EQUIVALENCE RATIO FOR DAUNORUBICIN TO DOXORUBICIN IN RELATION TO LATE HEART FAILURE

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Purpose
Based on hematologic toxicity data, the anthracycline dose equivalence ratio between daunorubicin and doxorubicin has typically been assumed to be 1:1. However, there is no consensus on an optimal equivalence ratio with respect to cardiac toxicity among childhood cancer survivors. We sought to determine the optimal equivalence ratio for daunorubicin to doxorubicin based on the risk of clinical heart failure (HF) in this population.

Patients and methods
Data from 15,815 survivors in four childhood cancer survivor cohorts were used: Emma Children's Hospital/Academic Medical Center (n=1,349), the National Wilms Tumor Study (n=365), 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 dauno- and doxorubicin doses (per 100 mg/m^2 increments) was estimated using Cox regression, adjusted for gender, age at diagnosis, treatment with any of other anthracycline agents, chest radiation, and cohort membership.

Results
The pooled study population had a median follow-up time of 17.3 years (range 0-35.0) since cohort entry. In total, 5,144 (32.5%) patients received doxorubicin while 2,243 (14.7%) patients received daunorubicin. Based on 271 HF cases, the cumulative incidence of HF at age 40 for the entire pooled cohort was 3.2% (95% Confidence Interval [CI] 2.8-3.7%). The average equivalence ratio of daunorubicin to doxorubicin HRs in increments of 100 mg/m^2 was 0.45 (95% CI 0.23-0.73). A similar equivalence ratio was obtained when the association between each agent and HF was modeled using a linear dose-response model, 0.49 (95% CI 0.28-0.70).

Conclusion
Compared with doxorubicin, daunorubicin appeared substantially less cardiotoxic among childhood cancer survivors than most current guidelines suggest. This may have implications for follow-up guidelines. Assuming similar cancer therapeutic efficacy, the feasibility of substituting doxorubicin with less cardiotoxic daunorubicin in childhood cancer treatment protocols should be investigated further.