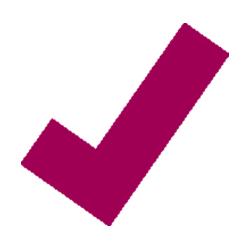# NHS England

Evidence review: Dexrazoxane for preventing cardiotoxicity in people aged under 25 years receiving high-dose anthracyclines or related drugs for the treatment of cancer

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Key points

Regulatory status:

Dexrazoxane is licensed for preventing chronic cardiotoxicity caused by anthracycline use in adults with advanced and/or metastatic breast cancer who have previously received a cumulative dose of 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin when further anthracycline treatment is needed (summary of product characteristics [SPC]: dexrazoxane).

Dexrazoxane is not licensed for preventing cardiotoxicity in children and young people aged under 25 years receiving high-dose anthracyclines or related drugs (doxorubicin 300 mg/m^2 or more or an equivalent dose of another anthracycline) for childhood 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).

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether using dexrazoxane is appropriate outside its authorised indications. Supporting information and advice is also available from the GMC.

Overview

This review considers the evidence for using dexrazoxane to prevent cardiotoxicity in people aged under 25 years receiving 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. 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 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/m^2 or more (or equivalent anthracycline) .

This evidence review includes a systematic review and meta-analysis of 5 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 3 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 5 RCTs included in the systematic review. However, it should be noted that the rates of clinical cardiotoxicity were low across the RCTs, with only 3 cases reported. Heart failure develops over a much longer time in children 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 (see Evidence summary tables for more details).

The systematic review and additional RCT assessed surrogate markers for cardiac damage, as well as actual clinical outcomes such as heart failure. 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 left ventricular fractional shortening and a better lower left ventricular thickness-to-dimension ratio (measures of the heart's ability to pump blood around the body). However, it is unclear whether these surrogate cardiac markers predict long-term cardiac dysfunction (abnormality or impairment of the heart, potentially leading to a heart attack 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 1 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 (see Evidence summary tables for more details). Other adverse events listed in the SPC as being very common (occurring in 1/10 people or more) for dexrazoxane include nausea, vomiting and alopecia.

Contents

1. Introduction

Background and current guidance

Anthracyclines (doxorubicin, daunorubicin, epirubicin and idarubicin) and related drugs (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. The 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 do require high cumulative doses of anthracycline, and these children have poor survival outcomes, high-risk disease and are at high-risk of acute anthracycline cardiotoxicity, limiting the intensity of the given chemotherapy (EMA: dexrazoxane 2017).

Around 1 in 10 childhood cancer survivors who received 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 with 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).

Using dexrazoxane to prevent cardiotoxicity in people aged under 25 years is controversial. A number of randomised controlled trials (RCTs) have investigated the cardioprotective benefits of dexrazoxane in adults, mostly in women with advanced breast cancer. However, results in adults cannot be generalised to children and young people because of differences between the populations in age, cumulative anthracycline dose, concurrent chest radiation and the likelihood of a pre-existing heart problem.

In 2011, the European Medicines Agency (EMA) reviewed the efficacy and safety data for dexrazoxane (EMA: dexrazoxane 2011). The review concluded that the available efficacy data in children was very limited, with only 1 adequately sized randomised controlled trial (RCT) that assessed troponin-T, a protein in the blood which is used as a surrogate marker for cardiac damage. The EMA review also considered safety data from 2 RCTs in children with Hodgkin's disease and acute lymphoblastic leukaemia (ALL), which found children treated with dexrazoxane had a 3-fold increase in second primary malignancies (particularly acute myeloid leukaemia [AML] and myelodysplastic syndrome [MDS]). A significant increased risk of other toxicities was also reported in children with Hodgkin's disease who were treated with dexrazoxane, including neutropenia, thrombocytopenia, sepsis and pulmonary toxicity. Following this review dexrazoxane was contraindicated in children and young people aged under 18 years.

In 2017, the EMA reviewed dexrazoxane again (EMA: dexrazoxane 2017). The updated review concluded that, in children and young people treated with higher cumulative doses of anthracycline, dexrazoxane can improve surrogate cardiac markers and reduce sub-clinical acute cardiotoxicity (asymptomatic changes in echocardiographic or biochemical measures). However the review noted that there is currently no established correlation between these cardiac markers and long-term cardioprotective effects of dexrazoxane. The EMA concluded that, among children with second primary malignancies, over a follow-up of more than 5 years, dexrazoxane did not appear to compromise long-term survival. Following this review, the contraindication was removed for people aged under 18 years who were receiving a cumulative dose of doxorubicin of 300 mg/m^2 or higher (or equivalent).

Product overview

Mode of action

The exact mechanisms by which anthracyclines cause cardiac damage and how dexrazoxane protects against this damage are not fully understood.

Anthracyclines form complexes with heavy metals, particularly iron, generating free radicals that can damage the heart (Asselin et al. 2016). Dexrazoxane can chelate (bond with) metal ions, preventing formation of anthracycline and heavy metal complexes and harmful free radicals, which may be how it prevents damage to the heart (summary of product characteristics [SPC]: dexrazoxane).

Regulatory status

Dexrazoxane is licensed for preventing chronic cardiotoxicity caused by anthracycline use in adults with advanced and/or metastatic breast cancer who have previously received a cumulative dose of 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin when further anthracycline treatment is needed (summary of product characteristics [SPC]: dexrazoxane).

Dexrazoxane is not licensed for preventing cardiotoxicity in children and young people aged under 25 years receiving anthracyclines or related drugs (doxorubicin 300 mg/m^2 or more or an equivalent dose of another anthracycline) for childhood 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).

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether using dexrazoxane is appropriate outside its authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

Dosing information varies for the licensed indication of dexrazoxane and can be found in the SPC.

Dosing information for dexrazoxane as adjuvant treatment for the preventing cardiotoxicity in children and young people aged under 25 years receiving anthracyclines or related drugs (doxorubicin 300 mg/m^2 or more, or equivalent anthracycline) for the treatment of cancer (an off-label indication) is discussed in the [summary of included studies section](#) of this evidence summary.

2. Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes ([PICO](#)) for this review was provided by NHS England's Policy Working Group for the topic (see the [literature search terms](#) section for more information). The research questions for this evidence review are:

1. In people aged under 25 years receiving anthracyclines or related drugs for the treatment of cancer, what is the clinical effectiveness of the addition of dexrazoxane to a planned cumulative dose of 300 mg/m^2 doxorubicin and above, or equivalent dose of another anthracycline or related drug compared with no dexrazoxane therapy?
2. What is the safety of dexrazoxane in people aged under 25 years who have received a planned cumulative dose of 300 mg/m^2 doxorubicin and above or equivalent dose of another anthracycline or related drug compared with no dexrazoxane therapy?
3. What is the cost-effectiveness of dexrazoxane therapy in people under 25 years receiving a planned cumulative dose of 300 mg/m^2 doxorubicin and above or equivalent dose of another anthracycline or related drug compared with no dexrazoxane therapy?
4. Does the evidence of clinical and cost-effectiveness identify any subgroups of people under 25 years receiving a planned cumulative dose of 300 mg/m^2 doxorubicin and above or equivalent dose of another anthracycline or related drug who would gain greater benefit from using dexrazoxane therapy compared with no dexrazoxane therapy:
   - as part of frontline therapy?
   - as part of frontline therapy and additional therapy combined for relapsed disease or second malignancy?

The searches for evidence to support the use of dexrazoxane for the prevention of cardiotoxicity in children and young people aged under 25 years were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on [search strategy](#) and [evidence selection](#).

The NICE [evidence summary: process guide](#) (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long-term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the [grade of evidence](#) section for more information).

3. Summary of included studies

This evidence review includes a systematic review and meta-analysis of 5 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, so additional outcomes are reported from the fully published article for this study (Asselin et al. 2016). Longer-term mortality data are provided by a follow-up study that collected long-term data from 3 RCTs, all of which were included in the Shaikh systematic review (Chow et al. 2015).

A summary of the included studies is shown in table 1 (see the evidence summary tables for full details).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Shaikh et al. 2016 Systematic review and meta-analysis of 5 RCTs and 12 NRSs Median follow-up across the 5 RCTs ranged from 3.3 years to 9.6 years. Median follow-up across the 12 NRSs ranged from 1 month to 8.2 years.	Children and young people with cancer receiving anthracycline chemotherapy (total n=1,254 in the RCTs; total n=3,385 in the NRSs). The RCTs included participants with sarcomas (1 RCT, n=41), high-risk acute lymphoblastic leukaemia (1 RCT, n=205), lower-risk Hodgkin's lymphoma (1 RCT, n=255), intermediate and high-risk Hodgkin's lymphoma (1 RCT, n=216) and T-cell acute lymphoblastic leukaemia or advanced stage lymphoblastic non-Hodgkin's lymphoma (1 RCT, n=537).	**Intervention:** Dexrazoxane In the 5 RCTs, the dose ratio of dexrazoxane to doxorubicin was 10:1 in 3 studies, 15:1 in 1 study and 20:1 in 1 study. In the 12 NRSs, the dose ratio of dexrazoxane to doxorubicin (or equivalent) was 10:1 or 20:1. **Comparator:** No dexrazoxane **Anthracycline treatment:** In all 5 RCTs, the anthracycline was doxorubicin, with cumulative dose of 100 to 410 mg/m^2. In the 12 NRSs, multiple types of anthracycline were used. The average cumulative dose of anthracycline ranged from 240 to 925 mg/m^2.	Reported outcomes included: • Clinical cardiotoxicity • Any cardiotoxicity (including sub-clinical cardiotoxicity) • Overall survival • Rates of second malignant neoplasms Sub-clinical cardiotoxicity was defined as asymptomatic changes in echocardiographic measures beyond specified thresholds.

