Equivalence Ratio for Daunorubicin to Doxorubicin in Relation to Late Heart Failure in Survivors of Childhood Cancer

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ABSTRACT

Purpose

Cumulative anthracycline dose is one of the strongest predictors of heart failure (HF) after cancer treatment. However, the differential risk for cardiotoxicity between daunorubicin and doxorubicin has not been rigorously evaluated among survivors of childhood cancer. These risks, which are based on hematologic toxicity, are currently assumed to be approximately equivalent.

Patients and Methods

Data from 15,815 survivors of childhood cancer who survived at least 5 years were used. Survivors were from the Emma Children's Hospital/Academic Medical Center ($n = 1,349$), the National Wilms Tumor Study ($n = 364$), the St Jude Lifetime Cohort Study ($n = 1,695$), and the Childhood Cancer Survivor Study ($n = 12,407$). The hazard ratio (HR) for clinical HF through age 40 years for doses of daunorubicin and doxorubicin (per 100-mg/m² increments) was estimated by using Cox regression adjusted for sex, age at diagnosis, treatment with other anthracycline agents and chest radiation, and cohort membership.

Results

In total, 5,144 (32.5%) patients received doxorubicin as part of their cancer treatment, whereas 2,243 (14.7%) received daunorubicin. On the basis of 271 occurrences of HF during a median follow-up time after cohort entry of 17.3 years (range, 0.0 to 35.0 years), the cumulative incidence of HF at age 40 years was 3.2% (95% CI, 2.8% to 3.7%). The average ratio of HRs for daunorubicin to doxorubicin was 0.45 (95% CI, 0.23 to 0.73). A similar ratio was obtained by using a linear dose-response model, which yielded an HR of 0.49 (95% CI, 0.28 to 0.70).

Conclusion

Compared with doxorubicin, daunorubicin was less cardiotoxic among survivors of childhood cancer than most current guidelines suggest. This may have implications for follow-up guidelines. The feasibility of substitution of doxorubicin with daunorubicin in childhood cancer treatment protocols to reduce cardiotoxicity should be additionally investigated.

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INTRODUCTION

Childhood cancer treatment has improved greatly over the last several decades, which has resulted in long-term survival for greater than 80% of children with cancer.¹ However, many treatment protocols include anthracyclines (eg, doxorubicin, daunorubicin, epirubicin, and idarubicin), and/or an anthraquinone (eg, mitoxantrone), which are associated with a dose-related risk of cardiotoxicity.²⁻⁴ In children, the reported incidence of anthracycline-associated clinical heart failure (HF) has been as high as 2% by 20 years after treatment,^{2,3} and incidence increases with extended follow-up.⁵ Other than the

cumulative dose, HF risk factors among survivors of childhood cancer include young age at diagnosis,² concurrent chest-directed radiation exposure,^{2,3} and, possibly, female sex.⁶

Prospective screening for late cardiotoxicity is recommended by national and international pediatric oncology organizations, and the cumulative anthracycline dose (ie, the sum dose from all types of anthracyclines) is an important factor in the determination of cardiomyopathy screening recommendations.^{7,8} However, no consensus exists regarding the optimal anthracycline equivalence ratio for conversion of doses of daunorubicin, epirubicin, idarubicin, and, possibly, mitoxantrone to doxorubicin-

equivalent doses to estimate the risk of late cardiotoxicity.⁹ Existing equivalence ratios (Table 1) are based in large part on doses that produce equivalent hematologic toxicity, with the assumption that hematologic toxicities and cardiotoxicities are correlated.¹⁹ A more accurate equivalence ratio that is based directly on risk for HF may help to refine the prediction of HF risks after treatment and to improve subsequent cardiac follow-up of survivors.

By using data from four large, well-characterized cohorts of survivors of childhood cancer with extensive follow-up, we sought to determine the optimal cardiotoxicity dose equivalence ratio for daunorubicin compared with doxorubicin, the two most commonly used anthracyclines, on the basis of the actual risk of HF among these survivors.

