Study Title

Derivation of anthracycline equivalence to doxorubicin in relation to late cardiotoxicity: epirubicin, idarubicin and mitoxantrone.

Working group

Primary: Chronic Disease Working Group
Secondary: Epidemiology & Biostatistics

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Background & Rationale

Around 30-40% of children with cancer receive anthracyclines (doxorubicin, daunorubicin, epirubicin and/ or idarubicin) as part of the treatment (1, 2). And a much smaller number receives the anthraquinone, mitoxantrone. However, anthracyclines and mitoxantrone have been associated with deterioration of cardiac function. Anthracycline-associated heart failure is well-described in children: the overall incidence of clinical heart failure (CHF) has been reported to be as high as 2% around 20 years after treatment (1, 2), and increasing further with extended follow-up, particularly among high-risk groups (3). Mitoxantrone-associated risk for CHF has not been fully enumerated, but heart failure has been reported between 0 to 6.7% (4). There are several known risk factors for developing anthracycline-associated CHF: young age at diagnosis, radiation dose and anthracycline dose, and in some studies, female sex (1, 5). Cumulative anthracycline dose is one of the strongest predictors for developing CHF, with a clear dose-response relationship (1, 2, 6). During treatment, consideration of cardiotoxicity is one of the main dose-limiting factors. In mitoxantrone-associated CHF, risk factors and the dose-response relationship is less well known.

Prospective screening for late cardiac toxicity has been highlighted by multiple national groups, and the cumulative anthracycline dose (sum of all types of anthracyclines) is an important factor in

considering which screening modality and what screening frequency should be used (7, 8). In order to correctly calculate the cumulative dose of anthracyclines, conversion of all types of anthracyclines and mitoxantrone into a doxorubicin equivalent would be helpful. Existing conversion formulas (Table 1) are in large part based on hematological toxicity equivalents with an assumption that hematological toxicity correlates with cardiotoxicity. Even assuming hematological toxicity translates to equivalent cardiotoxicity, discrepancies in existing published formulas can affect the classification of survivors with regards to screening recommendations (9).

In our recent work, we aimed to find the optimal equivalence ratio between doxorubicin and daunorubicin. To accomplish that, we performed an analysis on a large pooled cohort, and found that daunorubicin was about half as cardiotoxic as doxorubicin in relation to late (occurring after 5-years) CTCAE grade 3 or greater cardiomyopathy (10). This was in stark contrast to most published conversion formulas that suggested that the 2 agents would be largely equivalent (Table 1).

Table 1. Anthracycline toxicity equivalence ratios utilized by various cooperative groups and cohort studies for assessment of cardiotoxicity.

Group(s) using referenced ratio	Doxo-rubicin	Dauno-rubicin	Ida-rubicin	Epi-rubicin	Mitox-antrone
Children's Oncology Group	1 (ref)	1[†]	5	0.67	4
Bristol Royal Hospital for Sick Children	1 (ref)	1	-	1	-
AML collaborative group	1	1(ref)	5	-	5
Kyushu University, Fukuoka, Japan	1 (ref)	1	1	1	1
Taiwan Pediatric Oncology Group	1 (ref)	-	3	-	2
Childhood Cancer Survivor Study	1 (ref)	1	3	-	-
Dutch Childhood Oncology Group LATER	1 (ref)	1	-	0.67	-
Sookmyung Women's University, Seoul, Korea	1 (ref)	0.5	2	0.5	2.2

[†]Ratio of 1 reported in the current version of the COG guidelines (version 4, October 2013); prior versions used 0.83.