Asselin et al. 2016 RCT Median follow-up 9.2 years.	537 people aged between 1 and 21 years (mean age 9.8 years; 75.8% male) with newly diagnosed T-cell acute lymphoblastic leukaemia or advanced stage lymphoblastic non-Hodgkin lymphoma.	**Intervention:** Dexrazoxane Given at a 10:1 dexrazoxane to doxorubicin ratio. **Comparator:** No dexrazoxane **Anthracycline treatment:** Doxorubicin, cumulative dose 360 mg/m^2.	This RCT was included in abstract form in the systematic review by Shaikh et al. (2016). The full text of this RCT is included in this evidence review because not all outcomes were included in the systematic review. These outcomes are: • Overall survival • Serum troponin-T • Adverse events
Chow et al. 2015 Longer-term safety report from 3 RCTs Median follow-up 12.6 years.	The 3 RCTs included 1,008 participants across 133 centres. The median age at treatment was 12.6 years (range 1 to 22). Studies included people with low-risk Hodgkin's lymphoma (n=255), intermediate/high-risk Hodgkin's lymphoma (n=216) or T-cell acute lymphoblastic leukaemia or advanced stage lymphoblastic non-Hodgkin's lymphoma (n=537).	**Intervention:** Dexrazoxane Given at a 10:1 dexrazoxane to doxorubicin ratio. **Comparator:** No dexrazoxane **Anthracycline treatment:** Doxorubicin, cumulative dose varied between studies: 100–200 mg/m^2 (n=255), 180–300 mg/m^2 (n=216), 360 mg/m^2 (n=537).	Primary outcomes: Overall survival Cause-specific mortality, including death from original cancer, second cancer or cardiovascular cause.
Abbreviations: NRS, non-randomised study; RCT, randomised controlled trial			

Details of the excluded studies are listed in the section on evidence selection.

4. Results

An overview of the results for clinical effectiveness and safety and tolerability can be found in the evidence summary table. The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

Most outcomes are graded A, except adverse events, which is graded B.

Clinical effectiveness

This section considers the following research question: In people aged under 25 years receiving anthracyclines or related drugs for the treatment of cancer, what is the clinical effectiveness of the addition of dexrazoxane to a planned cumulative dose of 300 mg/m^2 doxorubicin and above, or equivalent dose of another anthracycline or related drug compared with no dexrazoxane therapy?

Clinical cardiotoxicity

In a systematic review by Shaikh et al. (2016), across 4 randomised controlled trials (RCTs) involving 991 children and young people, over a 3.3 to 9.6 year follow-up there was no statistically significant difference in clinical cardiotoxicity (including symptomatic heart failure) for dexrazoxane compared with no dexrazoxane (risk ratio [RR] 0.24, 95% confidence interval [CI] 0.03 to 2.09, p=0.88). The event rate was low, with only 3 cases of clinical cardiotoxicity occurring across the 4 RCTs, all in the no dexrazoxane group.

The same systematic review also reported on results from 8 non-randomised studies involving 741 children and young people. Across the non-randomised studies, significantly lower rates of clinical cardiotoxicity were observed in people treated with dexrazoxane (7 events) compared with no dexrazoxane (35 events; RR 0.29 [95% CI 0.14 to 0.61, p=0.001], number needed to treat [NNT] 13 [95% CI 9 to 22]). However, non-randomised studies are subject to bias and confounding, and are therefore less reliable compared with randomised studies.

Sub-clinical cardiotoxicity

A number of surrogate markers for cardiac damage (asymptomatic changes in echocardiographic or biochemical measures) are reported in the studies included in this evidence review.

Elevated serum cardiac troponin-T

Troponin-T is a protein released when cardiac muscle is damaged and is a marker of cardiac damage. Serum troponin-T levels above 0.01 nanograms/ml were considered elevated. Across 1 systematic review (that included results from 2 RCTs; Shaikh et al. 2016, n=158) and an additional RCT (Asselin et al. 2016, n=239), significantly fewer people treated with dexrazoxane had elevated troponin-T levels (around 10%) compared with people not treated with dexrazoxane (around 25%; for both studies p<0.05).

Left ventricular fractional shortening

Left ventricular function can be assessed by measuring changes in its dimensions and volumes between diastole and systole. The systematic review by Shaikh et al. (including data from 2 RCTs, n=301) found people treated with dexrazoxane had significantly higher (better) z-scores for left ventricular fractional shortening compared with people not treated with dexrazoxane, mean difference between groups 0.61 (95% CI 0.22 to 1.01, p=0.002). A z-score expresses deviation from a mean. A z-score of 0 is equal to the mean (a person without cardiac dysfunction). A z-score of −1 is equal to 1 standard deviation below the

mean, and a z-score of +1 is equal to 1 standard deviation above the mean. The clinical relevance of this difference is not clear.

<u>Left ventricular thickness-to-dimension ratio</u>

This measurement is used to predict left ventricular ejection fraction and volume. The systematic review by Shaikh et al. (including data from 2 RCTs, n=299) found people treated with dexrazoxane had significantly higher (better) z-scores for left ventricular thickness-to-dimension ratio compared with people not treated with dexrazoxane. Mean difference between groups 0.66 (95% CI 0.32 to 1.00, p<0.001). The clinical relevance of this difference is not clear.

Any cardiotoxicity

In the systematic review by Shaikh et al. (2016), across 4 RCTs (total n=990, follow-up 3.3 to 9.6 years), rates of any cardiotoxicity (including both clinical and sub-clinical cardiotoxicity) were significantly lower in children treated with dexrazoxane (5 events) compared with no dexrazoxane (17events). RR 0.29 (95% CI 0.13 to 0.64, p=0.003), NNT 41 (95% CI 24 to 157). It should be noted that most cardiotoxic events were sub-clinical (19/22 events, 86%).

Across 8 non-randomised studies (total n=531), Shaikh et al. (2016) found that rates of any cardiotoxicity were significantly lower in children treated with dexrazoxane (30 events) compared with no dexrazoxane (69events). RR 0.43 (95% CI 0.30 to 0.63, p<0.001), NNT 7 (95% CI 5 to 12).

Safety and tolerability

Second malignant neoplasms

In a systematic review of 5 RCTs (Shaikh et al. 2016, n=1,254, follow-up 3.3 to 9.6 years), there was no significant difference in rates of second malignant neoplasms for people treated with dexrazoxane (17 events) compared with those not treated with dexrazoxane (7 events; RR 2.37, 95% CI 0.98 to 5.74, p=0.06). The same systematic review also combined the results of 4 non-randomised studies, finding no significant difference in second malignant neoplasms rate for dexrazoxane (7 events) compared with no dexrazoxane (18 events; RR 0.85, 95% CI 0.35 to 2.07, p=0.72).

The long-term follow-up report of 3 RCTs by [Chow et al. 2015](#) (n=1,008, follow-up 12.6 years) found no significant difference in mortality due to second cancer in people treated with dexrazoxane (2%) compared with no dexrazoxane (1.6%, HR 1.24, 95% CI 0.49 to 3.15).

The [2017 EMA review of dexrazoxane](#) concluded that the available data were reassuring as regard to occurrence of second malignant neoplasms in children after being exposed to dexrazoxane, up to 12 years post-treatment. However, the EMA review also notes that the long-term risk of second malignant neoplasms in children treated with dexrazoxane is not currently known.

Relapse or disease progression

A study that reported on long-term follow-up from 3 RCTs (Chow et al. 2015, n=1,008) found that, over a median 12.6 year follow-up, there was no difference in relapse or disease progression rates for children and young people treated with dexrazoxane (15.6%) compared with those not treated with dexrazoxane (19.0%, HR 0.81, 95% CI 0.60 to 1.08).

Event-free survival rate

The systematic review by Shaikh et al. (2016) reported that, across 5 RCTs (n=1,254) there was no difference in event-free survival for children and young people treated with dexrazoxane compared with those not treated with dexrazoxane (HR 0.99, 95% CI 0.78 to 1.25, p=0.91).

Overall survival rate

The long-term report from 3 RCTs (n=1,008) by Chow et al. 2015 found that, over a median 12.6 year follow-up, there was no significant difference in all-cause mortality for dexrazoxane compared with no dexrazoxane (HR 1.03, 95% CI 0.73 to 1.45).

Adverse events

The RCT by Asselin et al. 2016 (n=537) reported no statistically significant difference between dexrazoxane and no dexrazoxane in rates of infection, haematological effects and CNS effects. The same RCT found that people treated with dexrazoxane were significantly less likely to have mucositis (33 events) compared with no dexrazoxane (52 events, p=0.02).

The 2017 EMA review of dexrazoxane noted that myelosuppression and infections are known to occur in people treated with dexrazoxane and are listed in the SPC for dexrazoxane. The EMA review also noted that in 3 studies (Wexler et al. 1996, Asselin et al. 2016 and Schwartz et al. 2009), the additive myelosuppressive effects of dexrazoxane did not delay chemotherapy treatment or require significant dose modifications of chemotherapy regimens.

The following adverse events are reported as being very common (occurring in 1/10 people or more) in the SPC for dexrazoxane:

- Anaemia
- Leukopenia (low white blood cell count)
- Nausea
- Vomiting
- Stomatitis (a sore or inflammation inside of the mouth)
- Alopecia
- Asthenia (lack of energy and strength).

