellow fever vaccine.
- Who require continuous infusion of anthracyclines over a period of longer than one hour.

8 Proposed Patient Pathway

Children and young people with cancer may be treated in either a Children's Cancer Principal Treatment Centre, a Paediatric Oncology Shared Care Unit (POSCU), a Teenage and Young Adult (TYA) Principal Treatment Centre and/or a TYA Designated Hospital, using pathways outlined in the service specification(s) for children and young people with cancer.

All treatment must be delivered in accordance with local Children's Cancer Network and/or local TYA Cancer Network protocols.

9 Proposed Governance Arrangements

Services must be delivered in accordance with the relevant service specification(s) for children and young people with cancer.

The use of dexrazoxane in children is unlicensed. Each provider organisation treating children with a medicine approved under this policy 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 can ask for documented evidence that these processes are in place. Further details on the use of dexrazoxane can be found within the MHRA SmPC.

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

10 Proposed Mechanism for Funding

Treatment will be funded by local specialised commissioning teams, through established funding routes for children and young people's cancer services.

11 Proposed Audit Requirements

Any audits should be carried out in line with local network protocols and the relevant service specification(s) for children and young people with cancer.

12 Documents That Have Informed This Policy Proposition

This document has been informed by:

- NHS England. 2019. Evidence review: Dexrazoxane for preventing cardiotoxicity in people aged under 25 years receiving high-dose anthracyclines or related drugs for the treatment of cancer.
- European Medicines Agency (EMA). Summary of Product Characteristics: Savene 20 mg/ml powder and solvent for concentrate for solution for infusion.

13 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or not for routine commissioning.

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