Study Title

Derivation of anthracycline equivalence to doxorubicin in relation to late cardiotoxicity

Working group

Primary: Chronic Disease Working Group
Secondary: Epidemiology & Biostatistics

Investigators

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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 (van der Pal 2012, Mulrooney 2009). However anthracyclines have been associated with deterioration of cardiac function. Anthracycline-associated heart failure is well-described in children: the incidence of clinical heart failure (CHF) has been reported to be as high as 2% around 20 years after treatment (van der Pal 2012, Mulrooney 2009), and increasing further with extended follow-up (Chow, submitted). There are several known risk factors for developing CHF: age at diagnose, gender, radiation dose and anthracycline dose. Cumulative anthracycline dose is one of the strongest predictors for developing CHF, with a clear dose-response relationship (Mulrooney 2009; van der Pal 2012; Blanco 2012).

Van der Pal, et al (2010) reported a 27% prevalence of subclinical heart failure (defined as shortening fraction <30%) among a subset of a Dutch cohort of childhood cancer survivors (n=525) with available echocardiographic data. 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 (DCOG guidelines; COG guidelines; UKCCSG guidelines).

However, there is no consensus on what the optimal anthracycline equivalence formula should be, in order to convert daunorubicin, epirubicin, idarubicin, and possibly anthraquinone (i.e. mitoxantrone) doses into doxorubicin equivalent dose with respect to late cardiotoxicity. Existing conversion

formulas (Table 1) are in large part based on haematological toxicity equivalents with an assumption that haematological toxicity correlates with cardiotoxicity. Even assuming haematological toxicity translates to equivalent cardiotoxicity, discrepancies in existing published formulas can affect the classification of survivors (Table 4). Only Keefe 2001 describes a conversion formulae based on cardiotoxicity equivalents (Table 1). The conversion formulae used in that instance was calculated by comparing the dose by which each agent was associated with a 5% incidence of cardiotoxicity. However important details are lacking from that reference, including the populations on which estimates were based, duration of follow-up, and how cardiotoxicity was determined.

Finally, although it is clear that chest radiotherapy in combination with anthracyclines further increases the risk of CHF (Mulrooney 2009; van der Pal 2012; Armstrong 2013), it is not clear what effects concurrent chest radiotherapy might have on any anthracycline conversion formula.

Specific aims

Primary: Determine if a more appropriate anthracycline cardiotoxicity (based on risk of CHF) equivalence formula for survivors of childhood cancer can be derived for doxorubicin versus daunorubicin.

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

Analysis framework

Outcome of interest

Anthracycline doxorubicin equivalence for cardiotoxicity.

Subject population

We propose a pooled analysis utilizing data from 4 well-annotated childhood cancer survivor cohorts:

The entire CCSS survivor cohort (treated 1970-1986) would be initially 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).

EKZ/AMC, NWTS and St. Jude life data will be analyzed (Table 2)

Exploratory variables

- *Treatment variables*
    - Anthracycline type and dose
    - Radiotherapy (RT)

        - Chest exposure (yes/no)
        - Heart exposure (yes/no, if available)
        - NB: 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

Statistical methods

We propose to examine the relative risk (RRs; may be expressed as hazard ratios depending on the final models chosen) of CHF with survivors who received no anthracyclines as the referent group. Models will be based on time to event, using either Cox PH hazards model, or additive forms of that model (Aalen 1989; Lin 1994). In addition, parametric models that allow incorporation of functional forms to determine different dose-response relationships will be examined (further discussed below). Data will be censored at time of select competing risk events (e.g. late relapse or second cancer given that late relapse or 2nd cancer treatment data are often not available, and death from other causes).