PATIENTS AND METHODS

Study Population

Cohorts of survivors of childhood cancer from the Emma Children's Hospital/Academic Medical Center (EKZ/AMC) cohort, the National Wilms Tumor Study (NWTs), the St Jude Lifetime Cohort Study (SJLIFE), and the Childhood Cancer Survivor Study (CCSS) have been described in detail previously.²⁰⁻²⁵ In brief, the EKZ/AMC cohort includes all patients who were younger than 18 years at diagnosis and treated for childhood cancer at the AMC in Amsterdam, the Netherlands, between 1966 and 2001 and who survived for at least 5 years after diagnosis. The NWTs cohort included patients who were younger than 16 years at diagnosis, who had a diagnosis of a kidney tumor, and who were treated at one of 250 sites in the United States, Canada, or other countries between 1969 and 2002. This analysis was restricted to those patients who survived a minimum of 5 years after diagnosis. The NWTs sample available to us had been selected as a nested HF case-cohort data set. The SJLIFE cohort enrolled patients with a diagnosis of a childhood malignancy who were treated, irrespective of age, at St Jude Children's Research Hospital between 1962 and 2001 at the time of this analysis. Cohort members had survived at least 10 years from diagnosis and were at least 18 years of age at cohort entry. The CCSS cohort included patients younger than 21 years at diagnosis with the most common types of childhood cancer who were treated at one of 26 institutions in North America between 1970 and 1986 and who survived at least 5 years after diagnosis. CCSS participants who also were members of NWTs and SJLIFE were counted only once, in the CCSS cohort.

HF Assessment

In all four cohorts, we restricted HF cases to those that occurred after cohort entry by age 40 years and that were defined in the Common Terminology Criteria

for Adverse Events, version 4.03,²⁶ as severe (grade 3; requiring medical treatment), life-threatening (grade 4), or fatal (grade 5). In EKZ/AMC and SJLIFE, HF occurrence was ascertained by means of medical records, death certificates, and prospective clinical cardiac assessments. In NWTs, HF occurrence was ascertained by using medical records, if possible, which were supplemented with death certificates. The CCSS relied on patient and/or family self-reports, if corroborated by concurrent use of appropriate cardiac medications, that were supplemented by death certificates. NWTs, similar to CCSS, also accepted self-reports, if corroborated by concurrent use of appropriate medications.

Statistical Analyses

Because of the limited number of individuals who received epirubicin, idarubicin, or mitoxantrone, we examined only the relationships for doxorubicin and daunorubicin. We used Cox proportional hazards models to determine different dose-response relationships a priori, by using 100-mg/m² dose increments of anthracycline with age as the time scale. For the first dose group, 1 to 200 mg/m² was used, because the number of events in the lower-dose groups was low. Doses of doxorubicin and daunorubicin were included in the same model and adjusted for each other. Models were also adjusted for sex, age at diagnosis, dose categories for chest radiotherapy (no chest radiotherapy or < 5, ≥ 5 to < 15, ≥ 15 to < 35, or ≥ 35 Gy), and an indicator for exposure to an anthracycline or anthraquinone other than doxorubicin or daunorubicin (eg, epirubicin, idarubicin, or mitoxantrone). We accounted for the possibility of any cohort-specific effect by stratifying our estimates by cohort.

Models accounted for second malignant neoplasms, with the exclusion of nonmelanoma skin cancers, and death as a result of other causes as competing risks. If a survivor of childhood cancer developed a second malignant neoplasm before surviving for 5 years, the patient was excluded from the analysis (in the EKZ/AMC, NWTs, and SJLIFE cohorts) or the treatment was taken into account (in CCSS). Individuals were censored at the time of HF grades 3 to 5, at age 40 years, or at the end of cohort follow-up, whichever occurred first. To incorporate the NWTs data with other cohort data, members of the NWTs subcohort were weighted by the subcohort sampling probability, which was calculated as $1 \div [322 \div 6,717] = 20.86$, on the basis of methods described by Prentice²⁷ and Barlow et al.²⁸ As a consequence, HF occurrences from NWTs that were selected outside the subcohort were censored; that is, they entered the risk set only when they became a case. They were weighted with a value of 1 at that time.

