Summary of findings tables, grading of the evidence and detailed conclusions of evidence dexrazoxane cardioprotection

RCTs

For detailed information on the included studies we refer to the Cochrane systematic review:
De Baat EC, Mulder RL, Armenian S, Feijen EAM, Grotenhuis H, Hudson MM, Mavinkurve-Groothuis AM, Kremer LCM, Van Dalen EC. Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines. Cochrane Database of Systematic Reviews 2022, Issue 9. Art. No.: CD014638.

Observational studies

Outcome	Study	No. of participants Diagnosis	Follow-up (median/mean, range) yr	Anthracycline (type, dose mg/m^2) Dexrazoxane (dose mg/m^2) RT involving the heart (dose)	Events n/N (%)	Effect size	Risk of bias
		Dexrazoxane vs control group					
1.1 Risk of clinical heart failure (n= 2 studies)	Getz (2020)	96 vs 918 AML	Since start of treatment, Median (IQR) 3.2 (2.4-4.2) vs 3.6 (2.5-4.8)	Daunorubicin (nm) Nm No	*CTCAE v3.0 Grade≥3 (SF<15% or LVEF<40%)* 3.8% vs 8.5% (Number of patients not reported)	Univariate HR (95% CI) Dexrazoxane vs control: 0.30 (0.07-1.23)	SB: low risk AB: low risk DB: unclear risk CF: high risk
	Kim (2019)	1035 vs 418 Various	Starting point not mentioned, Median (range): 4.95 (0-15.2) vs 10.4 (0-17.4) (p < 0.01)	Dox, dau, ida, epi and mitox, cumulative dose; median (range): 210 (17-753.9) vs 150 (15.4-665.1) (p < 0.01). Dexrazoxane dose; median (range): 2390 (125-36989) Nm, but RT on thorax n(%): 29 (2.8) vs 9 (2.2) (p=0.48).	*CHF* Overall: 2/1031 (0.2%) vs 3/416 (0.7%) > 400 mg/m2 anthracyclines: 0/172 (0%) vs 0/32 (0%)	*Fisher exact test** *Overall: p= 0.1* *>400mg/m2 anthracyclines: p=1*	SB: low risk AB: low risk DB: unclear risk CF: high risk

GRADE assessment:

Study design:	+2	Observational evidence for intervention questions
Study limitations:	-1	Limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding high in 2/2
Consistency:	0	No important inconsistency, both studies showed non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, large sample sizes but in 1/2 low total number of events and in 1/2 unclear number of event; in 1/2 no confidence interval available. .
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose response relationship, but small sample size and only evaluated in 1/2.
Plausible confounding:	0	No plausible confounding.

Quality of evidence:	⊕⊖⊖⊖ VERY LOW
Conclusion:	There is no significant effect of dexrazoxane versus no dexrazoxane treatment on the risk of clinical heart failure in childhood cancer patients treated with anthracyclines. (2 studies no significant effect; 2467 participants; unclear number of events; no multivariable analyses)

Abbreviations: AB, attrition bias; CHF, congestive heart failure; CF, confounding; dau, daunorubicin; DB, detection bias; Dox, doxorubicin; epi, epirubicin; ida, idarubicin; IQR, interquartile range; LVEF, left ventricular ejection fraction; mitox, mitoxantrone, n, number; nm, not mentioned; p, p-value; RT, radiotherapy; SB, selection bias; SF, shortening fraction; vs, versus; yr, year.
* *Fisher exact test was performed by the guideline authors based on the number as provided by the article.*