(adapted from Feijen et al. 2015 JCO; (10))

At present, there also is limited evidence regarding the appropriate anthracycline equivalence formulas to convert epirubicin, idarubicin, or mitoxantrone doses into doxorubicin equivalent dose with respect to late cardiotoxicity. A previous Cochrane review of RCT's that evaluated the cardiotoxic potential of doxorubicin and epirubicin showed no clear difference between doxorubicin and epirubicin (11). Aviles et al. (12) found that after a median follow-up of 11.5 year, mitoxantrone appeared more cardiotoxic than doxorubicin and epirubicin, and doxorubicin appeared more cardiotoxic than epirubicin, in adults with non-Hodgkin lymphoma. However, cumulative doses were not equivalent in the treatments, limiting the strength of their conclusions. Alderton et al. (13) performed a comparative study in mice between doxorubicin, mitoxantrone and epirubicin. They found that epirubicin was less cardiotoxic than mitoxantrone and doxorubicin, and that mitoxantrone was less cardiotoxic than doxorubicin.

Derivation of a more evidence-based equivalence formula for all anthracyclines and mitoxantrone in relation to doxorubicin in childhood cancer survivors could have implications for health screening guidelines for cardiotoxicity (currently determined by cumulative doses exposure to anthracycline and chest radiation). It may also influence the design of future treatment protocols for newly diagnosed childhood cancer patients. Cumulative anthracycline dose is a major dose-limiting factor

in treatment due to risk of cardiotoxicity; thus if epirubicin, idarubicin, or mitoxantrone are indeed less cardiotoxic compared with doxorubicin, clinicians may choose to preferentially use those agents in lieu of doxorubicin, which currently remains the most commonly used agent.

Specific aims

Following the successful modelling we performed to examine the cardiotoxicity equivalence ratio between doxorubicin and daunorubicin (14), we now propose to:

Primary: Determine the optimal equivalence ratio between doxorubicin and epirubicin, idarubicin and mitoxantrone for cardiotoxicity (based on CTCAE grade 3+ cardiomyoathy) for survivors of childhood cancer

Secondary: Model dose-response curves for each anthracycline/anthraquinone agent assessed, based on selected parametric models to determine the best fit.

Analysis framework

Outcome of interest

Equivalence ratio for cardiotoxicity between doxorubicin and epirubicin, doxorubicin and idarubicin, and doxorubicin and mitoxantrone.

Subject population

We propose a pooled analysis utilizing data from 3 well-annotated childhood cancer survivor cohorts:

The entire CCSS survivor cohort (diagnosis years 1970-1999) would be eligible. As the cohort is based on minimum 5-year survivorship, individuals who report development of CHF within 5 years of diagnosis will be excluded from analysis. Competing risks and censoring is described further below (see Statistical Methods).

Data from the Dutch Childhood Oncology Group Long-term effects of childhood cancer (DCOG LATER) and the St. Jude Lifetime cohort (SJLIFE) data will be analyzed (Table 2).

In the interval between our prior analysis examining daunorubicin and doxorubicin and now, all 3 cohorts have been expanded, resulting in significantly increased numbers of individuals exposed to epirubicin, idarubicin, and mitoxantrone.

Exploratory variables

- *Treatment variables (Table 3)*
    - Anthracycline type and dose
    - Radiotherapy (RT)
        - Chest exposure (yes/no)
        - Heart exposure (yes/no, if available)
        - Please note: Given potential model complexity, initial modeling will focus on yes/no exposures only.

- *Demographic variables*
    - Sex
    - Race/ethnicity
    - Age at cancer diagnosis
    - Current age / elapsed time since cancer diagnosis

Table 2. Characteristics of the study cohorts.