In a sensitivity analysis, we evaluated a second model to directly examine the effects of doxorubicin and daunorubicin exposures without other cardiotoxic exposures. We excluded all survivors who received chest radiotherapy and those who received more than one type of anthracycline or anthraquinone. Because of the smaller sample size available for this restricted model, anthracycline doses were collapsed into 150-mg/m² categories.

For the primary and secondary models, we calculated the equivalence ratio of the hazard ratios (HRs) for daunorubicin to doxorubicin in each dose category and then averaged these to obtain an equivalence ratio across all dose

Table 1. Anthracycline Toxicity Equivalence Ratios Used in Various Cooperative Groups and Cohort Studies for Assessment of Cardiotoxicity

Group or Study	Doxorubicin*	Daunorubicin	Idarubicin	Epirubicin	Mitoxantrone
Children's Oncology Group ¹⁰⁻¹²	1	1†	5	0.67	4
Bristol Royal Hospital for Sick Children ¹³	1	1		1	
AML Collaborative Group ¹⁴	1	1	5		5
Kyushu University, Fukuoka, Japan ¹⁵	1	1	1	1	1
Taiwan Pediatric Oncology Group ¹⁶	1		3		2
Childhood Cancer Survivor Study ²	1	1	3		
Dutch Childhood Oncology Group LATER ³	1	1		0.67	
Sookmyung Women's University, Seoul, Korea ^{17‡}	1	0.5	2	0.5	2.2

Abbreviations: AML, acute myelocytic leukemia; LATER, Longterm Effects of Childhood Cancer (Lange Termijn Effecten Kinderkanker).

*Reference value (except AML Collaborative Group, which used daunorubicin ratio of 1 as the reference value).

†Ratio of 1 reported in the current Children's Oncology Group guidelines, version 4, October 2013; previous versions used a ratio of 0.83.

‡All ratios listed are based on hematologic toxicity equivalence rather than cardiotoxicity with the exception of Sookmyung Women's University, which uses ratios that are based on the ratio proposed by Keefe.¹⁸

categories. To calculate the 95% CIs, we used the bootstrap method with replacement from the data with 1,000 replications. The ratios were recomputed from each of these data sets, and the standard deviation (SD) of the 1,000 estimates was used as the standard error in a Wald 95% CI. If the bootstrap distribution was extremely skewed, the CI was presented on the basis of the 2.5th and 97.5th percentiles of the bootstraps.

Finally, we modeled dose-response curves for each agent by using linear relative-rate models, with the assumption that events followed a Poisson distribution. Models were weighted as before and included a log-linear term to adjust for current age, cohort, sex, age at diagnosis, dose categories for chest radiotherapy, and exposure to an anthracycline other than doxorubicin or daunorubicin (ie, epirubicin, idarubicin, or mitoxantrone). Additional models were used to assess departures from linearity (eg, linear spline or linear exponential methods); the Akaike information criterion.²⁹ likelihood ratio tests (for nested models) were used for model comparisons.

R (version 2.15; R Foundation, Vienna, Austria) and SAS (version 9.3; SAS Institute, Cary, NC) software were used for analyses.

RESULTS

The pooled study population included 15,815 survivors (47.2%, female; Table 2), who had a median age at diagnosis of 6.7 years (range, 0.0 to 24.8 years) and a median follow-up time after cohort entry of 17.3 years (range, 0.0 to 35.0 years). In total, 5,144 patients (32.5%) received doxorubicin as part of their primary childhood cancer treatment, and the median dose was 255 mg/m² (interquartile range [IQR], 144 to 365 mg/m²). In contrast, 2,243 patients (14.7%) received daunorubicin, and the median dose was 111 mg/m² (IQR, 91 to 271 mg/m²); 175 patients (1.1%) received another type of anthracycline. Overall, 742 patients (4.7%) received more than one type of anthracycline, and 4,044 patients (25.6%) received radiotherapy to the chest at a median dose of 30 Gy (IQR, 20 to 38 Gy).

