Dexrazoxane guidelines for prevention of cardiotoxicity with anthracycline chemotherapy

NHS University Hospitals of Leicester NHS Trust

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Introduction and who this guideline applies to

This CYPICS network guideline has been developed by clinicians from Nottingham Children's Oncology Unit with consultation across the network including from the Leicester Royal Infirmary and has been ratified by the Leicester Children's Hospital guideline process.

This guideline applies to all children and young people under the age of 19 years who are receiving chemotherapy for malignant disease.

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Dexrazoxane guidelines for prevention of cardiotoxicity with anthracycline chemotherapy

	Title of Guideline	Dexrazoxane (Cardioxane®) guideline for prevention of cardiotoxicity with anthracycline chemotherapy
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	Directorate & Speciality	Directorate: Family Health – Children Speciality: Oncology / Haematology
	Date of submission of this one	July 2023
	Date when guideline to be reviewed	July 2028
	Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis)	Children and young people cared for by the East Midland Children's and Young Person's Integrated Cancer Service (EMCYPICS)
	Abstract	This guideline describes the criteria for prescribing and administering dexrazoxane in conjunction with anthracycline chemotherapy in order to reduce the risk of cardiotoxicity.
	Key Words	Paediatrics. Children. Dexrazoxane. Oncology. Haematology. Doxorubicin. Anthracycline.
	Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues?	
1a	meta-analysis of randomised controlled trials	
1b	At least one randomised controlled trial	
2a	at least one well-designed controlled study without randomisation	
2b	at least one other type of well-designed quasi-experimental study	
3	well –designed non-experimental descriptive studies (i.e. comparative / correlation and case studies)	
4	expert committee reports or opinions and / or clinical experiences of respected authorities	X
5	recommended best practise based on the clinical	X

	experience of the guideline developer	
	Consultation Process	Consultants, Nurses and Pharmacists in EMCYPICS.
	Target audience	Medical, nursing and pharmacy staff working in EMCYPICS
	This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert. Caution is advised when using guidelines after the review date.	

Document Control

Document Amendment Record

Version	Issue Date	Author
V1	2020	Jenni Hatton – Paediatric Oncology Pharmacist
V2	2023	Colin Ward – Lead Pharmacist EM CYPICS

Summary of changes from previous version

1. Update of references
2. Addition of dexrazoxane brand names to add clarity
3. Addition of AllTogether1 & EsPhALL 2017 trials to cumulative anthracycline doses table (appendix).

Introduction

Dexrazoxane (Cardioxane®) is a drug which protects the heart from the cardiotoxic side effects of anthracycline chemotherapy. Anthracyclines are used in many chemotherapy protocols in children and young adults and among their adverse effects are early or delayed heart failure.

Dexrazoxane is licensed in the UK in adults for the prevention of chronic cumulative cardiotoxicity caused by anthracycline use in advanced and/or metastatic breast cancer patients who have received a prior cumulative dose of 300 mg/m^2 of doxorubicin or a prior cumulative dose of 540 mg/m^2 of epirubicin when further anthracycline treatment is required.[i] It is unlicensed in the treatment of children and young people.

A commissioning policy was published by NHS England in February 2020[1] which recommends considering the use of dexrazoxane in children and young adults who are planned to receive a cumulative dose of at least 300mg/m^2 doxorubicin or equivalent doses of another anthracycline.

The commissioning policy should be referred to in full when considering using dexrazoxane and is available here: https://www.england.nhs.uk/wp-content/uploads/2020/03/Dexrazoxane-for-preventing-cardiotoxicity-in-children-and-young-people.pdf

Please note – there is another preparation of dexrazoxane (Savene®) which is licensed for management of extravasation. This is not covered in this guideline.

Prescribing

Dexrazoxane should only be prescribed in accordance with the clinical commissioning policy above. Provider organisations must register all patients using the NHS England prior approval web-based system (Accessed at https://www.blueteq-secure.co.uk/trust/).

Any use outside of this policy must be approved at the relevant MDT and via the appropriate local approval method (for example a one-off request to the Drug and Therapeutics Committee) as it will not be funded by NHS England.

Consent must be explicitly obtained for the use of dexrazoxane.

Dexrazoxane is dosed at 10 times the doxorubicin- equivalent anthracycline dose.

Examples:

- A dose of 50mg doxorubicin will require a dose of 500mg dexrazoxane.
- A dose of mitoxantrone of 10mg is equivalent to doxorubicin 40mg and so a dexrazoxane dose of 400mg is required.

