PROJECTED CARDIAC LATE-EFFECTS IN ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: With the advent of risk-stratified treatment, most children diagnosed with acute lymphoblastic leukemia (ALL) will become long-term survivors and face late-effects risks. Cohort studies, such as the Childhood Cancer Survivorship Study (CCSS) provide estimates of long-term outcomes, but are limited by follow-up. Simulation modeling can project outcomes beyond observational periods and assess variation among evolving treatment approaches.

Objective: To estimate cardiac disease risks by age 50 among pediatric ALL survivors by risk-stratified, treatment era-based subgroups

Methods: Using the Cancer Outcomes Microsimulation: Pediatric and Adolescent SurvivorShip (COMPASS) model based on data from the CCSS (treatment-related risks) and national databases (age-related risks), we projected cumulative incidence of heart failure (HF) and coronary artery disease/myocardial infarction (CAD/MI) among 5-year ALL survivors based on patient characteristics and treatment exposures. Subgroups were defined by chemotherapy/radiation (RT) combinations and intensity: "1970s-like"(>20Gy RT, no dexamethasone, no cytarabine) (n=695; mean follow-up age [range] = 38.5 years [8-61]), "1980s-like standard-risk (SR)" (>0 to ≤20Gy RT, no dexamethasone, ≤120mg/m^2 anthracycline) (n=611; 32.4 years [9-60]), "1980s-like high-risk (HR)" (any RT, no dexamethasone, >120mg/m^2 anthracycline, cytarabine) (n=348; 33.6 years [10-55]), "1990s-likeSR" (no RT, ≤120mg/m^2 anthracycline, ≤1,000mg/m^2 cyclophosphamide) (n=1347; 28.3 years [8-58]), and "1990s-likeHR" (dexamethasone, >120mg/m^2 anthracycline, >1,000mg/m^2 cyclophosphamide) (n=478; 28.1 years [11-48]). We simulated age, sex, and calendar year-matched individuals as the general population comparator to estimate absolute excess risks (AER) and relative risks (RR). We conducted 1,000 simulations and report the mean and 95% uncertainty intervals (UIs).

Results: Among 5-year ALL survivors, estimated overall survival at age 50 ranged from 86% (UI, 81-90) for the 1970s-like subgroup to 91% (87-95) for 1990s-likeHR. Cumulative HF and CAD/MI incidence at age 50 trended higher among HR subgroups (HF: 5.8% [1.6-13.3] for 1980s-likeHR and 6.3% [1.2-17.3] for 1990s-likeHR; CAD/MI: 4.9% [1.4-10.0] for 1980s-likeHR and 4.2% [0.6-13.6] for 1990s-likeHR) compared to the other subgroups (HF: 2.5%

[0.7-4.9] for 1970s, 3.7% [0.6-9.7] for 1980s-likeSR and 3.6% [0.8-9.6] for 1990s-likeSR; CAD/MI: 3.7% [1.8-6.6] for 1970s-like, 3.5% [1.0-7.9] for 1980s-likeSR and 3.5% [1.0-13.7] for 1990s-likeSR). All subgroups were projected to have elevated risks compared to the general population, albeit with considerable uncertainty. For example, for 1990s-likeSR, AER was 2.9% (0.4-8.6; RR 6.5 [1.5-20.8]) for HF and 2.9% (0.6-8.6; RR 9.4 [1.6-44.0]) for CAD/MI.

Conclusion: Projected estimates suggest all pediatric ALL survivors are at potentially elevated risk for cardiac complications before age 50. These findings underscore the importance of surveillance and continued follow-up of ALL survivors.