Cohort	CCSS	DCOG LATER	SJLIFE*
Population	31 North American centers, diagnosed age <21 years, 1970-1999, survived ≥5-years.	Nationwide, diagnosed <18 years, 1963-2001, survived ≥5-years.	Single US center, >10 year survival, any diagnosis age (if pediatric histology), ≥18 years at cohort entry, still alive at cohort entry, treated 1962-2001
Exposure information	Chemotherapy doses, radiotherapy fields and doses, select organ-specific dosimetry (based on average dose)	Chemotherapy doses, radiotherapy fields and doses, select organ-specific dosimetry (maximum). Chest radiotherapy fields defined similarly as CCSS.	Chemotherapy doses, radiotherapy fields and doses, no organ-specific dosimetry. Chest radiotherapy fields defined similarly as CCSS.
CHF definition	Self-report and death records, limited to CTCAE grades 3-5 occurring >5 years from cancer diagnosis: cardiomyopathy or congestive heart failure requiring medication, cardiac transplant, or leading to death	Medical and death records, prospective clinical assessment, limited to CTCAE grades 3-5 occurring >5 years from cancer diagnosis.	Medical and death records, prospective clinical assessment; limited to CTCAE grades 3-5 occurring >10 years from cancer diagnosis.
No. CHF cases‡	~400	116	46

CCSS, Childhood Cancer Survivor Study; CTCAE, Common Terminology Criteria for Adverse Events; DCOG LATER, Dutch Childhood Oncology Group Long-term effects of childhood cancer; SJLIFE, St. Jude Lifetime Cohort. *CCSS participants who also were part of SJLIFE were excluded from NWTS and SJLIFE for this analysis. ‡Limited to those occurring after cohort entry and by age 40.

Statistical methods

Taking the approach we used in our prior analysis [REF], we will use a Cox proportional hazards model to determine different dose-response relationship between doxorubicin and each alternative anthracycline agent or mitoxantrone individually, a priori using 100 mg/m^2 dose increments for doxorubicin and epirubicin and 20 mg/m^2 for idarubicin and mitoxantrone. Separate models will be built to study the equivalence ratio for doxorubicin and each one of the other agents (epirubicin/ idarubicin/ mitoxantrone). For any given model, the doses of doxorubicin and the other agent of interest will be included in the same model, adjusted for each other. Each model will also be adjusted for gender, age at diagnosis, chest radiotherapy (RT) dose categories, and an indicator for exposure to any other anthracycline exclusive of doxorubicin and the specific agent being compared.

We will then calculate the equivalence ratio of the HRs (epirubicin/ idarubicin/ mitoxantrone :doxorubicin) in each dose category, then average these to obtain an equivalence ratio across all dose categories. To calculate the 95% confidence intervals (CI), we will use the bootstrap method with replacement from the data with 1,000 replications. The ratios will be re-computed from each of

these datasets and the standard deviation of 1,000 estimates will be used as the standard error (SE) in a Wald 95% CI.

If the numbers in the different dose groups (Table 3) are found to be too low for the proposed models, we will consider either collapsing dose groups, or explore dose-response models with a continuous variable for dose. From our previous study [REF] examining daunorubicin:doxorubicin, results from our averaged ratio model was virtually identical to the dose-response model. However, the dose-response model assumes the equivalence ratio remains proportional as dose increases.

Other analytical issues

- This project will be based on the pooled data from CCSS, DCOG, and SJLIFE (see Tables 2-3). We will examine the possibility of any cohort-specific effect by examining estimates with and without stratifying by cohort.
- The analyses will be done with and without chest RT for several reasons: 1) to determine if RT is a synergistic in inducing CHF; 2) determine if radiation has a differential association with different types of anthracycline (although we may lack sufficient power to determine this). Note: we did not identify any RT synergistic effect in our prior analysis examining daunorubicin and doxorubicin.
- Examine the number of survivors treated with only a single anthracycline agent before examining survivors treated with multiple agents. The proposed modeling will be more straightforward if one does not need to deal with combination therapy. However, different agents are rarely given concurrently (i.e. same day), but typically alternated across different therapy courses (e.g. leukemia therapy), so one would not necessarily hypothesize about synergistic effects on cardiac function (i.e. departure from purely additive effects).
- It could be possible that some agents may produce relatively more acute or late toxicity within the late cardiovascular toxicity compared to other agents. If so, the proportionality assumption may be untenable. We should check this by allowing baseline hazards to be potentially different across the agents.