Outcome	Study	No. of participants Diagnosis	Follow-up (median/mean, range) yr	Anthracycline (type, dose mg/m^2) Dexrazoxane (dose mg/m^2) RT involving the heart (dose)	Events n/N (%)	Effect size	Risk of bias
		Dexrazoxane vs control group					
1.2 Risk of clinical and subclinical myocardial dysfunction combined (n= 4 studies)	Getz (2020)	96 vs 918 AML	Since start of treatment, Median (IQR) 3.2 (2.4-4.2) vs 3.6 (2.5-4.8)	Daunorubicin (nm) Nm No	*Grade≥2 (SF<24% or LVEF<50%)* 10.9% vs 23.4% (Number of patients not reported)	Univariate HR (95% CI) Dexrazoxane vs control: 0.40 (0.20-0.81)	SB: low risk AB: low risk DB: unclear risk CF: high risk
	Kim (2019)	1035 vs 418 Various	Starting point not mentioned, Median (range) 4.95 (0-15.2) vs 10.4 (0-17.4) (p < 0.01)	Dox, dau, ida, epi and mitox, cumulative dose; median (range): 210 (17-753.9) vs 150 (15.4-665.1) (p < 0.01). Dexrazoxane dose; median (range): 2390 (125-36989) Nm, but radiotherapy on thorax n(%): 29 (2.8) vs 9 (2.2) (p=0.48).	*Asymptomatic ventricular dysfunction and CHF:* Overall: 28/1031 (2.7%) vs 6/416 (1.4%). > 400 mg/m^2 of total cumulative anthracyclines: 7/172 (4.1%) vs. 2/32 (6.3%).	*Fisher exact test*** *Overall: p= 0.2* *>400 mg/m^2: p=0.6*	SB: low risk AB: low risk DB: unclear risk CF: high risk
	Caru (2019)	63 vs 51 ALL	From end of treatment, Mean (SD) 8.7 ± 3.3 vs 17.9 ± 3.4 (p<0.05)	Doxorubicin: 284.3 ± 53.7 vs 287.6 ± 68.6 Dexrazoxane: 2789.3 ± 469.4 Nm	*EF<55%* 13 (20.6%) vs 27 (52.9%).	p-value = not significant	SB: unclear risk AB: low risk DB: unclear risk CF: high risk
	Kang (2012)	135 vs 123* Various	Nm	Nm Nm Nm	*Anthracycline induced cardiotoxicity:* > 15% reduction of LVEF, a reduction in LVEF to less than 45% or evidence of CHF Prevalence: nm	Multivariate OR (95% CI) Control vs dexrazoxane (LA)***: 2.78 (1.14–6.78)	SB: unclear risk AB: unclear risk DB: unclear risk CF: high risk

GRADE assessment:		
Study design:	+2	Observational evidence for intervention questions
Study limitations:	-2	Limitations: Selection bias low in 2/4 and unclear in 2/4; Attrition bias low in 3/4 and unclear in 1/4; Detection bias unclear in 4/4; Confounding high in 4/4.
Consistency:	0	No important inconsistency, 2 studies showed significant decreased risk after dexrazoxane and 2 studies showed no significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	No important imprecision, 2/4 small sample size, 2/4 confidence interval not mentioned.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	In 1/4 no dose response relationship, in 3/4 dose response relationship not assessed
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⨁⊖⊖⊖ VERY LOW	
Conclusion:	There is a decreased risk of clinical and subclinical heart failure combined in childhood cancer patients treated with anthracyclines and dexrazoxane compared to anthracyclines without dexrazoxane. (4 studies, 2 significant effect; 2839 participants; unclear number of events; 1/4 multivariable analyses)	

Abbreviations: AB, attrition bias; CHF, congestive heart failure; CF, confounding; dau, daunorubicin; DB, detection bias; Dox, doxorubicin; epi, epirubicin; ida, idarubicin; IQR, interquartile range; LVEF, left ventricular ejection fraction; mitox, mitoxantrone, n, number; nm, not mentioned; p, p-value; RT, radiotherapy; SB, selection bias; SF, shortening fraction; vs, versus; yr, year.
* The dexrazoxane group was subdived into two groups:
LA: dexrazoxane was added at cumulative anthracycline dose<100 mg/m^2
HA: dexrazoxane was added at cumulative anthracycline dose>100 mg/m^2
** Fisher exact test was performed by the guideline authors based on the number as provided by the article.
*** In the text of the publication the OR of 2.78 is explained as following: "The patients without dexrazoxane administration was strongly associated with an increased risk of cardiotoxicity compared to the patients with early use of dexrazoxane (group LA+D) (OR, 2.78 [95% CI,1.114–6.781], P<0.025)." We assumed that the order of LA+D versus A is swapped in table 4. We chose to demonstrate the results according to the text of the publication.