Dose equivalences of the anthracyclines are as follows[ii]

Drug	To get equivalent doxorubicin does, multiply total dose by:	Dose equivalence to 300mg doxorubicin
Doxorubicin	1	300mg
Daunorubicin	0.5	600mg
Epirubicin	0.67	450mg
Idarubicin	5	60mg
Mitoxantrone	4	75mg

All dexrazoxane must be prescribed by an approved chemotherapy prescriber on a chemotherapy chart as part of an approved protocol. These should have been previously set up and checked on Chemocare® according to local procedures.

Current protocols in use within East Midlands Children and Young Persons Integrated Cancer Service (EMCYPICS) and their cumulative doses of anthracycline are below

Dexrazoxane must be administered by a chemotherapy-trained nurse as an intravenous infusion (infusion concentration 5mg/ml) via a central line over 15 minutes, given no more than 30 minutes prior to each dose of the anthracycline infusion. Timings should be specified on the prescription for clarity. If there are multiple doses of anthracycline in a course, dexrazoxane should be given prior to each dose.

Due to the short shelf life of dexrazoxane infusions, the subsequent anthracycline infusion must be given over 1 hour or less. Where a protocol specifies a different length of infusion

for the anthracycline, it is the responsibility of the patient's consultant to decide on the appropriate duration of infusion.

Clinical trial protocols should be consulted if appropriate. Some trials may not support the use of dexrazoxane. This must be clarified before prescribing.

Dose modifications

At higher doses of chemotherapy, where the dexrazoxane dose exceeds 1000 mg/m^2, myelosuppression may increase significantly.[i] Consideration should be given to capping the dose, this decision must be made by a consultant.

If the anthracycline dose is reduced, the dexrazoxane dose must also be proportionately reduced.

Dexrazoxane doses should be reduced in renal impairment if the creatinine clearance (CrCl) is less than 40ml/min/1.73m^2. Discuss this with the consultant and pharmacist.

Since dexrazoxane is a cytotoxic agent, with topoisomerase II inhibition activity, combination of dexrazoxane with chemotherapy may lead to an increased risk of second primary malignancy.

Pharmacy check and dispensing

Dexrazoxane will be checked and ordered along with the rest of the chemotherapy for that patient.

Due to its short shelf life (four hours), it will be made on the day it is to be administered. Ward / day care staff need to contact the aseptic pharmacy department to confirm the dose is going ahead.

Dexrazoxane is handled as a cytotoxic. It is diluted within the pharmacy aseptic unit using compound sodium lactate BP with a resulting pH of approximately 3[i].

Administration

Dexrazoxane should be given over 15 minutes, no more than 30 minutes prior to the anthracycline infusion.

Lines should be flushed with sodium chloride 0.9% or glucose 5%[iii].

Dexrazoxane must be handled and disposed of following guidance for the handling of cytotoxic drugs.

Appendix

The following tables show the current protocols in use in EMCYPICS which contain anthracyclines, and the cumulative doses in those protocols.

This list does not imply that dexrazoxane must be used but highlights those courses where it should be considered. The decision to use dexrazoxane must be made by the consultant for that patient in discussion with the relevant MDT.

Haematology

Protocol	Anthracycline dose per cycle	Infusion time	Cumulative dose (doxorubicin equivalent)	Exceeds intended dose of 300mg/m^2 doxorubicin?
AllTogether1	Induction B/F - Daunorubicin 100mg/m^2 Induction C - Daunorubicin 90mg/m^2 *Plus(If randomised)* Std Risk/IR-Low Standard DI - Doxorubicin 90mg/m^2 IR-High: Extended DI - Doxorubicin 30mg/m^2	1 hour 1 hour 1 hour 1 hour	140mg/m^2 MAXIMUM	No
EsPhALL 2017	Daunorubicin & doxorubicin		280mg/m^2	No
UKALL 2019 Interim Guidelines	Induction daunorubicin 100mg/m^2 DI doxorubicin 75mg/m^2	1 hour 1 hour	125mg/m^2	No
Interfant	Induction daunorubicin 30mg/m^2 x 2 OCTADAD daunorubicin 30mg/m^2 x 4	1 hour 1 hour	90mg/m^2	No
AML guidelines / Myechild	SR – Mitoxantrone 84mg/m^2 total IR – Mitoxantrone 84mg/m^2 and idarubicin 24mg/m^2 HR – Mitoxantrone 48mg/m^2 and idarubicin 24mg/m^2 OR Mitoxantrone	1 hour 1 hour 1 hour	SR - **336 mg/m^2** IR - **456 mg/m^2** HR – **336mg/m^2 or 456mg/m^2** (protocol states	Yes Yes Yes

