

# Equivalence ratio for daunorubicin to doxorubicin in relation to late heart failure

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## Introduction:

Cumulative anthracycline dose is one of the strongest predictors for occurrence of congestive heart failure (CHF) after childhood cancer treatment. However the relative cardiotoxicity of various anthracycline agents has not been rigorously evaluated. The aim of this study was to determine an appropriate equivalence ratio for daunorubicin to doxorubicin concerning CHF risk.

## Method:

Data from four childhood cancer survivor (CCS) cohorts: National Wilms Tumor Study, Childhood Cancer Survivor Study, St. Jude Lifetime Cohort Study, and Emma Children's Hospital/Academic Medical Center were used. CHF was defined as a Common Terminology Criteria for Adverse Events 4.02 grade  $\geq 3$ . Cox regression was used to calculate the hazard ratio (HR) for CHF through age 40 years for dauno- and doxorubicin doses (per 100 mg/m<sup>2</sup> increments). Models were adjusted for gender, age at diagnosis, presence of other anthracycline agents, chest radiation, and cohort. A weighted average daunorubicin/doxorubicin ratio across dose ranges was then calculated.

## Preliminary results:

The pooled cohort included 22,221 CCS of whom 9% and 37% received daunorubicin and doxorubicin, respectively. The cumulative incidence of CHF by age 40 years was 2.66%. In multivariable analysis, doxorubicin exposures of 100-199 mg/m<sup>2</sup> were associated with an increased hazard of CHF (HR 4.09; 95% CI 2.48-6.73); doses  $\geq 400$  mg/m<sup>2</sup> were associated with HR 22.72 (95% CI 15.61-33.08), compared to no doxorubicin exposure. In contrast, daunorubicin exposures at the same doses had HRs of 1.38 (95% CI 0.60-3.16) and 14.75 (95% CI 6.98-31.16) for CHF, respectively. The weighted average daunorubicin/doxorubicin ratio of HRs across the dose spectrum (100 to  $\geq 400$  mg/m<sup>2</sup>) was 0.43. This ratio was similar (0.45) in secondary analyses restricted to CCS not exposed to chest radiotherapy or presence of other anthracyclines.

## Conclusions:

Compared with doxorubicin, daunorubicin was less cardiotoxic among CCS followed through age 40 years. Currently used equivalence ratios based on hematologic toxicity and tumor efficacy (1 or 0.83) may need to be re-evaluated in relation to CHF risk, with potential implications for screening guidelines.

**References:**

van der Pal HJ, et al. Cardiac Function in 5-Year Survivors of Childhood Cancer. *ArchInternMed*. 2010;170(14):1247-1255.