Outcome	Study	No. of participants Diagnosis	Follow-up (median/mean, range) yr	Anthracycline (type, dose mg/m^2) Dexrazoxane (dose mg/m^2) RT involving the heart (dose)	Events n/N (%)	Effect size	Risk of bias
		Dexrazoxane vs control group					
2.1 Risk of reduced overall survival (n=2 studies)	Getz (2020)	96 vs 918 AML	Since start of treatment, Median (IQR) 3.2 (2.4-4.2) vs 3.6 (2.5-4.8)	Daunorubicin (nm) Nm No	5 year overall survival: 62/96 (65%) vs 569/918 (61.9%)	p-value = 0.613	SB: low risk AB: low risk DB: low risk CF: high risk
	Kim (2019)	1035 vs 418 Various	Starting point not mentioned, Median (range) 4.95 (0-15.2) vs 10.4 (0-17.4) (p < 0.01)	Dox, dau, ida, epi and mitox, cumulative dose; median (range): 210 (17-753.9) vs 150 (15.4-665.1) (p < 0.01). Dexrazoxane dose; median (range): 2390 (125-36989)	Overall survival: 905/1035 (87.4%) vs 361/418 (86.3%)	p-value = 0.06	SB: low risk AB: low risk DB: low risk CF: high risk

		Nm, but radiotherapy on thorax n(%): 29 (2.8) vs 9 (2.2) (p=0.48).
GRADE assessment:		
Study design:	+2	Observational evidence for intervention questions
Study limitations:	-1	Limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding high in 2/2
Consistency:	0	No important inconsistency; 2/2 studies demonstrate non-significant effects
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship not assessed.
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	There is no significant effect of dexrazoxane versus no dexrazoxane treatment on overall survival in childhood cancer patients treated with anthracyclines. (2 studies no significant effect; 2467 participants; unclear no events; no multivariable analyses)	

Abbreviations: AB, attrition bias; CHF, congestive heart failure; CF, confounding; dau, daunorubicin; DB, detection bias; Dox, doxorubicin; epi, epirubicin; ida, idarubicin; IQR, interquartile range; LVEF, left ventricular ejection fraction; mitox, mitoxantrone, n, number; nm, not mentioned; p, p-value; RT, radiotherapy; SB, selection bias; SF, shortening fraction; vs, versus; yr, year.

Outcome	Study	No. of participants Diagnosis	Follow-up (median/mean, range) yr	Anthracycline (type, dose mg/m²) Dexrazoxane (dose mg/m²) RT involving the heart (dose)	Events n/N (%)	Effect size	Risk of bias
		Dexrazoxane vs control group					
2.2 Risk of subsequent malignant neoplasm (3 studies)	Getz (2020)	96 vs 918 AML	Since start of treatment, Median (IQR) 3.2 (2.4-4.2) vs 3.6 (2.5-4.8)	Daunorubicin (nm) Nm No	1/nm vs 3/nm	p-value = nm	SB: low risk AB: unclear risk DB: low risk CF: high risk
	Kim (2019)	1035 vs 418 Various	Starting point not mentioned, Median (range) 4.95 (0-15.2) vs 10.4 (0-17.4) (p < 0.01)	Dox, dau, ida, epi and mitox, cumulative dose; median (range): 210 (17-753.9) vs 150 (15.4-665.1) (p < 0.01). Dexrazoxane dose; median (range): 2390 (125-36989) Nm, but radiotherapy on thorax n(%): 29 (2.8) vs 9 (2.2) (p=0.48).	12/880 (1.4%) vs 4/344 (1.2%)	Univariate HR (95% CI): Dexrazoxane vs. control: 3.46 (0.92-13.07) Multivariate* HR (95% CI): Total duration of anthracycline (mo) 1.05 (1.03-1.06) Time after last anthracycline (mo) 0.99 (0.98-0.99)	SB: low risk AB: low risk DB: unclear risk CF: high risk

