Age-Associated Vulnerability to Treatment-Related Late Cardiotoxicity: A Report from the Childhood Cancer Survivor Study (CCSS)

Background: Cardiovascular disease (CVD) is the most common non-cancer cause of death in long-term survivors of pediatric cancer. We investigated the role of age at diagnosis in modifying treatment-related late CVD risk in the CCSS population.

Methods: We evaluated CTCAE grade 3 – 5 CVD events occurring ≥5 years after diagnosis in 23,465 5-year survivors of pediatric cancer diagnosed 1970-1999. We estimated the rates of developing any CVD, including coronary artery disease (CAD) or heart failure (HF). Modifications of treatment effects by age at diagnosis were analyzed using piecewise exponential models adjusting for current age, race, and smoking.

Results: At a median age of 28.4 years (range 5.6-58.3) and follow up of 20.2 years (5 – 39.3), 239 CAD and 359 HF events occurred. The cumulative incidence of CVD, CAD, and HF were 4.8% (95% CI: 4.3-5.3), 2.4% (95% CI: 2.2-2.9), and 2.5% (95% CI: 2.2-2.9) by 30 years from diagnosis. Mean cardiac radiotherapy (CRT) doses of ≥10 Gy were associated with a progressively increasing risk of CVD (10 - <20 Gy: RR 3.6, 95% CI 2.1 – 6.2, $p < 0.01$; 20 - <30 Gy: RR 4.4, 95% CI 2.7 – 7.2, $p < 0.01$; ≥30 Gy: RR 7.5, 95% CI 4.9 – 11.5, $p < 0.01$) relative to those receiving no CRT. In those receiving a low mean CRT dose (0.1 - <10 Gy), younger children had higher rates of CVD (0 – 4 years: RR = 2.2, 95% CI = 1.0 – 4.6, $p = 0.04$; >4 - ≤13 years: RR = 2.1, 95% CI = 1.1 – 4.1, $p = 0.03$) compared to those >13 years, an effect not seen at higher doses. Among survivors exposed to anthracycline doses ≥250 mg/m^2, those age 0 – 4 at diagnosis had increased risk of both CAD (RR = 4.9, 95% CI 1.5 – 16.3, $p = 0.01$) and HF (RR = 3.0, 95% CI 1.6 – 5.0, $p < 0.01$). Cisplatin exposure ≥300 mg/m^2 was associated with increased risk of any CVD (RR = 1.8, CI = 1.2 – 2.6, $p < 0.01$), primarily attributable to increased risk of HF (RR = 2.3, 95% CI = 1.5 - 3.5, $p < 0.01$).

Conclusions: Among long-term survivors of pediatric cancer, increasing CRT dose is associated with increased risk for CVD in a dose-response relationship. Young children are at higher risk for CVD after low-dose CRT or high-dose anthracycline exposure. Cisplatin exposure significantly increases risk for CVD. These findings should inform future treatment and surveillance protocols.

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