	84mg/m^2 and idarubicin 24mg/m^2		540mg/m^2 assuming mitoxantrone 5:1)	
R3	Induction mitoxantrone 20mg/m^2	1 hour	80mg/m^2	No
Fla-ida	Idarubicin 24mg/m^2	1 hour	120mg/m^2 per course	Consider prior exposure and intended number of courses
Ph+ve ALL	Induction daunorubicin 100mg/m^2 HR2 - daunorubicin 30mg/m^2 DR II x 2 - doxorubicin 200mg/m^2 total	1 hour over 24 hours 1 hour	265mg/m^2	No

Solid Tumours

Protocol	**Anthracycline dose per cycle**	**Infusion time**	**Cumulative dose (doxorubicin equivalent)**	**Exceeds intended dose of 300mg/m^2 doxorubicin?**
Euramos	Doxorubicin 450mg/m^2	48 hours	**450mg/m^2**	Yes – consider infusion time of doxorubicin
Ewings – EE2012	VDC – Doxorubicin 375mg/m^2	48 hours	**375mg/m^2**	Yes – consider infusion time of doxorubicin
NRSTS	Doxorubicin 75mg/m^2 per cycle. For 3, 4 or 5 cycles depending on risk group.	4 – 6 hours	3 cycles = 225mg/m^2 4 cycles = **300mg/m^2** 5 cycles = **375mg/m^2**	Consider infusion time and number of cycles intended.
RMS 2005	Maximum 240mg/m^2 total		240mg/m^2	No
Far-RMS	IvaDo x 4 cycles	1 hour	240mg/m^2	No
Euronet PHL C2	OEPA 80mg/m^2 per course DECOPDAC 25mg/m^2 per course	1 – 6 hours	Max 260mg/m^2	No

Inter B NHL	Group B – Doxorubicin 120 mg/m^2 Group C1 and C3 - Doxorubicin 180 mg/m^2 DA-EPOCH – Remain on standard dose – Doxorubicin 240mg/m^2 Potential maximum Doxorubicin 396.8mg/m^2	 continuous	120mg/m^2 180mg/m^2 240 – **396.8mg/m^2**	No No Consider infusion duration and likelihood of threshold being reached.
ALCL	Doxorubicin 150mg/m^2 in total	1 hour	150mg/m^2	No
Wilms	See protocol. CCLG 202 renal guidelines includes information on dexrazoxane.			Depending on place in protocol.
Hepatoblastoma – Phitt	Group C – SIOPEL-3HR Doxorubicin 300mg/m^2 total Group C C5VD – Doxorubicin 360mg/m^2 total Group D1 and 2 – Doxorubicin 300mg/m^2 total Group E2 – Doxorubicin 240mg/m^2 Group F – PLADO and S only – Doxorubicin 360mg/m^2 Group F – PLADO and GEMOX - Doxorubicin 240mg/m^2	15 minutes – 6 hours	**300mg/m^2** **360mg/m^2** **300mg/m^2** 240mg/m^2 **360mg/m^2** 240mg/m^2	Yes Yes Yes No Yes No
Hepatoblast	Standard risk		240mg/m^2	No

oma CCLG guidelines	progressive disease PLADO Doxorubicin 240mg/m^2 total High risk – Doxorubicin 300mg/m^2 total Very High Risk – Block B = Doxorubicin 330mg/m^2 total Block C = Doxorubicin 300mg/m^2 total Recurrent – Carb/Dox – Doxorubicin 40mg/m^2 per course		 **300mg/m^2** **330mg/m^2** **300mg/m^2** depends on number of courses but would need 7+ courses to reach 300mg/m^2	 Yes Yes Yes Consider prior exposure and intended number of courses
LINES	CADO = Doxorubicin 60mg/m^2 per course. Max 4 courses (group 10)	1 – 6 hours	240mg/m^2 maximum	No

References:

[1] https://www.medicines.org.uk/emc/summary of product characteristics - CARDIOXANE 500mg powder for solution infusion *Last updated on emc: 02 Feb 2024* Accessed 21/6/2023

[1] NHS England Clinical Commissioning Policy: Dexrazoxane for preventing cardiotoxicity in children and young people (under 25 years) receiving high-dose anthracyclines or related drugs for the treatment of cancer. First published: February 2020

[1] COG Long Term Follow-up Guidelines Version 5 October 2018 Accessed 21/6/2023

[1] Injectable Medicines Guide - (medusaimg.nhs.uk) Accessed 21/6/2023

UHL Education and Training

None

Key Words

Paediatrics. Children. Dexrazoxane. Oncology. Haematology. Doxorubicin. Anthracycline.

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
SOP Lead (Name and Title) Emma Ross; Consultant Paediatric Oncologist	**Executive Lead** **Chief Medical Officer**
Details of Changes made during review: **New to UHL**	