Cost-effectiveness

This section considers the following research question: What is the cost-effectiveness of dexrazoxane therapy in people under 25 years receiving a planned cumulative dose of 300 mg/m^2 doxorubicin and above or equivalent dose of another anthracycline or related drug compared with no dexrazoxane therapy?

No studies were identified during literature searches (see search strategy for full details) to answer this research question. None of the studies included in this evidence review included an outcome investigating cost-effectiveness.

Subgroups of people who may gain greater benefit from treatment

This review did not find clear evidence for subgroups of people who would gain greater benefit from using dexrazoxane therapy compared with no dexrazoxane therapy, either as part of frontline therapy or as part of frontline therapy and additional therapy combined for relapsed disease or second malignancy.

5. Discussion

Evidence strengths and limitations

A systematic review by Shaikh et al. (2016) found no significant difference in clinical cardiotoxicity between dexrazoxane and no dexrazoxane across 4 RCTs. When the results of 8 non-randomised studies were combined in the same systematic review a significant reduction in clinical cardiotoxicity was observed in people treated with dexrazoxane compared with no dexrazoxane. The 2017 EMA review of dexrazoxane noted that such non-randomised studies are limited by their study design, including selection bias due to the absence of randomisation. In addition to this the EMA stated that there was a difference in follow-up time between the dexrazoxane group and control group in most non-randomised studies. The EMA concluded that the results of non-randomised studies should be interpreted with caution and were considered non-supportive during the EMA review.

The included studies were not of sufficient duration to assess the long-term cardioprotective effect of dexrazoxane treatment in children and young people with cancer who receive high-dose anthracycline therapy. Heart failure develops over a much longer time in children compared with adults receiving cancer treatment, meaning a very long follow-up would be required to observe a clinically significant difference in symptomatic heart failure (Chow et al. 2015). An analysis of participants from the Childhood Cancer Survivor Study (CCSS; Chow et al. 2015b) found that children considered at high-risk of clinical heart failure at the end of cancer treatment had a 41-fold relative risks of heart failure compared with siblings (controls). Despite this increased risk, the cumulative incidence of heart failure by the age of 40 years was 12%. The authors of Chow et al. (2015) note that the median age of participants at the end of the 12.6 year follow-up was 24 years, meaning follow-up would need to be considerably longer before a significant difference in clinical heart failure could be detected. The 2017 EMA review of dexrazoxane acknowledged an ongoing study enrolling participants from 3 RCTs (POG 9404 [Asselin et al. 2016], POG 9425 and POG 9426; all included in the systematic review by Shaikh et al.), that will report on up to 23 years follow-up in children and young people treated with dexrazoxane (Chow et al. 2016 [abstract only]). The EMA stated that the results of this study may provide more information on the long-term cardioprotective benefits of dexrazoxane.

Many studies included in this evidence review report on cardiac surrogate markers, including troponin-T levels and echocardiograph results. In their 2017 review of dexrazoxane, the EMA noted that developments in the way biochemical assays are performed, as well as enhanced imaging techniques, have improved the reliability and sensitivity of these

surrogate cardiac markers used in current clinical practice compared with the ones used in the studies of dexrazoxane in children and young (which were mainly conducted between 1996 and 2001). The EMA also stated that such surrogate cardiac markers are not yet known to correlate with long-term cardiac dysfunction and cannot be safely used to predict the long-term cardioprotective effect of dexrazoxane.

Second malignant neoplasms have been a safety concern with dexrazoxane. The systematic review by Shaikh et al. (2016) found no significant difference in second malignant neoplasms between dexrazoxane (17 cases) and no dexrazoxane (7 cases). The authors of the systematic review noted that the type of second malignant neoplasm varied across studies. They highlighted that an increase in acute myeloid leukaemia (AML) was only observed in the 2 RCTs that used etoposide (a topoisomerase II inhibitor which has been associated with second cancers) concurrently with doxorubicin and dexrazoxane in people with Hodgkin's lymphoma (a diagnosis with a higher risk of second malignant neoplasms). They also noted that an increase in brain tumours only occurred in 1 RCT that used cranial radiation in people with T-cell malignancies. All these factors can increase the risk of second malignant neoplasms, and the authors suggested that dexrazoxane may further increase the risk if used concurrently with other treatments that contribute independently to second cancer development.

Some studies included in the systematic review by Shaikh et al. (2016) used cumulative doses of doxorubicin below 300 mg/m^2. Of the 5 RCTs included in the systematic review, 1 study (n=255; POG 9426) used a doxorubicin dose of 100–200 mg/m^2 and 1 study (n=216; POG 9425) used a doxorubicin dose of 180–300 mg/m^2. The anthracycline dose in both these studies was dependant on the person's response to treatment and the number of chemotherapy courses (Tebbi et al. 2007). The studies do not report the actual doses received. The systematic review by Shaikh et al. does not report the outcomes by doxorubicin dose, and it is not clear whether the inclusion of participants receiving a cumulative dose below 300 mg/m^2 affected the results. However, results of the largest RCT in the systematic review, which used a cumulative dose of 360 mg/m^2 (POG 9404 [Asselin et al. 2016]; n=537) were consistent with the overall results of the systematic review.

All RCTs discussed in this evidence review used doxorubicin. The cardioprotective effect of dexrazoxane in children treated with other types of anthracycline has not been investigated in an RCT.

Selective reporting is an important limitation of the evidence included in this review. Two of the 5 RCTs included in the systematic review by Shaikh et al. (2016) have not published the results for cardiac outcomes (POG 9425 and POG 9426).

Other treatments

No other medicines are generally considered at the same stage in the treatment pathway for the prevention of cardiotoxicity in people aged under 25 years who are receiving high-dose anthracycline therapy.

There are a number of management strategies that can be used to reduce the risk of anthracycline-induced cardiotoxicity. Slowing the rate of infusion of anthracycline can lower the peak concentrations of anthracycline, possibly reducing the risk of cardiotoxicity in adults

([Geisberg and Sawyer 2010](#)). However, a randomised trial in children with acute lymphoblastic leukaemia found a longer infusions of doxorubicin did not reduce the incidence of sub-clinical cardiotoxicity ([Lipshultz et al. 2002](#)). Liposomal formulations of anthracyclines may also be used with a view to reducing cardiotoxicity. Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers have also been investigated for reducing the risk of cardiac damage in people receiving chemotherapy (Geisberg and Sawyer 2010).

6. Conclusion

A small number of children and young people with cancer require treatment with high doses of anthracyclines (cumulative dose of 300 mg/m^2 doxorubicin [or equivalent] or higher), and these children are at increased risk of short- and long-term cardiotoxicity.

The studies included in this evidence review suggest that dexrazoxane provides acute cardioprotection, as assessed using surrogate cardiac markers (including troponin-T levels and echocardiographic measurements). However, such surrogate cardiac markers are not yet known to correlate with long-term cardiac dysfunction and cannot be safely used to predict the long-term cardioprotective effect of dexrazoxane. No randomised controlled trials (RCTs) have demonstrated that dexrazoxane reduces rates of symptomatic heart failure or other clinical cardiac outcomes in children receiving high-dose anthracyclines, although a considerably longer follow-up is required before such outcomes can be appropriately assessed in this population.

A systematic review of 5 RCTs did not find a statistically significant increase in rates of second malignant neoplasms up to around 10 years after treatment with dexrazoxane. Higher rates of second malignant neoplasms observed in children treated with dexrazoxane in individual RCTs may be due to an increased risk of second malignant neoplasms when dexrazoxane is used in combination with other cancer treatments that can cause second cancers. The longer-term risk of second malignant neoplasms in children treated with dexrazoxane is not currently known.

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

Adverse events were reported in 1 RCT included in this review. Grade 3 and 4 toxicities reported in people treated with dexrazoxane included infection, haematological effects, mucositis and CNS events. Other adverse events listed in this summary of product characteristics for dexrazoxane include nausea, vomiting and alopecia.

7. Evidence summary table

<table>
<tr><td colspan="8">Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy</td></tr>
<tr>
<th>Study Design</th>
<th>Population characteristics</th>
<th>Intervention</th>
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<th>Outcome measures</th>
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</tr>
<tr><td colspan="8">Study reference 1: Shaikh et al. 2016</td></tr>
<tr>
<td>S1- Systematic review and meta-analysis of RCTs and comparative NRSs

Median follow-up across the 5 RCTs ranged from 3.3 years to 9.6 years.

Median follow-up across the 12 NRSs ranged from 1 month to 8.2 years.</td>
<td>The systematic review included 5 RCTs (total n=1,254) and 12 NRSs (total n=3,385) that compared dexrazoxane with no dexrazoxane in children and young people with cancer (median age across the studies ranged from 2 to 17 years) receiving anthracycline chemotherapy. The RCTs included participants with sarcomas (1 RCT, n=41), high-risk acute lymphoblastic leukaemia (ALL, 1 RCT, n=205), lower-risk Hodgkin's</td>
<td>Intervention:

Dexrazoxane

In the 5 RCTs, 635 participants were randomised to dexrazoxane. The dose ratio of dexrazoxane to doxorubicin was 10:1 in 3 studies, 15:1 in 1 study and 20:1 in 1 study.

In the 12 NRSs, 1,215 participants received dexrazoxane. The dose ratio of dexrazoxane to doxorubicin equivalent was 10:1 or 20:1.

Comparator:

No dexrazoxane

In the 5 RCTs, 619 participants were randomised to no dexrazoxane.