We included 271 occurrences of HF in the analysis (Table 2; Appendix Table A1, online only). Among these occurrences, 185 patients (68.1%) received doxorubicin (n = 95 without chest radiotherapy), whereas 18 (7.0%) received daunorubicin (n = 13 without chest radiotherapy); 11 patients (4.0%) received both doxorubicin and daunorubicin (n = 6 without chest radiotherapy). Four patients (1.1%) received either epirubicin or mitoxantrone with or without daunorubicin. Among the remaining patients with HF occurrences, 37 (13.7%) were treated with only chest radiotherapy, and 16 (5.9%) received no known potential cardiotoxic treatment. The overall cumulative incidence of HF at the age of 40 years was 3.2% (95% CI, 2.8% to 3.7%).

After multivariable adjustment, the average equivalence ratio between the HRs of doxorubicin and daunorubicin, in 100-mg/m² increments, was 0.45 (95% CI, 0.23 to 0.73; Table 3; Fig 1). Although radiotherapy to the chest was associated with the development of HF (15 to 35 Gy v none: HR, 2.87 [95% CI, 2.05 to 4.02]; ≥ 35 Gy v none: HR, 4.67 [95% CI, 3.29 to 6.61]), there was no evidence of an interaction between chest radiotherapy and either doxorubicin (*P* = .09) or daunorubicin (*P* = .73). To additionally clarify whether chest radiotherapy modified the relationships among anthracyclines and HF, we examined a second model that excluded all patients who were treated with chest radiotherapy and who received more than one type of anthracycline; 10,219 survivors (n = 117 HF occurrences) remained available for analysis. In this model, the average daunorubicin-to-doxorubicin ratio, which was based on 150-mg/m² increments, was estimated to be 0.41, but the 95% CI was wider (95% CI, 0.29 to 1.28; Table 3). Of note, median doses in both models of daunorubicin were

similar to those of doxorubicin across each 100- or 150-mg/m² dose increment. In other analyses, direct adjustment for cohort provided results similar to those of models stratified by cohort (data not shown). Exclusion of the NWTs data yielded results similar to our primary model results, though estimates tended to be slightly less precise (ratio, 0.46 [95% CI, 0.21 to 0.75] with NWTs exclusion v 0.45 [95% CI, 0.23 to 0.73] with the primary model).

In our dose-response analysis (Fig 1; Appendix Table A2, online only), the linear, linear-spline, and linear-exponential models all seemed to have a better fit (ie, lower Akaike information criterion) than the log-linear model. Because these models had similar log-likelihood values according to the excess relative risk of HF, we estimated a daunorubicin-to-doxorubicin ratio of 0.49 (95% CI, 0.28 to 0.70) by using the simplest model (ie, linear). This result was similar to the ratios derived by using Cox models that were based on dose increments of 100 mg/m².

DISCUSSION

Daunorubicin was less cardiotoxic than doxorubicin among survivors of childhood cancer; the daunorubicin-to-doxorubicin cardiotoxicity equivalence ratio was between 0.4 and 0.5. This contrasts with most commonly used equivalence ratios mentioned in cardiotoxicity screening guidelines that are primarily based on hematologic toxicity and antitumor efficacy. Our results were based on examinations of the HRs for clinically significant HF, with adjustment for other characteristics, such as chest radiotherapy, that may influence the risk of HF. The results were consistent when we used either our full data set or a more restricted data set that excluded patients exposed to chest radiotherapy and/or other anthracycline agents. In addition, we obtained similar results by using a parametric dose-response model.

Doxorubicin and daunorubicin have been assumed to have similar antitumor efficacy, though rigorous comparisons have been reported infrequently. In a small number of in vitro and animal studies, the drugs showed equivalent antitumor efficacy.^{30,31} Furthermore, a few human studies have shown similar antitumor efficacy.^{32,33} Moreover, dosages of doxorubicin and daunorubicin are comparable in most treatment protocols.^{33,34} However, randomized clinical trials to directly compare doxorubicin and daunorubicin with regard to their tumoricidal equivalence in children are lacking.^{9,19}