We will initially examine the overall RR, but then examine risk by dose increments (e.g. 50 mg/m2 if sample size is sufficient). Separate analyses will be conducted for each anthracycline agent (i.e. doxorubicin, daunorubicin, and possibly epirubicin). We recognize that power maybe limited for agents other than doxo- and daunorubicin (Table 3). For each agent, we will then examine the resulting RRs associated with each dose category, as well as the cumulative incidence of CHF by 30 years post diagnosis associated with each dose level. To help visualize these relationships, we will plot the resulting cumulative incidence associated with different dose levels for each agent, and separately, the RRs and 95% CIs for each dose level (x-axis: dose levels; y-axis: RRs) for each agent (Bonadonna 1993).

For both RR and cumulative incidence estimates, we will examine the ratio between estimates at each dose level between different agents with doxorubicin as the reference to derive the appropriate equivalent conversion formula. As there is the possibility that ratios between doxorubicin and other agents may differ across dose levels, or that the ratios between cumulative incidence and RR's differ markedly. In those cases, we will explore taking the weighted average ratio versus exploring whether multiple conversion ratios need to be accounted for at different dose levels, and greater weight will likely be given to the ratios of the absolute risk.

In secondary analyses, we will also model dose-response curves for each agent, based on various parametric models to determine the best fit (e.g. linear, linear-quadratic, exponential, etc). Examples of this include van der Pal 2010, Sigurdson 2005 (see Figures). Goodness of fit will be evaluated using likelihood ratio tests in nested models, comparing to the simplest form of the model.

Other analytical issues

- This project will be based on the pooled data from CCSS, EKZ/AMC, NWTS and SJLIFE (see Tables 2-4). 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).
- 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. AML therapy), so one would not necessarily hypothesize about synergistic effects on cardiac function (i.e. departure from purely additive effects).

Table 1. Various equivalence formulas.

Original reference	Doxo	Dauno	Ida	Epi	Mitox	Group(s) using referenced formula
Andolina 2010, Abosoudah 2011, Visscher 2011	1	0.83	5	0.67	4	COG
Bu'Lock 1999	1	1		1		Bristol
Creutzig 2007, Temming 2011	1	1	5		5	AML coll
Godoy 1997	1	1	1	1	1	Japan
Liang 2006	1		3		2	TPOG
Mulrooney 2009	1	1	3			CCSS
Van der Pal 2010	1	1		0.67		Netherlands
Keefe 2001 (cardiotoxicity)	1	0.5	2	0.5	2.2	Korea

Table 2. Characteristics of the study cohorts.

Cohort	CCSS	AMC	NWTS*†	SJLIFE*
Population	26 North American centers, diagnosed age <21 years, 1970-1986, survived ≥5-years.	Single Dutch center, diagnosed <18 years, 1966-1997, survived ≥5-years.	North American clinical trial group, kidney tumors only, diagnosed age <16 years, from 1969-2002.	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 and EQD2 doses). Chest radiotherapy fields defined similarly as CCSS.	Chemotherapy doses, radiotherapy fields and doses, no organ-specific dosimetry Chest radiotherapy included any whole abdomen or left flank radiotherapy exposures.	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; self-report accepted if patient also reported being on appropriate medications; 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‡	285	26	48	19

AMC, Emma Children's Hospital Academic Medical Center; CCSS, Childhood Cancer Survivor Study; CTCAE, Common Terminology Criteria for Adverse Events; EQD2, equivalent dose in 2-Gray fractions; NWTS, National Wilms Tumor Study Group; SJLIFE, St. Jude Lifetime Cohort. *CCSS participants who also were part of NWTS and/or SJLIFE were excluded from NWTS and SJLIFE for this analysis. †Nested case-cohort design used for this analysis, with 48 heart failure cases and 316 randomly selected members of the overall cohort (≥5-year survivors as of 12/31/2012, n=6760). ‡Limited to those occurring after cohort entry and by age 40.

Table 3. Distribution of anthracycline derivatives in each cohort.

