Evidence tables IGHG 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

Getz et al. Effect of Dexrazoxane on Left Ventricular Systolic Function and Treatment Outcomes in Patients With Acute Myeloid Leukemia: A Report From the Children's Oncology Group. JCO, 2020, 2398-2406

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Multicenter prospective cohort Treatment era 2011-2016 Follow-up (yrs, median - IQR) Dexrazoxane group group: 3.2 (2.4-4.2) Control group: 3.6 (2.5-4.8)	Type and number of participants Childhood, adolescent and young adult AML patients (USA) Dexrazoxane group: n=96 (51% female) treated with dexrazoxane at every anthracycline course Control group: n=918 (47.5% female) treated without dexrazoxane Diagnoses AML (de novo) (100%) Age at diagnosis Dexrazoxane group: <30 yrs (98% <21yrs) Control group: <30 yrs (98% <21yrs)	Chemotherapy *Anthracyclines* Type: Daunorubicin Cumulative dose: nm Peak dose†: nm Infusion duration: nm *Dexrazxane/control intervention:* Route of delivery: nm Dosing: nm Timing: nm Treatment length: nm *Other chemotherapy:* mitoxantrone, cytarabine, etoposide, with or without bortezmib (50%) Radiotherapy involving the heart Dexrazoxane group: no Control group: no	Outcome definitions - Echocardiogram or MUGA: LVSD defined as 1. SF<28% or EF<55% 2. grade≥2 (SF<24% or EF<50%) CTCAE v3.0 3. grade≥3 (SF<15% or EF<40%) CTCAE v3.0 - 5 year overall survival: time to death - Secondary malignant neoplasm: nm - Non cardiac toxicities: durations of neutropenia or rates of mucositis and bloodstream infection Results Dexrazoxane group vs control group *LVSD incidence (unadjusted HR):* 1. 26.5% vs 42%; HR 0.55 (95% CI 0.36- 0.86) 2. 10.9% vs 23.4%; HR 0.40 (95% CI 0.20-0.81) 3. 3.8% vs 8.5%; HR 0.30 (95% CI 0.07-1.23) *5 year overall survival:* 65% vs 61.9%; p=0.613 *SMN:*	Difference in cardiotoxic treatment between the groups is unclear. The dose of dexrazoxane is unclear (ratio to daunorubicin and cumulative dose). **Risk of bias** A. Selection bias: Low Reason: 1,014/1,092 (92.6%) of the original cohort included in the study group B. Attrition bias: Low risk for cardiac function Reason: compliance with cardiac monitoring was high (ie, 91% during on protocol therapy, 75% overall) and did not differ by dexrazoxane exposure Unclear for SMN and non-cardiac toxicities

	Age at follow-up Dexrazoxane group group: nm. Control group: nm Prior anthracyclines or cardiac RT: nm, but unlikely since it was a "de novo" diagnosis. Prior cardiac dysfunction: unclear	Surgery Dexrazoxane group: no Control group: no HSCT Dexrazoxane group: 8 (8.3%) Control group: 67 (7.3%)	1/nm vs 3/nm; 1 unknown morphology, 1 myelodysplastic syndrome, 1 glioma, 1 T-cell acute lymphoblastic leukaemia *Non cardiac toxicities:* No observable differences in course length, durations of neutropenia or hospitalization, ICU admissions, or rates of mucositis and bloodstream infection by dexrazoxane exposure	Reason: the number of assessed participants is not mentioned Low risk for overall survival. Reason: assessed in 100% of the study group. C. Detection bias: Unclear for cardiac function, SMN and non-cardiac toxicities Reason: blinding not mentioned Low risk for overall survival Reason: NA for this outcome D. Confounding: High risk Reason: Only unadjusted comparisons are presented. There was a significant difference in follow-up duration between the dexrazoxane group and control group.

Abbreviations: AML, acute myeloid leukemia; EF, ejection fraction; HSCT, hematopoietic stem-cell transplantation; ICU, intensive care unit; IQR, interquartile range; iv, intravenous; LVSD, left ventricular systolic dysfunction; na, not applicable; nm, not mentioned; SF, shortening fraction; SMN, second malignant neoplasms; RT, radiotherapy; USA, United Stated of America; yrs, years.