In 2001, Keefe¹⁸ reported a daunorubicin-to-doxorubicin cardiotoxicity equivalence ratio of 0.5, which is similar to the ratio we found in this study. The equivalence ratio in that review was derived by comparing the dose at which each agent was associated with a 5% cumulative incidence of cardiotoxicity, although the exact source of those data and the exact method of derivation were not fully specified. Early seminal works by von Hoff et al^{36,37} suggested a 5% incidence of HF with approximately 700 to 800 mg/m² of daunorubicin,³⁶ compared with 400 to 500 mg/m² of doxorubicin.³⁷ In other studies of anthracycline-related cardiotoxicity, investigators have attempted to evaluate the differences between derivatives.^{19,38} For example, van der Pal et al³⁸ reported a 27% prevalence of subclinical HF, which was defined as a shortening fraction less than 30%, among a Dutch cohort of 525 survivors of childhood cancer survivors who had available echocardiographic data. This cohort was included in our analysis. Although a trend suggested that daunorubicin was less cardiotoxic than doxorubicin in that analysis, a definitive conclusion could not be

Table 2. Patient Characteristics of 15,815 Eligible Survivors of Childhood Cancer

Characteristic	EKZ/AMC Cohort		NWTSA		SJLIFE		CCSS ^b		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Survivors ^c	1,349	8.5	364	2.3	1,695	10.7	12,407	78.4	15,851	100
Sex										
Male	743	55.1	163	44.8	876	51.7	6,565	52.9	8,347	52.8
Female	606	44.9	201	55.2	819	48.3	5,842	47.1	7,468	47.2
Median (range) age at diagnosis, years	5.9 (0-17.8)		3.2 (0.0-18.6)		8.4 (0.0-24.8)		6.9 (0.0-21.0)		6.7 (0.0-24.8)	
Primary childhood cancer diagnosis										
Acute lymphoblastic leukemia	302	22.4	0	0	482	28.4	3,777	30.4	4,561	29.5
Other leukemia	30	2.2	0	0	71	4.2	434	3.5	535	3.5
Hodgkin lymphoma	103	7.6	0	0	203	12.0	1,672	13.5	1,978	12.5
Other lymphoma	166	12.3	0	0	111	6.5	913	7.4	1,190	7.5
Brain tumor	120	8.9	0	0	214	12.6	1,607	13.0	1,941	12.3
Neuroblastoma	85	6.3	0	0	56	3.3	825	6.6	966	6.1
Kidney tumor	180	13.3	364	100	97	5.7	1,072	8.6	1,713	10.8
Soft tissue sarcoma	131	9.7	0	0	135	8.0	1,085	8.8	1,351	8.5
Bone tumor	126	9.3	0	0	97	5.7	1,022	8.2	1,245	7.9
Other malignant neoplasm	106	7.9	0	0	229	13.5	0	0	335	2.1
Patients with heart failure available for analysis ^c	26	6.9	49	13.1	25	6.6	275	73.3	375	100
Patients excluded										
For second malignancy before heart failure	2	7.7	6	12.2	0	0	40	14.5	48	12.8
For heart failure occurrence after age 40 years	0	0	1	2.0	6	24.0	49	17.8	56	14.9
Total in HF analysis	24	92.3	42	85.7	19	76.0	186	67.6	271	72.3
Doxorubicin										
No	952	70.6	179	49.3	1,120	66.1	8,402	67.7	10,653	67.4
Yes	397	29.4	185	50.7	575	33.9	3,987 ^d	32.1	5,144	32.5
Median (IQR) dose, mg/m ²	180 (120-360)		184 (117-281)		200 (152-317)		276 (144-378)		255 (144-365)	
Daunorubicin										
No	1,210	89.7	364	100	1,243	73.3	10,737	86.5	13,554	85.7
Yes	139	10.3	0	0	452	26.7	1,652 ^e	13.3	2,243	14.2
Median (IQR) dose, mg/m ²	120 (100-160)		—		99 (50-104)		150 (98-334)		111 (91-271)	
Epirubicin										
No	1,217	90.2	364	100	1,692	99.8	12,407	100	15,680	99.1
Yes	132	9.8	0	0	3	0.2	0	0	135	0.9
Median (IQR) dose, mg/m ²	300 (200-420)		—		270 (83-400)		—		300 (200-420)	
Idarubicin										
No	1,346	99.8	364	100	1,681	99.2	12,406	100	15,798	99.9
Yes	3	0.2	0	0	14	0.8	1	<0.01	18	0.1
Median (IQR) dose, mg/m ²	36 (36-36)		—		16 (11-22)		178		20 (11-36)	
Mitoxantrone										
No	1,323	98.1	364	100	1,677	98.9	12,407	100	15,771	99.7
Yes	26	1.9	0	0	18	1.1	0	0	44	0.3
Median (IQR) dose, mg/m ²	12 (12-20)		—		50 (36-56)		—		34.6 (12-50)	
Direct chest radiotherapy										
No	1,082	80.2	206	56.6	1,197	70.6	8,855	71.4	11,340	71.7
Yes	228 ^f	16.9	158 ^g	43.4	498	29.4	3,160 ^h	25.5	4,044	25.6
Median (IQR) dose, Gy	25 (18-35)		12 (11-23)		26 (15-35)		31 (20-40)		30 (20-38)	
Median (range) follow-up, years	15.1 (0.0-35.00)		9.1 (0.0-33.0)		7.3 (0.1-22.0)		18.1 (0.0-33.6)		17.3 (0.0-35.0)	
Median (range) attained age, years	27.2 (5.8 to 40.0)		19.0 (6.0 to 40.0)		28.8 (18.1 to 40.0)		31.4 (5.6 to 40.0)		30.5 (5.6 to 40.0)	