In the 12 NRSs, 2,170 participants received no dexrazoxane.</td>
<td>Clinical effectiveness

Clinical effectiveness</td>
<td>Clinical cardiotoxicity

Defined as symptomatic congestive heart failure (CHF), use of medication to treat CHF, heart transplant or cardiac cause of death

Any cardiotoxicity (clinical or sub-clinical cardiotoxicity)

Sub-clinical cardiotoxicity was defined as asymptomatic changes in echocardiographic</td>
<td>Randomised trials

Across 4 RCTs (total n=991), there was no statistically significant difference in clinical cardiotoxicity for children treated with dexrazoxane (0 events) compared with no dexrazoxane (3 events). RR 0.24 (95% CI 0.03 to 2.09, p=0.88). Follow-up was 3.3 to 9.6 years.

Non-randomised trials

Across 8 NRSs (total n=741), rates of clinical cardiotoxicity were significantly lower in children treated with dexrazoxane (7 events) compared with no dexrazoxane (35 events). RR 0.29 (95% CI 0.14 to 0.61, p=0.001), number needed to treat (NNT) 13 (95% CI 9 to 22).

Randomised trials

Across 4 RCTs (total n=990), rates of clinical or sub-clinical cardiotoxicity were significantly lower in children treated with dexrazoxane (5 events) compared with no dexrazoxane (17 events). RR 0.29 (95% CI 0.13 to 0.64, p=0.003), NNT 41 (95% CI 24 to 157). Follow-up was 3.3 to 9.6 years.</td>
<td>S1 Meta-analysis of existing data analysis

8/10

The research aims and design of the study are clearly stated. The design is appropriate for the aims and objectives of the study, although the follow-up of the included studies is not sufficient to assess the long-term effects of dexrazoxane, which may take decade to develop. Results for cardiac outcomes have not been published for some studies included in the</td>
<td>Direct study focusing on people with the indication and characteristics of interest.</td>
</tr>
</table>

					Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy		
Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
	lymphoma (1 RCT, n=255), intermediate and high-risk Hodgkin's lymphoma (1 RCT, n=216) and T-cell ALL or advanced stage lymphoblastic non-Hodgkin lymphoma (1 RCT, n=537). Studies that did not have a control arm or comparison population were excluded, along with studies in which most participants were over 18 years and studies not reporting cardiotoxicity or second malignant neoplasm outcomes.	**Anthracycline treatment:** In all 5 RCTs, the anthracycline was doxorubicin, with a cumulative dose of 100 to 410 mg/m². In all RCTs, dexrazoxane was started at the first dose of doxorubicin. In the 12 NRSs, multiple types of anthracycline were used. The average cumulative dose of anthracycline ranged from 240 to 925 mg/m². In 11/12 NRSs, dexrazoxane was started with the first dose of anthracycline.		measures beyond specified thresholds (for example, a decline in ejection fraction to <50% shortening fraction to <28% or a decrease of ≥10% from baseline)	**Non-randomised trials** Across 8 NRSs (total n=531), rates of clinical or sub-clinical cardiotoxicity were significantly lower in children treated with dexrazoxane (30 events) compared with no dexrazoxane (69 events). RR 0.43 (95% CI 0.30 to 0.63, p<0.001), NNT 7 (95% CI 5 to 12)	systematic review, and adverse events are not reported. Results generally support the author's conclusions, although firm conclusions on the impact of dexrazoxane on clinical cardiotoxicity cannot be made due to low event rate in the RCTs. The results are generalisable, although the authors did not report sub-group analysis by anthracycline dose.	
			Clinical effectiveness	Elevated troponin-T, defined as levels above 0.01 nanogram/ml	In 1 RCT (n=158), significantly fewer children treated with dexrazoxane (21%) had elevated troponin-T levels, compared with children who received no dexrazoxane (50%). RR 0.41 (95% CI 0.26 to 0.67, p<0.001), NNT 4 (95% CI 3 to 7). Follow-up was 9.6 years.		
			Clinical effectiveness	Left ventricular fractional shortening z-score	Across 2 RCTs (total n=301), z-scores were significantly higher (better) in children treated with dexrazoxane compared with no dexrazoxane (MD 0.61, 95% CI 0.22 to 1.01, p=0.002).		
			Clinical effectiveness	Left ventricular thickness-to-dimension ratio z-score	Across 2 RCTs (total n=299), z-scores were significantly higher (better) in children treated with dexrazoxane compared with no dexrazoxane (MD 0.66, 95% CI 0.32 to 1.00, p<0.001).		
			Safety	Second malignant neoplasms (SMNs)	**Randomised trials** Across 5 RCTs (total n=1,254), there was no statistically significant difference in SMNs between dexrazoxane (17 events) and no		

Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
					dexrazoxane (7 events) groups, RR 2.37 (95% CI 0.98 to 5.74, p=0.06). Follow-up was 3.3 to 9.6 years. **Non-randomised trials** Across 4 NRSs (total n=2,685), there was no statistically significant difference in SMNs between dexrazoxane (7 events) and no dexrazoxane (18 events) groups, RR 0.85 (95% CI 0.35 to 2.07, p=0.72).		
			Safety	Overall survival	Across 3 RCTs (total n=512), there was no significant difference in overall survival for participants treated with dexrazoxane compared with the no dexrazoxane group. HR 0.85, 95% CI 0.44 to 1.64, p=0.63.		
			Safety	Event-free survival	Across 5 RCTs (total n=1,254), there was no significant difference in event-free survival for participants treated with dexrazoxane compared with the no dexrazoxane group. HR 0.99, 95% CI 0.78 to 1.25, p=0.91. Follow-up was 3.3 to 9.6 years.		

Critical appraisal summary: This systematic review and meta-analysis includes 5 RCTs and 12 NRSs involving a total of 4,639 children and young people treated with dexrazoxane. The inclusion of non-randomised studies may have introduced bias, specifically selection bias, although the results from the randomised and non-randomised studies are reported separately. The dose of anthracycline and dexrazoxane differed across the studies, and the review does not report results by dose. Rates of clinical cardiotoxicity and second malignant neoplasms across the studies were low, and the systematic review may not be appropriately powered to detect a difference between treatments. The follow-up was not long enough to assess the long-term risks and benefits of dexrazoxane treatment, which may not become apparent until decades after treatment.

Abbreviations: ALL, acute lymphoblastic leukaemia; CI, confidence interval; CHF, congestive heart failure; HR, hazard ratio; MD, mean difference; NRS, non-randomised study; NNT, number needed to treat; RCT, randomised controlled trial; RR, risk ratio; SMN, Second malignant neoplasm

Study reference 2: Asselin et al. 2016

Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy							
Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
P1- Randomised controlled trial	537 people aged between 1 and 21 years (mean age 9.8 years; 75.8% male) with newly diagnosed T-cell acute lymphoblastic leukaemia or advanced stage lymphoblastic non-Hodgkin lymphoma.	**Intervention:** Dexrazoxane, given at a dexrazoxane to doxorubicin ratio of 10:1 (n=273) **Comparator:** No dexrazoxane (n=264) **Cancer treatment:** All participants received vincristine, prednisone, methotrexate, mercaptopurine, 1 dose per week for a total of 20 weeks of *Escherichia coli* L-asparaginase, and doxorubicin with intrathecal chemotherapy and cranial radiation. The cumulative dose of doxorubicin was 360 mg/m^2	Clinical effectiveness	Acute cardiac toxicity Note: this outcome is included in the SR by Shaikh et al. 2016 (under any cardiotoxicity [clinical or sub-clinical])	In total 5 people (0.9%) had grade 3 or 4 cardiac toxicity during treatment. Toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0, in which grade3 events are severe and grade 4 life-threatening or disabling. 2 people had arrhythmias (1 in each treatment group) 3 people had decreased left ventricular fractional shortening (all 3 in the no dexrazoxane group). All participants recovered and completed chemotherapy, including doxorubicin.	P1 Primary research using quantitative approaches 8/10 The research aims and design of the study are clearly stated. The design is appropriate for the aims and objectives of the study, although the follow-up was not sufficient to assess the long-term effects of dexrazoxane, which may take decade to develop. Results generally support the author's conclusions, although firm conclusions on the impact of dexrazoxane on clinical cardiotoxicity cannot be made due to the low event rate and	Direct study focusing on people with the indication and characteristics of interest.
			Clinical effectiveness	Serum cardiac troponin-T	At a median of 21 days after starting treatment (range 1 to 571 days), troponin-T levels were measured in 239 participants (45%). Significantly fewer people treated with dexrazoxane had elevated troponin-T levels (3/125, 2.4%) compared with the no dexrazoxane group (10/114, 8.8%), p=0.04.		
			Clinical effectiveness	Left ventricular fractional shortening z-score Note: this outcome is included in the SR by Shaikh et al. 2016	At baseline, the mean z-score was 0.34 in the dexrazoxane group and 0.37 in the no dexrazoxane group (no statistically significant difference between groups, p=0.893, n=307). At the end of doxorubicin treatment, mean z-scores had reduced to −0.90 in the dexrazoxane group and −1.68 in the no dexrazoxane group (no statistically		

						Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy		

Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
					significant difference between groups, p=0.053, n=143). At 3 years, z-scores had improved to −0.05 in the dexrazoxane group and −0.77 in the no dexrazoxane group (statistically significant difference between groups, p=0.005, n=167).	relatively short follow-up.	
			Clinical effectiveness	Left ventricular thickness-to-dimension ratio z-score Note: this outcome is included in the SR by Shaikh et al. 2016	At baseline, the mean z-score was −0.11 in the dexrazoxane group and 0.16 in the no dexrazoxane group (no statistically significant difference between groups, p=0.151, n=302). At the end of doxorubicin treatment, mean z-scores had reduced to −0.38 in the dexrazoxane group and −0.73 in the no dexrazoxane group (no statistically significant difference between groups, p=0.091, n=143). At 3 years, z-scores had improved to −0.09 in the dexrazoxane group, but remained at −0.75 in the no dexrazoxane group (statistically significant difference between groups, p=0.006, n=165).		
			Safety	Event-free survival Note: this outcome is included in the SR by Shaikh et al. 2016	There was no statistically significant difference in 5-year event-free survival for children treated with dexrazoxane (76.7%, standard error [SE] 2.7%) compared with no dexrazoxane (76.0%, SE 2.9%), p=0.9.		

	Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy						
Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
			Safety	Overall survival	Across both treatment arms, the overall survival rates at 5 and 10 years were 82.1% (SE 1.7%) and 80.6% (SE 2.4%) respectively. There was no statistically significant difference between groups, p=0.9.		
			Safety	Second malignant neoplasms (SMNs) Note: this outcome is included in the SR by Shaikh et al. 2016	SMNs were diagnosed in 8 children from the dexrazoxane group and 3 children from the no dexrazoxane group. 5-year cumulative incidence rates of SMNs were 0.7% (SE 0.5%) in the dexrazoxane group and 0.8% (SE 0.5%) in the no dexrazoxane group; no statistically significant difference (p=0.1653). 10-year cumulative incidence rates of SMNs were 1.8% (SE 0.9%) in the dexrazoxane group and 1.2% (SE 0.7%) in the no dexrazoxane group.		

					Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy		
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
			Safety	Grade 3 and 4 toxicities	**Infection** No significance difference in infections in the dexrazoxane group (173 events) compared with the no dexrazoxane group (168 events, p=0.64) **Haematological effects** No significance difference in haematological effects in the dexrazoxane group (243 events) compared with the no dexrazoxane group (237 events, p=0.26) **Mucositis** Mucositis occurred more frequently in people not treated with dexrazoxane (52 events) compared with the dexrazoxane group (33 events, p=0.02) **CNS effects** No significance difference in CNS effects in the dexrazoxane group (28 events) compared with the no dexrazoxane group (23 events, p=0.46) **Toxic death** Toxic death occurred in 6 people treated with dexrazoxane and in 3 people not treated with dexrazoxane (p-value not reported)		

Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy

Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
Critical appraisal summary: This is the largest RCT in children and young people with cancer treated with dexrazoxane. Rates of clinical cardiotoxicity and second malignant neoplasms were low, and the study may not be appropriately powered to detect a difference between treatments. The follow-up was not long enough to assess the long-term risks and benefits of dexrazoxane treatment, which may not become apparent until decades after treatment.							
Abbreviations: CI, confidence interval; CNS, central nervous system; RCT, randomised controlled trial; RR, risk ratio; SE, standard error; SMN, Second malignant neoplasm							
Study reference 3: Chow et al. 2015							
P1 – Longer-term safety report from 3 RCTs	The 3 RCTs included 1,008 participants across 133 centres. The median age at diagnosis in the 3 studies was between 9.6 and 14.8 years (range across the 3 studies 1.0 to 22.0 years). Studies included people with low-risk Hodgkin's lymphoma (n=255), intermediate/high-risk Hodgkin's lymphoma (n=216) or T-cell acute lymphoblastic leukaemia or advanced stage	**Intervention:** Dexrazoxane Given at a 10:1 dexrazoxane to doxorubicin ratio **Comparator:** No dexrazoxane **Anthracycline treatment:** Doxorubicin, cumulative dose varied between studies: 100–200 mg/m^2 (n=255), 180–300 mg/m^2 (n=216), 360 mg/m^2 (n=537).	Primary Safety	All-cause mortality	Over a median 12.6 year follow-up (range 0 to 15.5 years), 13.2% (67/507) of participants treated with dexrazoxane died, compared with 13.0% (65/501) in the no dexrazoxane group. There was no statistically significant difference between groups, HR 1.03 (95% CI 0.73 to 1.45).	P1 Primary research using quantitative approaches 8/10 The research aims and design of the study are clearly stated. The design is appropriate for the aims and objectives of the study, although the follow-up of the included studies is not sufficient to assess the long-term effects of dexrazoxane, which may take decade to develop. Results	Direct study focusing on people with the indication and characteristics of interest.
			Primary Safety	Specific-cause mortality	Over the median 12.6 year follow-up: **Original cancer** was the cause of death in 9.5% (48/507) of participants treated with dexrazoxane compared with 10.6% (53/501) in the no dexrazoxane group. No statistically significant difference between groups, HR 0.90 (95% CI 0.61 to 1.32). **Second cancer** was the cause of death in 2.0% (10/507) of participants treated with dexrazoxane compared with 1.6% (8/501) in the no dexrazoxane group. No statistically significant difference between groups, HR 1.24 (95% CI 0.49 to 3.15). Of the 18 deaths, 12 were from AML/MDS (7 in dexrazoxane group), 2 from new non-Hodgkin lymphomas (1 in dexrazoxane		

Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
	lymphoblastic non-Hodgkin lymphoma (n=537).				group) and 4 from new solid tumours (2 in dexrazoxane group). **Other toxicity** was the cause of death in 1.4% (7/507) of participants treated with dexrazoxane compared with 0.6% (3/501) in the no dexrazoxane group. No statistically significant difference between groups, HR 2.31 (95% CI 0.60 to 8.95). Infection was the underlying reason for 7 deaths due to other toxicity (5 in dexrazoxane group). No participants died as a result of a cardiovascular cause, although it was listed as a secondary cause in 4 participants (1 acute MI and 1 stroke in the dexrazoxane group and 2 cases of cardiomyopathy/heart failure in the no dexrazoxane group).	are limited to mortality and disease progression outcomes; key outcomes including non-fatal cardiotoxicity and non-fatal adverse events are not reported. Results generally support the author's conclusions, although firm conclusions on the impact of dexrazoxane on clinical cardiotoxicity cannot be made due to low event rate in the RCTs.	
			Secondary Safety	Risk of relapse or disease progression	Over the median 12.6 year follow-up, 15.6% (79/507) of participants treated with dexrazoxane experienced relapse or progressive disease, compared with 19.0% (95/501) in the no dexrazoxane group. No statistically significant difference between groups, HR 0.81 (95% CI 0.60 to 1.08).		

Critical appraisal summary: This study reports on a longer-term follow-up from 3 RCTs, adding over 4 years follow-up to that reported in the original study publications. The dose of anthracycline differed across the 3 RCTs. Rates of clinical cardiotoxicity and second malignant neoplasms across the studies were low, and the systematic review may not be appropriately powered to detect a difference between treatments. The follow-up was not long enough to assess the long-term risks and benefits of dexrazoxane treatment, which may not become apparent until decades after treatment.

Abbreviations: AML, acute myeloid leukaemia; CI, confidence interval; HR, hazard ratio; MD, mean difference; MDS, myelodysplastic syndrome; RCT, randomised controlled trial

8. Grade of evidence table

					Use of dexrazoxane vs. no dexrazoxane to prevent cardiotoxicity in children and young people with cancer receiving anthracycline chemotherapy
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Clinical cardiotoxicity	Shaikh et al. 2016	8/10	Direct study	A	This outcome looked at how many people had symptoms of clinical cardiotoxicity, which was defined in the study as symptomatic congestive heart failure, use of medication for congestive heart failure, heart transplant or death from cardiac causes. The combined results of 4 randomised controlled trials (RCTs) involving 991 children and young people found no significant difference in clinical cardiotoxicity for people treated with dexrazoxane (0 events) compared with no dexrazoxane (3 events, risk ratio [RR] 0.24, 95% confidence interval [CI] 0.03 to 2.09, p=0.88). It should be noted that the total number of events occurring during the RCTs was very low, meaning the studies may have been underpowered to detect a difference. The combined results of 8 non-randomised studies (NRSs) involving 741 children and young people found significantly lower rates of clinical cardiotoxicity in people treated with dexrazoxane (7 events) compared with no dexrazoxane (35 events). RR 0.29 (95% CI 0.14 to 0.61, p=0.001), number needed to treat (NNT) 13 (95% CI 9 to 22). Results from RCTs suggest that dexrazoxane did not reduce clinical cardiotoxicity over a 3.3 to 9.6 year follow-up. Reductions in cardiotoxicity were seen in people treated with dexrazoxane in non-randomised studies, however this evidence is subject to bias and confounding, and is therefore less reliable. These results should be considered with a degree of caution, since heart failure develops over a much longer time in children compared with adults receiving cancer treatment, meaning a very long follow-up would be required to observe a clinically significant difference in symptomatic heart failure. At the time of final follow-up in these studies participants were in their early 20s, and symptomatic heart failure may not develop for another 20 or 30 years.
All cardiotoxicity (including clinical and sub-clinical)	Shaikh et al. 2016	8/10	Direct study	A	This outcome looked at how many people had any type of cardiotoxicity, including clinical cardiotoxicity (for example, symptomatic heart failure) and sub-clinical cardiotoxicity (asymptomatic changes in echocardiographic or biochemical measures). The combined results of 4 RCTs involving 990 children and young people found rates of clinical or sub-clinical cardiotoxicity were significantly lower in people treated with dexrazoxane (5 events) compared with no dexrazoxane (17 events). RR 0.29 (95% CI 0.13 to 0.64, p=0.003), NNT 41 (95% CI 24 to 157). The combined results of 8 NRSs involving 531 children and young people found rates of clinical or sub-clinical cardiotoxicity were significantly lower in children treated with dexrazoxane (30 events) compared with no dexrazoxane (69 events). RR 0.43 (95% CI 0.30 to 0.63, p<0.001), NNT 7 (95% CI 5 to 12).