†i.e. max. received in 1 week

Seif et al. Dexrazoxane Exposure and Risk of Secondary Acute Myeloid Leukemia in Pediatric Oncology Patients. Pediatr Blood Cancer 2015;62:704–709

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Treatment era 1999 - 2011 Follow-up Yrs (median IQR) Dexrazoxane group vs control group: 0.8 (0.5–1.8) vs. 0.7 (0.3–1.6). Since first anthracycline exposure	Type and number of participants Patients with non-AML malignancy treated with anthracycline or anthracenedione within one year of first identified cancer admission (multinational) Dexrazoxane group: N= 1406 (41.5% female) treated with dexrazoxane Control group: N= 14126 (41.8% female) treated without dexrazoxane Diagnoses Various cancer types Age at diagnosis Dexrazoxane group vs control group: n(%) <10 yrs: 480 (34) vs 7062 (50) 10-20yrs: 875 (62) vs 6780 (48) >20 yrs: 51 (4) vs 280 (2) Age at follow-up nm Prior anthracyclines nm Prior cardiac RT: nm Prior cardiac dysfunction: nm	Chemotherapy *Anthracyclines:* Type: doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone Cumulative dose: nm Peak dose†: nm Infusion duration: nm *Dexrazxane/control intervention:* Route of delivery: intravenous Dosing: nm Timing: nm Treatment length: nm *Other chemotherapy:* etoposide (dexrazoxane group: 51%, control group: 46%). Radiotherapy involving the heart Nm Surgery Nm HSCT Nm	Outcome definitions Secondary AML: A patient was determined to have secondary AML if an ICD-9 code for AML was assigned in a hospitalization starting at least 90 days after the first observed hospitalization containing an anthracycline exposure and manual review of the chemotherapy billed during the hospitalization inclusive of an AML ICD-9 code was consistent with a standard AML chemotherapy induction regimen. Results Dexrazoxane group vs control group n(%) *Secondary AML:* 3/1046 (0.21%) vs 77/14126 (0.55%) *Multivariable model* risk of secondary AML:* - Etoposide exposure OR=2.36, 95% CI 1.48–3.79, P=0.0003 - Dexrazoxane exposure OR=0.38, 95% CI 0.12–1.27, P=0.1166 *Subgroup analyses risk of secondary AML:* Lymphoma-only: dexrazoxane OR=1.41, 95% CI 0.17–11.46,P=0.75 Lymphoma-excluded: dexrazoxane OR=0.25, 95% CI 0.06–1.07, P=0.0608	Mitoxantrone was labelled as anthracycline. *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. Significant longer follow-up time and more patients were treated with etoposide in the dexrazoxane group compared to control group. **Risk of bias** A. Selection bias: Unclear risk Reason: Number of eligible patients with anthracycline exposure within one year after diagnosis is not reported. B. Attrition bias: Low risk Reason: 100% was assessed for secondary AML

				C. Detection bias: Unclear Reason: blinding nm D. Confounding: high risk Reason: the propensity score was included in the model but follow-up and other cancer treatment were not incorporated.

Abbreviations: AML, acute myeloid leukemia; HSCT, hematopoietic stem-cell transplantation; IQR, interquartile range; iv, intravenous; na, not applicable; nm, not mentioned; OR, odds ratio; p, p-value; RT, radiotherapy; yrs, years.
†i.e. max. received in 1 week

Kim et al. Risk Factor Analysis for Secondary Malignancy in Dexrazoxane-Treated Pediatric Cancer Patients. Cancer Res Treat. 2019;51(1):357-367