Abbreviations: CCSS, Childhood Cancer Survivor Study; EKZ/AMC, Emma Children's Hospital/Academic Medical Center cohort; IQR, interquartile range; NWTSA, National Wilms Tumor Study; SJLIFE, St Jude Lifetime Cohort Study.

^aThe EKZ/AMC cohort did not have preexisting chemotherapy dose information available; a nested case-cohort design was used for this analysis.

^bUnknown treatment in 18 survivors in the CCSS.

^cPercentages in this row represent the proportion of the total overall population for analysis.

^dIn CCSS, 401 doxorubicin doses were missing.

^eIn CCSS, 133 daunorubicin doses were missing.

^fIn EKZ/AMC, 39 chest radiotherapy treatment options (yes/no) and 22 chest radiotherapy doses were missing.

^gIn the NWTSA, four chest radiotherapy doses were missing.

^hIn the CCSS < 392 chest radiotherapy options (yes/no) and 22 chest radiotherapy doses were missing.

Table 3. HRs for Heart Failure Based on Doxorubicin and Daunorubicin Dose Categories

Model and Dose Category	Daunorubicin				Doxorubicin								
	Dose, mg/m ²		HR*	95% CI	Dose, mg/m ²		HR	95% CI	Daunorubicin-to-Doxorubicin Ratio				
	Median	IQR			Median	IQR			Ratio	95% CI	Mean	95% CI	
Primary model*												0.45	0.23 to 0.73
None			Reference			Reference			—				
≤ 0.1 to < 200 mg/m ²	100	75-118	1.09	0.57 to 2.08	122	80-169	2.80	1.75 to 4.49	0.39	0.04 to 0.78			
≤ 200 to < 300 mg/m ²	246	221-270	3.16	1.16 to 8.61	253	226-278	6.31	4.11 to 9.69	0.50	0.00 to 1.12			
≤ 300 to < 400 mg/m ²	350	328-371	4.33	1.73 to 10.84	347	318-370	13.19	9.04 to 19.25	0.33	0.03 to 0.62			
≤ 400 mg/m ²	480	432-545	10.72	5.13 to 22.42	459	430-505	18.43	12.82 to 26.50	0.58	0.09 to 1.12			
Secondary model†												0.41	0.29 to 1.28‡
None			Reference			Reference			—				
≤ 0.1 to < 150 mg/m ²	99	51-103	1.35	0.18 to 10.42	102	71-122	3.97	1.14 to 13.76	0.34	0.14 to 2.60‡			
≤ 150 to < 300 mg/m ²	213	183-251	2.83	0.37 to 21.57	211	180-258	9.29	4.58 to 18.86	0.30	0.21 to 1.37‡			
≤ 300 mg/m ²	379	346-449	20.17	8.83 to 46.06	391	345-455	34.74	19.24 to 62.73	0.58	0.25 to 1.08‡			

Abbreviations: HR, hazard ratio; IQR, interquartile range.