					These results suggest that dexrazoxane significantly reduces the risk of any cardiotoxicity over follow-ups of less than about 9 years, although it should be noted that that the majority of cases were sub-clinical. Surrogate cardiac markers are not yet known to correlate with long-term cardiac dysfunction and cannot be safely used to predict the long-term cardioprotective effect of dexrazoxane.
Elevated serum cardiac troponin-T	Shaikh et al. 2016	8/10	Direct study	A	This outcome looked at how many people had elevated serum cardiac troponin-T. Troponin-T is a protein released when cardiac muscle is damaged and is a marker of cardiac damage. Troponin-T levels above 0.01 nanogram/ml were considered elevated. Across 1 systematic review (including 2 RCTs) and 1 RCT, 20/207 (9.7%) people receiving dexrazoxane had elevated troponin-T levels, compared with 48/190 (25.3%) people not receiving cardioprotection. Rates of raised troponin-T levels was significantly lower for people treated with dexrazoxane in both studies (both p<0.05). These results suggest that people treated with dexrazoxane are less likely to have raised troponin-T levels compared with people not treated with dexrazoxane, meaning they were less likely to have damage to their heart muscle.
	Asselin et al. 2016	8/10	Direct study		Troponin-T is a surrogate marker of cardiac damage. Follow-up in all studies was less than 10 years and it is not clear whether such surrogate markers correlate with long-term cardiac dysfunction, for example symptomatic heart failure.
Left ventricular fractional shortening z-score	Shaikh et al. 2016	8/10	Direct study	A	This outcome looked at left ventricular fractional shortening, reported using z-score. Left ventricular fractional shortening is measured used echocardiography and looks at the degree of shortening of the left ventricular diameter between end-diastole and end-systole. It is used as a measure of the heart's ability to pump blood around the body. A z-score (standard score) expresses deviation from a mean. A z-score of 0 is equal to the mean (a person without cardiac dysfunction). A z-score of −1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. Across 1 systematic review (including 2 RCTs, n=301), people receiving dexrazoxane had significantly higher (better) z-scores compared with people not receiving cardioprotection. The mean difference (MD) between groups was 0.61 (95% CI 0.22 to 1.01, p=0.002). These results suggest that people treated with dexrazoxane are less likely to have left ventricular fractional shortening compared with people not treated with dexrazoxane, meaning their hearts may be working better. Left ventricular fractional shortening is a surrogate marker of cardiac damage. Follow-up in the studies was less than 10 years and it is not clear whether such surrogate markers correlate with long-term cardiac dysfunction, for example symptomatic heart failure.

Left ventricular thickness-to-dimension ratio z-score	Shaikh et al. 2016	8/10	Direct study	A	This outcome looked at left ventricular thickness-to-dimension ratio, reported using z-score. Left ventricular thickness-to-dimension ratio is measured used echocardiography and is used to predict left ventricular ejection fraction and volume. It is used as a measure of the heart's ability to pump blood around the body. A z-score (standard score) expresses deviation from a mean. A z-score of 0 is equal to the mean (a person without cardiac dysfunction). A Z-score of −1 is equal to 1 standard deviation below the mean, and a Z-score of +1 is equal to 1 standard deviation above the mean.

Across 1 systematic review (including 2 RCTs, n=299), children and young people receiving dexrazoxane had significantly higher z-scores compared with those not receiving dexrazoxane. Mean difference between groups 0.66 (95% CI 0.32 to 1.00, p<0.001).

These results suggest that people treated with dexrazoxane are more likely to have a lower left ventricular thickness-to-dimension ratio z-score compared with people not treated with dexrazoxane, meaning their hearts may be working better.

Left ventricular thickness-to-dimension ratio is a surrogate marker of cardiac damage. Follow-up in the studies was less than 10 years and it is not clear whether such surrogate markers correlate with long-term cardiac dysfunction, for example symptomatic heart failure. |
| Second malignant neoplasms (SMNs) | Shaikh et al. 2016 | 8/10 | Direct study | A | This outcome looked at how many people were diagnosed with second malignant neoplasms (SMNs).

In a systematic review including 5 RCTs (median follow-up 3.3 to 9.6 years, n=1,254), there was no statistically significant difference in rates of SMN for children and young people treated with dexrazoxane (17 events) compared with those not treated with dexrazoxane (7 events), RR 2.37 (95% CI 0.98 to 5.74, p=0.06). The same systematic review also reported SMN rates from 4 NRSs and found no difference in SMN rates between dexrazoxane (7 events) and no dexrazoxane (18 events) groups, RR 0.85 (95% CI 0.35 to 2.07, p=0.72).

These results suggest that dexrazoxane does not significantly increase the short-term risk of SMNs in children and young people. However, the authors of the systematic review suggested that the risk of SMNs may be increased when dexrazoxane is given in addition to treatments known to cause second cancers, for example etoposide or cranial radiation. The longer-term impact of dexrazoxane on SMNs beyond 10 years is not currently known. |

Overall survival rate	Chow et al. 2015	8/10	Direct study	A	This outcome looked at how many participants were alive at the last follow-up. A long-term report from 3 RCTs (n=1,008) found that, over a median 12.6 year follow-up, there was no significant difference in overall survival rate for dexrazoxane compared with no dexrazoxane, HR 1.03 (95% CI 0.73 to 1.45). These results suggest that dexrazoxane does not reduce overall survival up to 12.6 years after treatment. The impact on overall survival beyond this point is not known.
Event-free survival rate	Shaikh et al. 2016	8/10	Direct study	A	This outcome looked at how long a person lives with their disease for without it getting worse. The systematic review reported that, across 5 RCTs (n=1,254) there was no difference in event-free survival for children and young people treated with dexrazoxane compared with those not treated with dexrazoxane, HR 0.99 (0.78 to 1.25, p=0.91). These results suggest that dexrazoxane does not reduce event-free survival for around 3.3 to 9.6 years after treatment. The event-free survival beyond this point is not known.
Relapse or disease progression	Chow et al. 2015	8/10	Direct study	A	This outcome looked at how many people experienced a relapse of their cancer or disease progression. Over a 12.6 year follow-up, across 3 RCTs (n=1,008), there was no difference in the number of people having a relapse or disease progression with dexrazoxane (15.6%) compared with no dexrazoxane (19.0%), hazard ratio 0.81 (95% CI 0.60 to 1.08). These results suggest that dexrazoxane does not increase the risk of disease relapse or progression up to 12.6 years after treatment. The risk of relapse or progression beyond this point is not known.

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| | | | | | This outcome looked at how many people had grade 3 (severe) or grade 4 (life-threatening or disabling) adverse effects.

The RCT (n=537, median follow-up 9.2 years) reported no statistically significant differences between dexrazoxane and no dexrazoxane in rates of infection, haematological adverse effects and central nervous system (CNS) adverse effects. The RCT found that people treated with dexrazoxane were significantly more likely to have mucositis (52 events) compared with no dexrazoxane (33 events, p=0.02).

The following adverse events are reported as being very common (occurring in 1/10 people or more) in the SPC for dexrazoxane: |
|---|---|---|---|---|---|
| Grade 3 and 4 toxicities | Asselin et al. 2016 | 8/10 | Direct study | B | • Anaemia
• Leukopenia (low white blood cell count)
• Nausea
• Vomiting
• Stomatitis (a sore or inflammation inside of the mouth)
• Alopecia
• Asthenia (lack of energy and strength).

These results suggest that children and young people treated with dexrazoxane are more likely to have mucositis compared with those not treated with dexrazoxane. Haematological events and infections occurred in people treated with dexrazoxane and those not treated with dexrazoxane. |

9. Literature search terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People with cancer aged 25 and under receiving a cumulative dose of 300 mg/m^2 or higher of doxorubicin or equivalent dose of another anthracycline or related drug (that is, lifetime exposure). Equivalent doses for other anthracycline drugs: • daunorubicin 450 mg/m^2 • epirubicin 540 mg/m^2 • idarubicin 150 mg/m^2 • mitoxantrone 140 mg/m^2

I – Intervention	Dexrazoxane
Which intervention, treatment or approach should be used?	plus standard treatment
C – Comparison	No cardioprotection
What is/are the main alternative/s to compare with the intervention being considered?	plus standard treatment
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	**Critical to decision-making:** Cardiomyopathy Other measure of acute and chronic cardiotoxicity: • Echocardiogram markers (for example, left ventricular dimensions, wall thickness and shortening, ejection fraction) • Cardiac failure • Reduced exercise tolerance • Troponin • Electrocardiogram (ECG) disturbances Overall survival Cardiotoxicity related mortality **Important to decision-making:** • Relapse rate • Other toxicities / adverse events • Quality of life • Cost-effectiveness
Assumptions / limits applied to search	

Inclusion Criteria
Peer reviewed publications
English language

Exclusion Criteria
Abstracts
Letters
Commentaries
Conference papers
Studies without comparators
Papers published greater than 10 years ago

10. Search strategy

Database: Medline

Platform: Ovid

Version: Ovid MEDLINE(R) 1946 to October 23, 2018

Search date: 24/10/18

Number of results retrieved: 88

Search strategy:

1   dexrazoxane.tw. (478)

2   DEXRAZOXANE/ (61)

3   (ICRF-187 or ICRF187 or "ICRF 187").tw. (251)

4   (ADR-529 or ADR529 or "ADR 529").tw. (25)

5   V03AF02.tw. (0)

6   NSC-169780.tw. (7)

7   (cardioxan* or savene or zinecard or totect).tw. (59)

8   or/1-7 (665)

9   exp Cardiomyopathies/ (87314)