Table 3. Distribution of anthracycline derivatives in each cohort.

Anthracycline	CCSS, n=22,343 N (%)*	DCOG LATER, n=5,848† N (%)*	SJLIFE, n=3,056 N (%)*	TOTAL, n=31,247 N (%)*
None	**11,391 (51.0)**	**3,100 (53.0)**	**1,262 (41.3)**	**15,753 (50.4)**
Doxorubicin	**8,264(37.0)**	**1,901 (32.5)**	**1,103 (36.1)**	**11,268 (36.0)**
0.1-<200 mg/m^2	3428(41.5)	1180 (62.0)	563 (51.0)	5171 (45.9)
200-<400 mg/m^2	3136(37.9)	377 (19.8)	458 (41.5)	3971 (35.2)
≥400 mg/m^2	1174(14.2)	286 (15.1)	76 (6.9)	1536 (13.6)
Unknown dose	526(6.4)	58 (3.1)	6 (0.6)	590 (5.3)
Daunorubicin	**3,602(16.1)**	**1,121 (19.2)**	**774 (25.3)**	**5,497 (17.6)**
0.1-<200 mg/m^2	2205(61.2)	947 (84.5)	702 (90.8)	3854 (70.1)
200-<400 mg/m^2	957 (26.6)	126 (11.2)	56 (7.2)	1139 (20.7)
≥400 mg/m^2	269 (7.5)	11 (1.0)	12 (1.6)	292 (5.3)
Unknown dose	171 (4.7)	37 (3.3)	3 (0.4)	211 (3.9)
Idarubicin	**200 (0.9)**	**69 (1.2)**	**27 (0.9)**	**296 (0.9)**
0.1-<20 mg/m^2	40 (20.0)	10 (14.5)	12 (44.4)	62 (20.9)
20-<40 mg/m^2	73 (36.5)	50 (72.5)	12 (44.4)	135 (45.6)
40-<60 mg/m^2	48 (24.0)	0 (0.0)	2 (7.4)	50 (16.9)
≥60 mg/m^2	29 (14.5)	2 (2.9)	1 (3.7)	32 (10.8)
Unknown dose	10 (5.0)	7 (10.1)	0 (0.0)	17 (5.7)
Epirubicin	**4 (0.0)**	**347 (5.9)**	**4 (0.1)**	**355 (1.1)**
0.1-<200 mg/m^2	1 (25.0)	75 (21.6)	1 (25.0)	77 (21.9)
200-<400 mg/m^2	0 (0.0)	186 (53.6)	2 (50.0)	188 (52.8)
≥400 mg/m^2	0 (0.0)	83 (23.9)	1 (25.0)	84 (23.6)
Unknown dose	3 (75.0)	3 (0.9)	0 (0.0)	6 (1.7)
Mitoxantrone	**136 (0.6)**	**146 (2.5)**	**30 (1.0)**	**312 (1.0)**
0.1-<20 mg/m^2	1 (0.7)	58 (39.7)	0 (0.0)	59 (18.9)
20-<40 mg/m^2	48 (35.3)	23 (15.8)	11 (36.7)	82 (26.3)
40-<60 mg/m^2	25 (18.4)	24 (16.4)	12 (40.0)	61 (19.6)
≥60 mg/m^2	40 (29.4)	34 (23.3)	6 (20.0)	80 (25.6)
Unknown dose	22 (16.2)	7 (4.8)	1 (3.3)	30 (9.6)
Unknown	**68 (0.3)**	**39 (0.7)**		**107 (0.3)**