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cohort study Treatment era 1996 to 2012 Follow-up, yrs (median, range) Dexrazoxane group vs control group: 4.95 (0-15.2) vs 10.4 (0-17.4) (p < 0.01). Starting point nm	Type and number of participants Korean hospitals. Patients treated with any anthracycline. Treated with dexrazoxane N= 1035 (39.7% female) Control group N=418 (41.6% female) (P=0.5 for sex) Diagnoses Various cancer types. Age at diagnosis, yrs (median, range) Dexrazoxane group vs control group: 6 (0-21) vs 5 (0-26)* (p=0.1) Age at follow-up Dexrazoxane group: nm Control group: nm Prior anthracyclines: nm Prior cardiac RT: nm Prior cardiac dysfunction: nm	Chemotherapy *Anthracyclines:* Type: doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone Cumulative dose[a,b]: dexrazoxane group vs control group: median (range) 210 (17-753.9) vs 150 (15.4-665.1) (p < 0.01) Peak dose†: nm Infusion duration: nm *Dexrazoxane intervention:* Route of delivery: nm Dosing: median (range) 2390 mg/m^2 (125-36989) Timing: nm Treatment length: median (range) days 167 (1-2,974) *Other chemotherapy:* Dexrazoxane group vs control group *n (%):* Etoposide: 447 (43) vs 122 (29) Dose mg/m^2: median (range) 1820 (40-15430) vs 1830 (120-6340) (p=0.52) Cyclophosphamide: 718 (69) vs 297 (71) Dose mg/m^2: median (range) 4030 (4-74110) vs 2570 (310-35370) (p<0.01) Radiotherapy involving the heart: nm, but radiotherapy on thorax: Dexrazoxane group vs control group *n (%):* 29 (2.8) vs 9 (2.2) (p=0.48). Dose: nm	Outcome definitions Cardiac events could be detected during and after the administration of anthracyclines Asymptomatic ventricular dysfunction = nm Congestive heart failure = nm Cardiomyopathy = nm Overall survival = nm SMN = nm Results Dexrazoxane group vs control group: Overall: - Asymptomatic ventricular dysfunction: 26/1031 (2.5%) vs 3/416 (0.7%). - CHF= 2/1031 (0.2%) vs 3/416 (0.7%). Fisher exact test**: p= 0.1 - Cardiomyopathy = 7/1031 (0.7%) vs 4/416 (1.0%). - Asymptomatic ventricular dysfunction + CHF = 28/1031 (2.7%) vs 6/416 (1.4%).Fisher exact test**: p= 0.2 In patients who received more than 400 mg/m2 of total cumulative anthracyclines: - Asymptomatic ventricular dysfunction = 7/172 (4%) vs 2/32 (6.3%). - CHF= 0/172 vs 0/32. Fisher exact test**: p=1 - Cardiomyopathy = 0/172 vs. 2/32 (6.3%). - Asymptomatic ventricular dysfunction + CHF= 7/172 (4.1%) vs. 2/32 (6.3%). Fisher exact test**: p=0.6. Overall survival = 905/1035 (87.4%) vs 361/418 (86.3%) (p= 0.06) SMN: n= 12/880 (1.4%) vs 4/344 (1.2%) Univariate analysis of SMN risk factors: unadjusted HR (95% CI) - Dexrazoxane group vs. non-dexrazoxane group 3.46 (0.92-13.07) p= 0.07	Mitoxantrone was labelled as anthracycline. Significant differences between dexrazoxane and control group: Significant shorter follow-up time and higher cumulative anthracycline and cyclophosphamide dose in dexrazoxane group compared to control group. In addition, the dose of radiation on thorax is unclear. Only patients who received dexrazoxane with every anthracycline dose were included in the study. Unclear how congestive heart failure and cardiomyopathy differ. ***Unclear which variables are included in the multivariable model. **Risk of bias** A. Selection bias: Low risk Reason: the complete original cohort was analysed. B. Attrition bias: All outcomes: Low risk Reason: all outcomes were assessed in >75% of the participants. Cardiac outcomes (99.6% vs 99.5% overall and 100% in both groups for patients with more than 400 mg/m2), survival (100% in both groups), SMN (85% vs 82%).

		Surgery: Dexrazoxane group vs control group: nm HSCT: Dexrazoxane group vs control group: 0 vs 0	- Age (yr) 0.97 (0.85-1.09) p= 0.55 - Sex (female vs. male) 2.30 (0.82-6.47) p=0.11 - Syndrome or genetic disease (yes vs. no) 3.14 (0.03-23.39) p=0.50 - G-CSF (yes vs. no) 5.05 (1.03-91.25) p= 0.09 - Previous radiation (yes vs. no) 3.12 (1.15-8.45) p= 0.03 - Cumulative dose of etoposide (mg/m2) 1.31 (1.16-1.47) p< 0.01 - Cumulative dose of cyclophosphamide (mg/m2) 1.08 (1.06-1.10) p< 0.01 - Cumulative dose of total anthracyclines (mg/m2) 2.88 (1.82-4.58) p< 0.01 - Total duration of anthracycline (mo) 1.06 (1.05-1.07) p< 0.01 - Time after last anthracycline (mo) 0.98 (0.97-0.99) p< 0.01 - Total duration of chemotherapy (mo) 1.05 (1.04-1.07) p< 0.01 Multivariate analysis: adjusted* HR (95% CI) - Total duration of anthracycline (mo) 1.05 (1.03-1.06) < 0.01 - Time after last anthracycline (mo) 0.99 (0.98-0.99) < 0.01	C. Detection bias: Unclear for cardiac outcomes and SMN. Reason: blinding not mentioned Low risk for OS Reason: not relevant for this outcome D. Confounding: Unclear for the multivariable analysis Reason: It is not clear which variables were included in the multivariable model. For the univariate model of SMN and univariate analysis of cardiac outcomes and overall survival the risk of confounding are high.

