Conclusions of evidence for the effects of anthracycline treatment with versus without dexrazoxane

Study type	Conclusion of evidence	Effect (95% CI)[1] dxz vs. no dxz	GRADE - Quality of evidence
Clinical heart failure			
Children RCT	No significant difference between treatment groups	Pooled RR 0.20 (0.01 – 4.19)	Low (3 studies) (1-3)
Adults RCT	Lower risk in dexrazoxane treated group	Pooled RR 0.22 (0.11 – 0.43)	Low* (7 studies) (4-10)
Children obs	No significant difference between treatment groups	Single studies	Very low (2 studies) (11, 12)
Cardiomyopathy/heart failure as primary cause of death			
Children RCT	No events in both treatment groups	Not estimable	Low (3 studies) (13)
Adults RCT	No studies	No studies	No studies
Children obs	No studies	No studies	No studies
Clinical heart failure and subclinical myocardial dysfunction combined			
Children RCT	Lower risk in dexrazoxane treated group (def 1)	RR 0.33 (0.13 – 0.85)	Low (1 study) (14)
	No significant difference between treatment groups (def 2; only best-case analysis)	Fisher exact non-significant	Very low (1 study) (1)
Adults RCT	Lower risk in dexrazoxane treated group (def 1)	Pooled RR 0.37 (0.24 – 0.56)	Low* (3 studies) (4, 5, 10)
	Lower risk in dexrazoxane treated group (def 2)	Pooled RR 0.46 (0.33 – 0.66)	Low* (2 studies) (8, 9)
Children obs	Lower risk in dexrazoxane treated group	Single studies	Very low (4 studies) (11, 12, 15, 16)
Tumor response			
Children RCT	No significant difference between treatment groups (def 1; only best-case analysis)	RR 1.01 (0.95 – 1.07)	Very low (1 study) (17)
	No significant difference between treatment groups (def 2)	RR 0.92 (0.84 – 1.01)	Low (1 study) (3)
Adults RCT	No significant difference between treatment groups	Pooled RR 0.91 (0.79 – 1.04)	Low* (6 studies) (4-6, 8-10)
Children obs	No studies	No studies	No studies
Progression-free survival			
Children RCT	No studies	No studies	No studies
Adults RCT	In favor of dexrazoxane treated group (def 1)	HR 0.62 (0.43 – 0.90)	Very low* (1 study) (5)
	No significant difference between treatment groups (def 2)	HR 0.95 (0.64 – 1.40)	Very low* (1 study) (6)
	No significant difference between treatment groups (def 3)	Pooled HR 1.18 (0.97 – 1.43)	Low* (2 studies) (8, 9)
Children obs	No studies	No studies	No studies

Overall survival/mortality			
Children RCT	No significant difference between treatment groups	Pooled HR 1.01 (0.72 – 1.42)	Low (3 studies) (13)
Adults RCT	No significant difference between treatment groups	Pooled HR 1.04 (0.88 – 1.23)	Low* (4 studies) (5, 6, 8, 9)
Children obs	No significant difference between treatment groups	Single studies	Very low (2 studies) (11, 12)
Adverse effects: subsequent malignant neoplasm			
Children RCT	Higher risk in dexrazoxane treated group (in available and worst-case analysis)	Pooled RR 3.08 (1.13 – 8.38)	Low (3 studies) (1, 3, 18)
	No significant difference between treatment groups (in best case analysis)	Pooled RR 2.51 (0.96 – 6.53)	Low (4 studies) (1, 3, 18, 19)
Adults RCT	No studies	No studies	No studies
Children obs	No significant difference between treatment groups	Single studies	Very low (3 studies) (11, 12, 20)

[1] Results from available case analysis (available, worst and best analysis demonstrated similar results if not stated otherwise).* Quality of the evidence from adult RCTs was downgraded with one level to account for indirectness.

Clinical heart failure and subclinical myocardial dysfunction combined (RCTs children):
Definition 1: 1) evidence of clinical congestive heart failure, 2) a reduction in LVEF as measured by MUGA to < 45% or 3) a decrease in LVEF as measured by MUGA of > 20 percentage points from baseline.
Definition 2: 1) clinical heart failure (no definition provided) or 2) subclinical myocardial dysfunction defined as decreased LVFS; however it was stated that toxicity was graded according to NCI CTCAEv2 criteria, grade 3 or higher but LVFS is not included in that definition.

Tumor response (RCTs children):
Definition 1: no definition of complete remission provided.
Definition 2: disappearance of active Hodgkin lymphoma (gallium negative, ≥ 70% decrease in the sum of the products of the perpendicular diameters of measurable lesions, and negative bone marrow or bone scan if initially positive).

Progression-free survival (RCTs adults):
Definition 1: time from first date of complete response, partial response or stable disease until the date progressive disease was first noticed
Definition 2: time to progression; starting point nm
Definition 3: time from randomization to progression either on or off treatment

CI= confidence interval, dxz = dexrazoxane, def= definition, obs = observational, RCT = randomized controlled trials, RR= risk ratio, HR= hazard ratio, vs = versus.