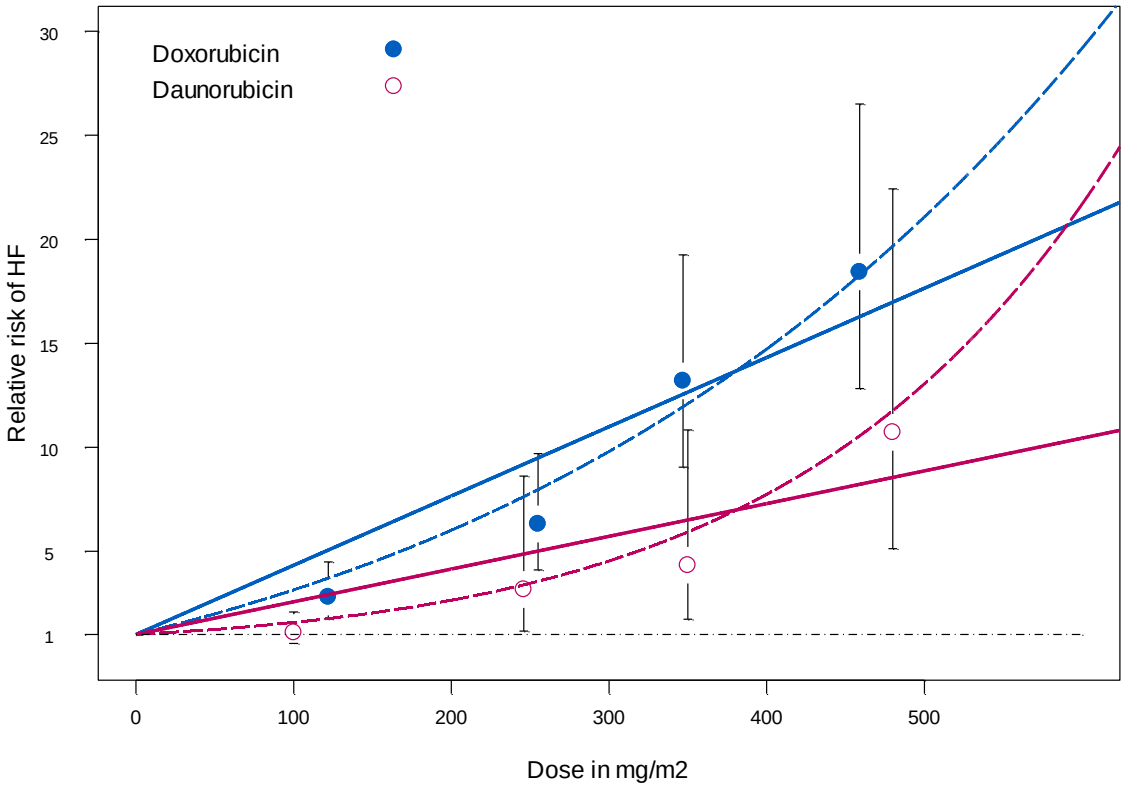
CCSS, Childhood Cancer Survivor Study; DCOG LATER, Dutch Childhood Oncology Group Long-term effects of childhood cancer; SJLIFE, St. Jude Lifetime Cohort.

* Total percentages may exceed 100% because some patients may have received more than 1 type of anthracycline.

†Survivors with cardiac follow-up

Proposed tables and figures:

Dose-response curves for each anthracycline/ anthraquinone agent assessed (see example for daunorubicin/doxorubicin)



From: Feijen et al. 2015 JCO

Table with the hazard ratios and Doxorubicin to epirubicin, idarubicin and mitoxantrone ratio (see example below for daunorubicin/doxorubicin)

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

Model and Dose Category	Daunorubicin				Doxorubicin				Daunorubicin-to-Doxorubicin Ratio			
	Dose, mg/m²				Dose, mg/m²							
	Median	IQR	HR*	95% CI	Median	IQR	HR	95% CI	Ratio	95% CI	Mean	95% CI
Primary model*											0.45	0.23 to 0.73
None			Reference				Reference		—			
≤ 0.1 to < 200 mg/m²	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/m²	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/m²	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/m²	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/m²	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/m²	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/m²	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.

From: Feijen et al. 2015 JCO

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