Abbreviations: CHF, congestive heart failure; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; IQR, interquartile range; iv, intravenous; na, not applicable; nm, not mentioned; mo, months; SMN, second malignant neoplasms; OS, overall survival; p, p-value; RT, radiotherapy; yrs, years.

[a] Dose data of 3 vs 7 patients were not available.

[b] Cumulative dose of total anthracyclines=Cumulative dose of total anthracyclines (mg/m^2) = daunorubicin (mg/m^2) x 0.833 + doxorubicin (mg/m^2) + idarubicin (mg/m^2) x 5 + epirubicin (mg/m^2) x 0.67 + mitoxantrone (mg/m^2) x 4

†i.e. max. received in 1 week

* Since the median age at diagnosis was 6 vs 5 years we assumed that in >75% of the cohort the age at diagnosis was <22 years, in addition the authors use “pediatric patient” to describe the study population. ** Fisher exact test was performed by the authors based on the number as provided by the article.***Unclear which variables are included in the multivariable model.

Caru et al. Doxorubicin treatments induce significant changes on the cardiac autonomic nervous system in childhood acute lymphoblastic leukemia long-term survivors. Clinical Research in Cardiology, 2019

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross sectional Treatment era 1987 and 2010 Follow-up, mean (SD) yrs Dexrazoxane group vs control group 8.7 ± 3.3 vs 17.9 ± 3.4 from end of treatment (p<0.05)	Type and number of participants Treated according to DFCI-ALL 87-01 to 05-01 protocols, without relapse or refractory ALL, and had been diagnosed at least 5 years earlier. Canadian hospital. Dexrazoxane goup: n=63 (% female unclear) Control group: n=51 (% female unclear) Diagnoses ALL Age at diagnosis <19 years Age at follow-up, mean (SD) yrs. Dexrazoxane group vs control group: 19.6 ± 5.5 vs 28.3 ± 5.3 p < 0.05 Prior anthracyclines: nm Prior cardiac RT: nm Prior cardiac dysfunction: nm	Chemotherapy *Anthracyclines:* Type: doxorubicin Cumulative dose mg/m^2 (mean (SD)): Dexrazoxane group vs control group: 284.3 ± 53.7 vs 287.6 ± 68.6 Peak dose†: nm Infusion duration: nm *Dexrazoxane intervention:* Route of delivery: nm Dosing mg/m2 (mean (SD)): 2789.3 ± 469.4 Timing: nm Treatment length: nm *Other chemotherapy:* nm Radiotherapy involving the heart: nm Surgery: nm HSCT: 0 vs 0	Outcome definitions Reduced ejection fraction: <55% on echocardiography Results Reduced ejection fraction *n(%)* Dexrazoxane group vs control group: M-mode: 13/63 (20.6%) vs 27/51 (52.9%). Biplane: 25/63 (39.7%) vs 26/51 (51.0%). For both methods, there was no significant difference between the groups.	Significant differences between dexrazoxane and control group: age at follow-up and follow-up duration. Other factors as gender, and cardiac RT are unclear. Part of the study population included in the Lipshultz study included in the Cochrane systematic review. We only included high risk patients in this table as none of the standard risk patients received dexrazoxane. **Risk of bias** A. Selection bias: unclear Reason: the original cohort including the number of high risk patients is not mentioned. B. Attrition bias: low risk Reason: all patients had an echocardiogram. C. Detection bias: unclear Reason: not mentioned D. Confounding: high Reason: for the univariate model the risk of confounding is high.

Abbreviations: ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem-cell transplantation; iv, intravenous; n, number; na, not applicable; nm, not mentioned; RT, radiotherapy; SD, standard deviation; yrs, years.