10   ((cardio or cardiac or heart) and (damage or dysfunction or failure or disease*)).ti,ab. (434078)

11   (cardioprotect* or (cardio adj1 protect*)).tw. (17074)

12   (cardiomyopath* or cardiotoxic*).tw. (65655)

13   or/9-12 (514137)

14   8 and 13 (465)

15   chemotherap*.tw. (321046)

16   ("cancer treatment*" or "cancer therap*").tw. (72093)

17   exp Anthracyclines/ (64071)

18   anthracycline*.tw. (12062)

19   (doxorubicin or Adriamycin or doxil or daunorubicin or cerubidine or daunoXome or epirubicin or ellence or idarubicin or aclarubicin or mitoxantrone or novantrone).tw. (59002)

20   or/15-18 (415638)

21   14 and 20 (423)

22   limit 21 to english language (384)

23   limit 22 to yr="2008 -Current" (132)

24   limit 23 to (letter or historical article or comment or editorial or news or case reports) (2)

25   23 not 24 (130)

26   animals/ not humans/ (4474785)

27   25 not 26 (89)

28   remove duplicates from 27 (88)

Database: Medline in-process

Platform: Ovid

Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 23, 2018

Search date: 24/10/18

Number of results retrieved: 20

Search strategy:

1   dexrazoxane.tw. (39)

2   DEXRAZOXANE/ (0)

3   (ICRF-187 or ICRF187 or "ICRF 187").tw. (8)

4   (ADR-529 or ADR529 or "ADR 529").tw. (1)

5   V03AF02.tw. (0)

6   NSC-169780.tw. (0)

7   (cardioxan* or savene or zinecard or totect).tw. (2)

8   or/1-7 (44)

9   exp Cardiomyopathies/ (0)

10   ((cardio or cardiac or heart) and (damage or dysfunction or failure or disease*)).ti,ab. (41916)

11   (cardioprotect* or (cardio adj1 protect*)).tw. (1858)

12   (cardiomyopath* or cardiotoxic*).tw. (6743)

13   or/9-12 (46397)

14   8 and 13 (28)

15   chemotherap*.tw. (36095)

16   ("cancer treatment*" or "cancer therap*").tw. (12449)

17   exp Anthracyclines/ (0)

18   anthracycline*.tw. (1028)

19   (doxorubicin or Adriamycin or doxil or daunorubicin or cerubidine or daunoXome or epirubicin or ellence or idarubicin or aclarubicin or mitoxantrone or novantrone).tw. (4874)

20   or/15-18 (46210)

21   14 and 20 (21)

22   limit 21 to english language (21)

23   limit 22 to yr="2008 -Current" (20)

Database: Medline epubs ahead of print

Platform: Ovid

Version: Ovid MEDLINE(R) Epub Ahead of Print October 23, 2018

Search date: 24/10/18

Number of results retrieved: 4

Search strategy:

1   dexrazoxane.tw. (5)

2   DEXRAZOXANE/ (0)

3   (ICRF-187 or ICRF187 or "ICRF 187").tw. (0)

4   (ADR-529 or ADR529 or "ADR 529").tw. (0)

5   V03AF02.tw. (0)

6   NSC-169780.tw. (0)

7   (cardioxan* or savene or zinecard or totect).tw. (0)

8   or/1-7 (5)

9   exp Cardiomyopathies/ (0)

10   ((cardio or cardiac or heart) and (damage or dysfunction or failure or disease*)).ti,ab. (8224)

11   (cardioprotect* or (cardio adj1 protect*)).tw. (324)

12   (cardiomyopath* or cardiotoxic*).tw. (1209)

13   or/9-12 (9009)

14   8 and 13 (4)

15   chemotherap*.tw. (6923)

16   ("cancer treatment*" or "cancer therap*").tw. (2855)

17   exp Anthracyclines/ (0)

18   anthracycline*.tw. (195)

19   (doxorubicin or Adriamycin or doxil or daunorubicin or cerubidine or daunoXome or epirubicin or ellence or idarubicin or aclarubicin or mitoxantrone or novantrone).tw. (931)

20   or/15-18 (9294)

21   14 and 20 (4)

22   limit 21 to english language (4)

23   limit 22 to yr="2008 -Current" (4)

Database: Medline daily update

Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update October 23, 2018

Search date: 24/10/18

Number of results retrieved: 0

Search strategy

1   dexrazoxane.tw. (0)

2   DEXRAZOXANE/ (0)

3   (ICRF-187 or ICRF187 or "ICRF 187").tw. (0)

4   (ADR-529 or ADR529 or "ADR 529").tw. (0)

5   V03AF02.tw. (0)

6   NSC-169780.tw. (0)

7   (cardioxan* or savene or zinecard or totect).tw. (0)

8   or/1-7 (0)

9   exp Cardiomyopathies/ (91)

10   ((cardio or cardiac or heart) and (damage or dysfunction or failure or disease*)).ti,ab. (564)

11   (cardioprotect* or (cardio adj1 protect*)).tw. (29)

12   (cardiomyopath* or cardiotoxic*).tw. (79)

13   or/9-12 (646)

14   8 and 13 (0)

15   chemotherap*.tw. (442)

16   ("cancer treatment*" or "cancer therap*").tw. (200)

17   exp Anthracyclines/ (93)

18   anthracycline*.tw. (5)

19   (doxorubicin or Adriamycin or doxil or daunorubicin or cerubidine or daunoXome or epirubicin or ellence or idarubicin or aclarubicin or mitoxantrone or novantrone).tw. (92)

20   or/15-18 (647)

21   14 and 20 (0)

Database: Embase

Platform: Ovid

Version: Embase 1974 to 2018 Week 43

Search date: 24/10/18

Number of results retrieved: 136

Search strategy:

1   dexrazoxane.tw. (756)

2   (ICRF-187 or ICRF187 or "ICRF 187").tw. (523)

3   (ADR-529 or ADR529 or "ADR 529").tw. (63)

4   V03AF02.tw. (0)

5   NSC-169780.tw. (19)

6   (cardioxan* or savene or zinecard or totect).tw. (317)

7   or/1-6 (1270)

8   exp cardiomyopathy/ (122048)

9   ((cardio or cardiac or heart) and (damage or dysfunction or failure or disease*)).ti,ab. (731087)

10   (cardioprotect* or (cardio adj1 protect*)).tw. (27492)

11   (cardiomyopath* or cardiotoxic*).tw. (111909)

12   or/8-11 (830428)

13   7 and 12 (749)

14   chemotherapy/ (139600)

15   chemotherap*.tw. (551320)

16   ("cancer treatment*" or "cancer therap*").tw. (122657)

17   exp anthracycline/ (19671)

18   anthracycline*.tw. (20932)

19   (doxorubicin or Adriamycin or doxil or daunorubicin or cerubidine or daunoXome or epirubicin or ellence or idarubicin or aclarubicin or mitoxantrone or novantrone).tw. (95548)

20   or/15-18 (660134)

21   13 and 20 (551)

22   limit 21 to english language (481)

23   limit 22 to yr="2008 -Current" (249)

24   23 not (letter or editorial).pt. (247)

25   24 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (168)

26   nonhuman/ not (human/ and nonhuman/) (4225614)

27   25 not 26 (136)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR) & CENTRAL

Platform: Wiley

Version:

   CDSR –Issue 10 of 12, October 2018

   CENTRAL – Issue 9 of 12, September 2018

Search date: 29th May 2018

Number of results retrieved: CDSR 1; CENTRAL 15

Strategy:

#1   dexrazoxane:ti,ab   81

#2   MeSH descriptor: [Dexrazoxane] this term only   18

#3   (ICRF-187 or ICRF187 or "ICRF 187"):ti,ab 27

#4   (ADR-529 or ADR529 or "ADR 529"):ti,ab   8

#5   V03AF02:ti,ab 0

#6   NSC-169780:ti,ab   0

#7   (cardioxan* or savene or zinecard or totect):ti,ab   12

#8   {or #1-#7}   108

#9   MeSH descriptor: [Cardiomyopathies] explode all trees   1778

#10   ((cardio or cardiac or heart) and (damage or dysfunction or failure or disease*)):ti,ab   45059

#11   (cardioprotect* or (cardio NEAR/1 protect*)):ti,ab   1572

#12   (cardiomyopathy* or cardiotoxic*):ti,ab   3182

#13   {or #9-#12}   48041

#14   #8 and #13   76

#15   chemotherap*:ti,ab   43670

#16   ("cancer treatment*" or "cancer therap*"):ti,ab   2485

#17   MeSH descriptor: [Anthracyclines] explode all trees 5136

#18   anthracycline*:ti,ab   2036

#19   (doxorubicin or Adriamycin or doxil or daunorubicin or cerubidine or daunoXome or epirubicin or ellence or idarubicin or aclarubicin or mitoxantrone or novantrone):ti,ab   8989

#20   {or #15-#18}   47435

#21   #14 and #20 53

#14 and #20 with Cochrane Library publication date Between Oct 2008 and Oct 2018, in Cochrane Reviews   1

#14 and #20 with Publication Year from 2008 to 2018, in Trials   15

Ran a second, broad search in CDSR to identify broadly relevant Cochrane Reviews that would not have been picked up by the full strategy. A set of 8 results was added to the database results:

#1   anthracycline*:ti,ab   2036

#2   (cardiotoxic* or cardiac or cardio or cardioprotect* or cardiomyopathy*):ti,ab   46426

#3   #1 and #2 with Cochrane Library publication date Between Jan 2008 and Oct 2018, in Cochrane Reviews 8

CRD – incorporating DARE; HTA database; NHS EED

Version:

DARE – March 2015 (legacy database)

HTA – ongoing

NHS EED – March 2015 (legacy database)

Search date: 29th May 2018

Number of results retrieved: DARE 1; HTA 0; NHS EED 0

Strategy:

1 (dexrazoxane) OR (ICRF-187 or ICRF187 or "ICRF 187") OR (ADR-529 or ADR529 or "ADR 529") 5

2 (V03AF02) OR (NSC-169780) 0

3 MeSH DESCRIPTOR dexrazoxane 0

4 (cardioxan* or savene or zinecard or totect) 1

5 #1 OR #2 OR #3 OR #4 5

Limited to 2008-2018 1

11. Evidence selection

A literature search was conducted which identified 167 unique references (107 duplicates were removed from the initial search; see search strategy for full details). These references were screened using their titles and abstracts and 21 references were obtained and assessed for relevance. Of these, 3 references are included in the evidence summary. The remaining 18 references were excluded and are listed in the following table.