Anthracycline	CCSS, n=13,060 N (%)*	AMC, n=1362 N (%)*	NWTS, n=365 N (%)*	SJLIFE, n=1695 N (%)*
None	7506 (57.5)	798 (58.6)	180 (50.1)	692 (40.8)
Doxorubicin	3416 (26.2)	392 (28.8)	179 (49.0)	572 (33.7)
Daunorubicin	1425 (10.9)	138 (10.1)	0	450 (26.5)
Idarubicin	1 (0.0)	3 (0.2)	0	14 (0.8)
Epirubicin	0†	132 (9.7)	0	3 (0.2)
Mitoxantrone	0†	25 (1.8)	0	18 (1.1)
Unknown dose information	1194 (9.1)	9 (0.7)	6 (1.6)	5 (0.3)

* Total percentages may exceed 100% because some patients may have received more than 1 type of anthracycline.
† Epirubicin and mitoxantrone were given to 4 and 11 individuals, respectively, but doses were unknown.

Table 4. Effect on anthracycline dose categories using alternative equivalence formulas.

Anthracycline dose, mg/m^2	CCSS, n=13,060 N (%)		AMC, n=1362 N (%)		SJLIFE, n=1695 N (%)	
	Formula 1	**Formula 2**	**Formula 1**	**Formula 2**	**Formula 1**	**Formula 2**
None	7506 (57.5)	7506 (57.5)	799 (58.7)	799 (58.7)	692 (40.8)	692 (40.8)
<100	422 (3.2)	513 (3.9)	32 (2.3)	63 (4.6)	218 (12.9)	368 (21.7)
100-249	1354 (10.4)	1353 (10.4)	263 (19.3)	236 (17.3)	549 (32.4)	402 (23.7)
≥250	2584 (19.8)	2494 (19.1)	259 (19.0)	255 (18.7)	231 (13.6)	228 (13.5)
Unknown	1194 (9.1)	1194 (9.1)	9 (0.7)	9 (0.7)	5 (0.3)	5 (0.3)

Formula 1: doxorubicin 1 mg/m2 = daunorubicin 1, idarubicin 3, epirubicin 0.67, mitoxantrone 4
Formula 2: doxorubicin 1 mg/m2 = daunorubicin 0.83, idarubicin 5, epirubicin 0.67, mitoxantrone 4

Figures. Examples of dose-response curves from Sigurdson, Lancet 2005 (radiotherapy & thyroid cancer risk); van der Pal, Archives Int Med 2010 (doxorubicin dose & change in systolic function)

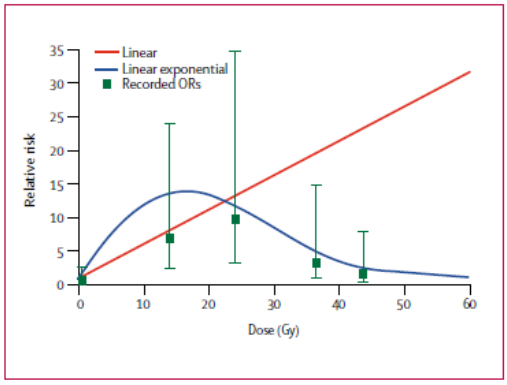

Figure 1: **Thyroid-cancer risk by radiation dose in cases and controls after adjustment for first cancer**
Linear dose-response model for relative risk calculated as: 1+0·5117(dose). Linear-exponential dose-response model for relative risk calculated as 1+1·316[dose]e(−0·00189[dose×dose]). Vertical lines=95% CIs for OR.

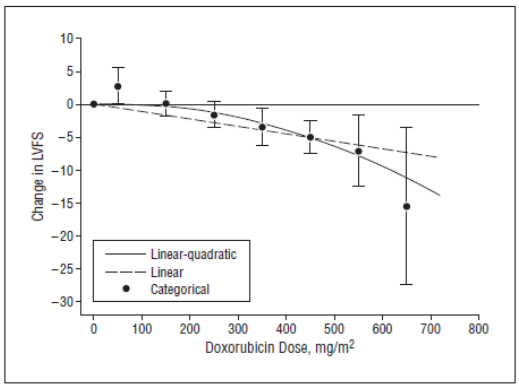

Figure. Shape of dose response for cumulative dose of doxorubicin. LVSF indicates left ventricular shortening fraction.

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