

EQUIVALENCE RATIOS FOR LATE CARDIOMYOPATHY AFTER DOXORUBICIN AND OTHER ANTHRACYCLINES/ANTHRAQUINONES

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Purpose

Determine the optimal dose equivalence ratio for late-onset cardiomyopathy between doxorubicin and other anthracyclines/anthraquinones.

Patients and methods

Childhood cancer survivors who survived ≥ 5 -years (N=28,423) from three cohorts were used: Dutch Childhood Oncology Group (n=5,741), Childhood Cancer Survivor Study (n=20,367), and St. Jude Lifetime Cohort (n=2,315; ≥ 10 -year survivors). Cardiomyopathy (CTCAE grade 3+) cases were ascertained and drug doses were converted to doxorubicin hematologic toxicity-equivalent (mg/m²) dose per current Children's Oncology Group recommendations (daunorubicin=1; epirubicin=0.67, idarubicin=5, mitoxantrone=4), and categorized to <150, 150-299, ≥ 300 mg/m². Agent-specific Cox proportional hazard models were created to evaluate cardiomyopathy risk, adjusted for chest radiotherapy, cancer diagnosis age, sex, and exposure to any other anthracycline/anthraquinone. An agent-specific equivalence ratio (relative to doxorubicin) was computed for each dose category as the ratio of hazard ratios, and then a weighted average determined the overall agent-specific equivalence ratio across all dose categories. Confidence intervals (CI) were based on 1000 bootstrap samples.

Results

With a median of 14.3 years (range 0-35.0) since cohort entry, 399 cardiomyopathy cases were observed. In total, 9,329 patients received doxorubicin (253 cardiomyopathy cases), while 4,433 received daunorubicin (66 cases), 342 epirubicin (9 cases), 241 idarubicin (5 cases), and 265 mitoxantrone (19 cases). Relative to doxorubicin, equivalence ratios were 0.63 (95%CI 0.35-0.95) for daunorubicin, 1.25 (95%CI 0.16-2.78) for epirubicin, and 2.63 (95%CI 1.15-4.99) for mitoxantrone. Data were too sparse to generate estimates for idarubicin. Ratios based on a continuous linear dose-response relationship were similar for daunorubicin and epirubicin. Mitoxantrone's relationship to doxorubicin may be better characterized with a linear-exponential model.

Conclusion

Daunorubicin was associated with a decreased cardiomyopathy risk versus doxorubicin, consistent with our prior work. Mitoxantrone was associated with a greater cardiomyopathy risk versus doxorubicin.

Mitoxantrone's current hematologic-based dose equivalency may underestimate its association with long-term cardiomyopathy by 2 to 3-fold, or more at higher doses.