Study reference	Reason for exclusion
Abdel-Qadir H, Ong G, Fazelzad R et al. (2017) Interventions for preventing cardiomyopathy due to anthracyclines: a Bayesian network meta-analysis. Annals of oncology : official journal of the European Society for Medical Oncology 28(3), 628-633	Population – average age over 25 years
Asselin B, Devidas M, Zhou T et al. (2012) Cardioprotection and safety of dexrazoxane (DRZ) in children treated for newly diagnosed T-cell acute lymphoblastic leukemia (T-ALL) or advanced stage lymphoblastic leukemia (T-LL). Journal of clinical oncology 30(15 SUPPL. 1),	Publication – abstract only
Benetou D, Stergianos E, Geropeppa M et al. (2018) Late-onset cardiomyopathy among survivors of childhood lymphoma treated with anthracyclines: a systematic review. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese ,	Outcomes – study does not report details of trials involving dexrazoxane, instead reporting on disease outcomes in children receiving anthracyclines
Choi HS, Park ES, Kang HJ et al. (2010) Dexrazoxane for preventing anthracycline cardiotoxicity in children with solid tumors. Journal of Korean medical science 25(9), 1336-42	Intervention – mean doxorubicin dose less than 300 mg/m^2
Kalam K and Marwick T H (2013) Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: A systematic review and meta-analysis. European Journal of Cancer 49(13), 2900-2909	Population – average age over 25 years
Kim In-Ho, Lee Ji Eun, Youn Ho-Joong et al. (2017) Cardioprotective Effect of Dexrazoxane in Patients with HER2-Positive Breast Cancer Who Receive Anthracycline-Based Adjuvant Chemotherapy Followed by Trastuzumab. Journal of breast cancer 20(1), 82-90	Population – average age over 25 years

Kim H, Kang HJ, Park KD et al. (2018) Risk Factor Analysis for Secondary Malignancy in Dexrazoxane-Treated Pediatric Cancer Patients. Cancer research and treatment : official journal of Korean Cancer Association ,	Not prioritised – higher quality evidence reporting the same outcomes included in the evidence review.
Liesse K, Harris J, Chan M et al. (2018) Dexrazoxane Significantly Reduces Anthracycline-induced Cardiotoxicity in Pediatric Solid Tumor Patients: A Systematic Review. Journal of pediatric hematology/oncology 40(6), 417-425	Evidence – unclear methodology.
Limat S, Daguindau E, Cahn J Y, et al. (2014) Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma. Journal of clinical pharmacy and therapeutics 39(2), 168-74	Intervention – the study was designed to compare the cardiotoxicity of 2 chemotherapy regimens, not the cardioprotective effect of dexrazoxane.
Lipshultz SE, Scully RE, Lipsitz SR, et al. (2010) Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. The Lancet. Oncology 11(10), 950-61	Not prioritised – results of this RCT included in a systematic review already included in this evidence review.
Paladio-Hernandez J and Martinez-Morales J (2015) Cost-Effectiveness of Cardioprotective Effect of Dexrazoxane (Cardioxane) in Advanced/Metastatic Breast Cancer Patients Treated with Anthracycline-Based Chemotherapy in Mexico. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 18(7), A454	Population – average age over 25 years
Schloemer NJ, Brickler M, Hoffmann R et al. (2017) Administration of Dexrazoxane Improves Cardiac Indices in Children and Young Adults With Acute Myeloid Leukemia (AML) While Maintaining Survival Outcomes. Journal of pediatric hematology/oncology 39(5), e254-e258	Not prioritised – higher quality evidence reporting the same outcomes included in the evidence review.
Schwartz CL, Wexler LH, Krailo MD et al. (2016) Intensified Chemotherapy With Dexrazoxane Cardioprotection in Newly Diagnosed Nonmetastatic Osteosarcoma: A Report From the Children's Oncology Group. Pediatric Blood and Cancer 63(1), 54-61	Evidence – not appropriate comparator. Although the study included 2 treatment arms all participants received dexrazoxane, limiting comparison with no cardioprotection to historical comparisons to an older study.
Seif A E, Walker D M, Li Y, et al. (2015) Dexrazoxane exposure and risk of secondary acute myeloid leukemia in pediatric oncology patients. Pediatric Blood and Cancer 62(4), 704-709	Not prioritised – higher quality evidence reporting the same outcomes included in the evidence review.
Sun F, Qi X, Geng C et al. (2015) Dexrazoxane protects breast cancer patients with diabetes from chemotherapy-induced cardiotoxicity. The American journal of the medical sciences 349(5), 406-12	Population – average age over 25 years
van Dalen , E C, Caron H N, Dickinson H O, and Kremer L C. M (2011) Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database of Systematic Reviews (6)	Population – results for people <25 years and >25 years reported together. Majority of included studies had average age over 25 years.

Vrooman LM, Neuberg DS, Stevenson KE et al. (2011) The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukaemia: a report from the Dana-Farber Cancer Institute ALL Consortium. European journal of cancer (Oxford, and England : 1990) 47(9), 1373-9	Not prioritised – results of this study included in a systematic review already included in this evidence review.
Wang P, Zhang S, Zhang X B, et al. (2013) Protective effect of dexrazoxane on cardiotoxicity in breast cancer patients who received anthracycline-containing chemotherapy. Zhonghua zhong liu za zhi [chinese journal of oncology] 35(2), 135-139	Population – average age over 25 years

Three studies were identified by specialists involved in this evidence review as being clinically impactful. These are listed in the following table:

Study	Comment
Asselin BL, Devidas M, Chen L et al. (2016) Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404. Journal of Clinical Oncology 34(8), 854–62	Included in evidence review
Chow EJ, Asselin BL, Schwartz CL et al. (2015) Late Mortality After Dexrazoxane Treatment: A Report From the Children's Oncology Group. Journal of Clinical Oncology 33(24), 2639–45	Included in evidence review
Schwartz CL, Wexler LH, Krailo MD et al. (2016) Intensified Chemotherapy With Dexrazoxane Cardioprotection in Newly Diagnosed Nonmetastatic Osteosarcoma: A Report From the Children's Oncology Group. Pediatric Blood and Cancer 63(1), 54-61	Excluded from evidence review Evidence – not appropriate comparator. Although the study included 2 treatment arms all participants received dexrazoxane, limiting comparison with no cardioprotection to historical comparisons to an older study.

12. Related NICE guidance and NHS England clinical policies

The NHS England drugs list v13 (April 2018) states that dexrazoxane to prevent anthracycline cardiotoxicity is not routinely commissioned.

NICE has not issued any guidelines or advice on preventing anthracycline cardiotoxicity with dexrazoxane.

13. Terms used in this evidence summary

Abbreviations

Term	Definition
CHF	Congestive heart failure
CI	Confidence interval
HR	Hazard ratio
NNT	Number needed to treat
NRS	Non-randomised study
RCT	Randomised controlled trial
RR	Risk ratio
SE	Standard error
SMN	Second malignant neoplasm

Medical definitions

Term	Definition
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 and is a marker of cardiac damage

14. References

Asselin BL, Devidas M, Chen L et al. (2016) Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404. Journal of Clinical Oncology 34(8), 854–62

Chow EJ, Asselin BL, Schwartz CL et al. (2015) Late Mortality After Dexrazoxane Treatment: A Report From the Children's Oncology Group. Journal of Clinical Oncology 33(24), 2639–45

Chow EJ, Chen Y, Kremer LC et al. (2015b) Individual prediction of heart failure among childhood cancer survivors. Journal of Clinical Oncology 33(5), 394–402

Geisberg CA and Sawyer DB (2010) Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage. Current Hypertension Reports 12 (6), 404–10

Lipshultz SE, Giantris AL, Lipsitz SR et al. (2002) Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91-01 acute lymphoblastic leukemia protocol. Journal of Clinical Oncology 20(6), 1677–82.

Schwartz CL, Constine LS, Villaluna D et al. (2009) A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. Blood 114, 2051–59

Shaikh F, Dupuis LL, Alexander S et al. (2016) Cardioprotection and Second Malignant Neoplasms Associated With Dexrazoxane in Children Receiving Anthracycline Chemotherapy: A Systematic Review and Meta-Analysis. Journal of the National Cancer Institute 108(4) pii: djv357. doi: 10.1093/jnci/djv357

Tebbi CK, London WB, Friedman D et al. (2007) Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. Journal of Clinical Oncology 25(5), 493–500

van Dalen EC, Caron HN, Dickinson HO et al. (2011) Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database of Systematic Reviews (6)

Wexler LH, Andrich MP, Venzon D et al. (1996) Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. Journal of Clinical Oncology 14(2), 362–72.