	Seif (2015)	1406 vs 14 126 Various	Since first anthracycline exposure, Median (IQR) 0.8 (0.5–1.8) vs. 0.7 (0.3–1.6).	Dox, dau, ida, epi and mitox (nm) Nm Nm	Secondary AML: 3/1046 (0.21%) vs 77/14126 (0.55%)	Multivariable OR (95% CI)** Dexrazoxane exposure yes vs no: 0.38 (0.12–1.27) Etoposide exposure yes vs no: 2.36 (1.48–3.79) *Subgroup analysis* OR (95% CI) Lymphoma-only Dexrazoxane exposure yes vs no: 1.41 (0.17–11.46) Lymphoma-excluded Dexrazoxane exposure yes vs no: 0.25 (0.06–1.07)	SB: unclear risk AB: low risk DB: unclear risk CF: high risk

GRADE assessment:

Study design:	+2	Observational evidence for intervention questions
Study limitations:	-2	Limitations: Selection bias low in 2/3; Attrition bias low in 2/3; Detection bias unclear in 2/3; Confounding high in 3/3
Consistency:	0	No important inconsistency; 2/3 studies demonstrate non-significant effects, 1 study unclear.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship not assessed.
Plausible confounding:	0	No plausible confounding

Quality of evidence: ⊕⊖⊖⊖ VERY LOW

Conclusion: There is no significant effect of dexrazoxane versus no dexrazoxane treatment on subsequent malignant neoplasms in childhood cancer patients treated with anthracyclines. (2 studies no significant effect, 1 study unclear; 17 999 participants; unclear number of events; one useful multivariable analysis)

Abbreviations: AB, attrition bias; CHF, congestive heart failure; CF, confounding; dau, daunorubicin; DB, detection bias; Dox, doxorubicin; epi, epirubicin; ida, idarubicin; IQR, interquartile range; LVEF, left ventricular ejection fraction; mitox, mitoxantrone, n, number; nm, not mentioned; p, p-value; RT, radiotherapy; SB, selection bias; SF, shortening fraction; vs, versus; yr, year.

*Unclear which variables are included in the multivariable model.

** A propensity score was established to balance patient-level confounders that may have altered the likelihood of exposure to dexrazoxane. The propensity score represents the probability that a patient would receive dexrazoxane based on specified observed covariates The propensity score was calculated by adjusted multivariable logistic regression with dexrazoxane exposure as the outcome, and covariates including age, gender, race, insurance, diagnosis group, and hospital as predictors. The five-strata propensity score was included as a categorical covariate in the logistic regression model to adjust for possible confounding.

Outcome	Study	No. of participants Diagnosis	Follow-up (median/mean, range) yr	Anthracycline (type, dose mg/m^2) Dexrazoxane (dose mg/m^2) RT involving the heart (dose)	Events n/N (%)	Effect size	Risk of bias
Dexrazoxane vs control group							
2.3 Risk of toxicity other than cardiac damage (n=1 study)	Getz (2020)	96 vs 918 AML	Median (IQR) 3.2 (2.4-4.2) vs 3.6 (2.5-4.8)	Daunorubicin (nm) Nm No	No observable differences in course length, durations of neutropenia or hospitalization, ICU admissions, or rates of mucositis and bloodstream infection by dexrazoxane exposure	p-value = nm	SB: low risk AB: unclear risk DB: unclear risk CF: high risk

GRADE assessment:

Study design:	+2	Observational evidence for intervention questions
Study limitations:	-2	Limitations: Selection bias low; Attrition bias unclear; Detection bias unclear; Confounding high.
Consistency:	0	Not applicable; only 1 study included.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Number of event not mentioned, only one study included.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Dose response relationship not assessed.
Plausible confounding:	0	No plausible confounding.

Quality of evidence: ⨁⊖⊖⊖ VERY LOW

Conclusion: There is no significant effect of dexrazoxane versus no dexrazoxane treatment on toxicities other than cardiac damage in childhood cancer patients treated with anthracyclines. (1 study, no observable differences, but no effect size reported, 1014 participants; unclear number of events; no multivariable analyses)

Abbreviations: AB, attrition bias; CHF, congestive heart failure; CF, confounding; dau, daunorubicin; DB, detection bias; Do, doxorubicin; epi, epirubicin; ida, idarubicin; IQR, interquartile range; LVEF, left ventricular ejection fraction; mitox, mitoxantrone, n, number; nm, not mentioned; p, p-value; RT, radiotherapy; SB, selection bias; SF, shortening fraction; vs, versus; yr, year.