†i.e. max. received in 1 week

Kang et al. Cardioprotective effect of early dexrazoxane use in anthracycline treated pediatric patients. J Chemother. 2012 Oct;24(5):292-6.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cohort study (retrospective) Treatment era 1997 to 2005 Follow-up, nm (serial cardiac assessment at different cumulative doses of anthracyclines)	Type and number of participants Korean hospital. Newly diagnosed paediatric cancer patients who received anthracyclines with or without dexrazoxane. 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 N: total group (%female) Dexrazoxane LA: n=85 (31.8%) Dexrazoxane HA: n=50 (38%) Control group: n=123 (44.7%) Diagnoses leukemia, lymphoma, myelodysplastic syndrome, Ewing sarcoma, osteosarcoma, neuroblastoma, hepatoblastoma and other solid tumors. Age at diagnosis years (median, range) Dexrazoxane group LA: 6 (0.1-15) Dexrazoxane HA: 6 (0.2-17) Control group: 6 (0.2-15) Age at follow-up, nm	Chemotherapy *Anthracyclines:* Type: nm (cumulative dose was calculated by using a conversion chart for doxorubicin equivalents) Cumulative dose mg/m^2: nm Peak dose†: nm Infusion duration: nm *Dexrazxane/control intervention:* Route of delivery: iv Dosing mg/m^2: ratio to doxorubicin dose = 10-20:1 Timing: 15 minutes immediately preceding anthracycline treatments Treatment length: nm *Other chemotherapy:* nm Radiotherapy involving the heart nm Surgery nm HSCT nm	Outcome definitions Anthracycline induced cardiotoxicity: greater than 15% reduction of LVEF, reduction in LVEF to less than 45%, or evidence of CHF. Results *Univariate analysis for the risk of anthracycline induced cardiotoxicity:* - Significant (p-value<0.05): age at diagnosis, timing of dexrazoxane administration - Not significant (p-value>0.05): Total cumulative dose of anthracycline, disease type, gender, obesity, cardiac radiation therapy, type of anthracyclines, anthracycline dose based on body weight or body surface area, dose of dexrazoxane, and hematopoietic stem cell transplantation. *Multivariate analysis for the risk of anthracycline induced cardiotoxicity:* Dexrazoxane administration LA vs HA: OR 2.45, 95% CI 0.85–7.04 (p-value 0.096) Control vs LA: OR 2.78, 95% CI 1.14–6.78 (p-value 0.025)[a] Age <10 vs ≥ 10 years: OR 2.81, 95% CI 1.12–7.02 (p-value 0.028)	They describe that they investigated the cumulative anthracycline dose and cardiac RT as risk factor of cardiotoxicity, however they used a strict p-value (p=0.05) as threshold for further testing. The cumulative anthracycline dose per group are not provided. In addition, there is no data on occurrence of cardiotoxicity after anthracycline treatment. These results reflect acute cardiotoxicity. **Risk of bias** A. Selection bias: unclear Reason: nm how many patients were eligible for the original cohort. B. Attrition bias: unclear Reason: nm how many patients were excluded because of missing echocardiography records, also unclear how many patients are analysed at each dose. C. Detection bias: unclear Reason: nm if the outcome assessors were blinded D. Confounding: high risk Reason: based on univariate analysis the gender, cumulative anthracycline dose and cardiac RT were not related to cardiotoxicity. However the non-significant univariate results of anthracycline dose could hypothetically reflect protection of dexrazoxane at

	Prior anthracyclines No (for all three groups) Prior cardiac RT: nm Prior cardiac dysfunction: No (for all three groups)			higher anthracycline doses. It should be analysed in one multivariate model. The influence of follow-up time is probably low since all patients are evaluated at the same cumulative anthracycline dose.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CHF, congestive heart failure; EF, ejection fraction; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; ICU, intensive care unit; IQR, interquartile range; iv, intravenous; LVSD, left ventricular systolic dysfunction; n, number; na, not applicable; nm, not mentioned; mo, months; SF, shortening fraction; SMN, second malignant neoplasms; OR, odds ratio; OS, overall survival; p, p-value; RT, radiotherapy; SD, standard deviation; USA, United Stated of America; yrs, years.

†i.e. max. received in 1 week

[a] 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.