*Model was adjusted for sex; age at diagnosis; chest radiotherapy dose; and exposure to another anthracycline besides doxorubicin or daunorubicin, such as epirubicin, idarubicin, or mitoxantrone. It was also stratified by cohort.

†Model was adjusted for sex and age at diagnosis and was also stratified by cohort.

‡The CIs of the ratios are the 2.5th and 97.5th percentiles of the bootstraps.

drawn because of limited statistical power. By pooling data from this Dutch cohort with those from other well-annotated cohorts of survivors of childhood cancer, we gained sufficient statistical power to demonstrate a significant difference between daunorubicin and doxorubicin with regard to HF risk. Nevertheless, in the current study, the numbers of survivors treated with epirubicin, idarubicin, and mitoxantrone remained too small to allow for similar comparisons.

Because of limited follow-up after age 40 years, we were able to robustly examine the risk of HF only through this age. Therefore, we cannot say whether the relatively lower cardiotoxicity profile of daunorubicin will persist with extended follow-up. Research suggests that the cumulative incidence of HF among survivors of childhood cancer increases with age.³⁹ Another limitation of this study is the lack of patients exposed to anthracycline doses in excess of 500 mg/m² (5% of those exposed to anthracyclines). It is possible that our ratio may

not apply at these high exposure levels.^{36,37} However, few contemporary protocols feature doses of anthracycline greater than this level. Finally, we were unable to account for the possible effects of conventional cardiovascular risk factors for HF, such as hypertension, diabetes, dyslipidemia, and obesity, because these outcomes were not collected uniformly across all four cohorts. When they were collected by self report, the time of onset was frequently unknown.⁴⁰ However, we have no reason to suspect that these risk factors would be distributed differently for patients who received doxorubicin versus daunorubicin.

Although the cohorts we examined used heterogeneous methods for ascertainment of HF, the pooled data represent one of the largest samples of survivors of childhood cancer in which HF was examined. As a result, the pooled data provided increased power to detect significant differences in HF risk between doxorubicin and daunorubicin. Restriction of HF occurrences to those defined as grade 3 or greater (ie, clinical HF) also reduced issues related to different definitions of subclinical cardiotoxicity across cohorts. A recent study that was based on this data set demonstrated that prediction of HF, by using the same available treatment exposures we used in this analysis, was generally robust across these four cohorts. This finding suggests that the occurrences reported from the CCSS on the basis of self report are likely not significantly misclassified.⁵

Daunorubicin seems to be associated with less cardiotoxicity than doxorubicin. However, this observation needs to be confirmed with other studies. If confirmed, this may have implications in several areas. Screening guidelines for cardiotoxicity are generally defined by using both the cumulative dose of anthracycline received and the presence of chest radiation as part of the treatment. The use of a lower ratio may reclassify patients who received relatively high doses of daunorubicin who were previously considered to be at higher risk; now, they would be at somewhat lower risk. Although the available data suggest similar antitumor efficacy between doxorubicin and daunorubicin, randomized clinical trials to directly compare the two agents with regard to tumoricidal equivalence are lacking for most pediatric cancers.¹⁹ However, if equivalent antitumor efficacy is assumed; given the current results, a switch from doxorubicin to daunorubicin warrants investigation, because this may reduce cardiac-related toxicity without compromising

Fig 1. Relative risk of heart failure (HF) per dose group. Circles are the result of the Cox proportional hazard model that is based on categoric dose increments. Lines represent the linear (solid) and linear exponential (dashed) modeled continuous dose-response relationship. Horizontal dashed line represents the null hazard ratio. Bars were placed at the median dose for each category per Table 3.

relapse-free survival. Additional research also is needed to determine the long-term cardiotoxicity profiles of these drugs in survivors of childhood cancer older than age 40 years and in those who receive other types of anthracyclines and anthraquinones.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERM

Anthracycline: Class of antineoplastic agents derived from *Streptomyces* bacteria used to treat a variety of hematologic and solid malignancies. Anthracyclines have a well-established dose-related risk of cardiomyopathy and congestive heart failure. Anthracyclines include agents like daunorubicin, doxorubicin, epirubicin, and idarubicin.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Equivalence Ratio for Daunorubicin to Doxorubicin in Relation to Late Heart Failure in Survivors of Childhood Cancer

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Appendix**Table A1.** Distribution of Anthracycline and Chest RT Exposures Among 271 Heart Failure Occurrences

Exposure	Heart Failure Occurrences (N = 271)	
	No.	%
No known	15*	5.5
Daunorubicin only	13*†	4.8
Daunorubicin + chest RT	5	1.8
Daunorubicin + mitoxantrone + chest RT	1	0.4
Doxorubicin only	95*†	35.1
Doxorubicin + chest RT	87	32.1
Doxorubicin + daunorubicin	6	2.2
Doxorubicin + daunorubicin + chest RT	5	1.8
Epirubicin only	2	0.7
Epirubicin + mitoxantrone	1	0.4
Chest RT only	37	13.7
Either anthracycline or chest RT unknown	4	1.5

Abbreviation: RT, radiotherapy.

*Occurrences eligible to be part of our secondary analysis excluded those in which patients received chest RT or more than one type of anthracycline and/or anthraquinone or received an anthracycline other than doxorubicin or daunorubicin.

†One patient with heart failure who was treated with only daunorubicin, and five patients who were treated with only doxorubicin did not have dose information. This left 117 heart failure occurrences available for our secondary analysis.

Table A2. Results for Primary Model That Show Significant Effects for Both Drugs

Description	Akaike Information Criterion	Model*
Log-linear model with categorical dose for both drugs†	4409.5	Risk = $\exp(\Sigma\alpha X) \exp(1.03 \text{ doxo1} + 1.80 \text{ doxo2} + 2.56 \text{ doxo3} + 2.89 \text{ doxo4} + 0.10 \text{ daun1} + 1.10 \text{ daun2} + 1.45 \text{ daun3} + 2.40 \text{ daun4})$
Linear for both drugs	4398.6	Risk = $\exp(\Sigma\alpha X) [1 + 0.033 \text{ doxo_dose} + 0.016 \text{ daun_dose}]$
Linear exponential for both drugs	4393.4	Risk = $\exp(\Sigma\alpha X) [1 + 0.018 \text{ doxo_dose} \times \exp(0.002 \text{ doxo_dose}) + 0.004 \text{ daun_dose} \times \exp(0.004 \text{ daun_dose})]$
Linear spline at 250 mg/m ² for both drugs	4392.6	Risk = $\exp(\Sigma\alpha X) [1 + 0.022 \text{ doxo_dose} + 0.041 \times \max(0, \text{doxo_dose} - 250) + 0.008 \text{ daun_dose} + 0.031 \times \max(0, \text{daun_dose} - 250)]$
Linear spline at 300 mg/m ² for both drugs	4393.7	Risk = $\exp(\Sigma\alpha X) [1 + 0.026 \text{ doxo_dose} + 0.039 \times \max(0, \text{doxo_dose} - 300) + 0.007 \text{ daun_dose} + 0.052 \times \max(0, \text{daun_dose} - 300)]$

Abbreviations: daun, daunorubicin; doxo, doxorubicin.

* $\exp(\Sigma\alpha X)$ contains baseline covariates: sex, age at diagnosis, chest radiotherapy dose, current age, cohort, and exposure to another anthracycline besides doxorubicin or daunorubicin (eg, epirubicin, idarubicin, or mitoxantrone).

†Results differ slightly from the Cox model because of the use of Poisson regression and age adjustment. Doxo1/Daun1 (0.1 to 199 mg/m²), doxo2/daun2 (200 to 299 mg/m²), doxo3/daun3 (300 to 399 mg/m²), doxo4/daun4 (≤ 400 mg/m²). Doxo_dose and daun_dose are continuous values (in mg/m²).