# Childhood Cancer Survivorship, Late Cardiotoxicity, and CV Prevention

*Saro Armenian, DO, MPH[1], Daniel Lenihan, MD[2]*

*[1] City of Hope Comprehensive Cancer Center, Duarte, California, United States*

*[2] Division of Cardiovascular Medicine, Vanderbilt University, Nashville, Tennessee, United States*

Received: 20.07.2016. Accepted: 18.08.2016.



The initial presentation in this session was a comprehensive outline of *Late onset cardiotoxicity: incidence, risk and individual risk prediction* by Dr Gregory Armstrong from St. Jude's Children's Hospital in Memphis, TN. He presented many primary studies from the Childhood Cancer Survival Study that indicated the extent and prognosis related to CV outcomes in long-term survivors of childhood cancer. He reported on the high quality data that has been systematically collected for the past 2 decades. The degree that cancer therapy, whether radiation or chemotherapy or the combination, can affect the CV outcomes of patients is profound [1, 2]. It is difficult to discern what exact profiles of patients are at highest risk but certainly the dose of radiation and chemotherapy is an important modifier of risk. Additionally, underlying CV risk factors that developed over time can have a major impact of overall outcomes [2]. Understanding what screening tests are most effective in detecting CV issues at a modifiable state is of paramount importance [3, 4]. These data inform our current strategies for optimal cancer survivorship cancer [5].

The second presentation in this session was *Genetic variants and the risk for cardiotoxicity* presented by Dr Smita Bhatia of the University of Alabama-Birmingham in Birmingham, AL. She is a recognized international leader in defining genetic determinants that may indicate those are risk for cardiotoxicity, especially associated with anthracycline treatment. Her presentation outlined many years of careful descriptive research attempting to detail those genetic variations that could be responsible for the susceptibility for cardiotoxicity [6]. This groundbreaking research has the potential to lead to the implementation of personalized cancer care, balancing the need for excellent cure rate with minimal long term cardiotoxicity [7].

**Correspondence:**
Saro Armenian, DO, MPH
City of Hope National Medical Center
1500 East Duarte Rd, Duarte, CA 91010-3000
e-mail: sarmenian@coh.org

Daniel J. Lenihan, MD
Division of Cardiovascular Medicine
Vanderbilt Heart and Vascular Institute
1215 21st Ave South, Suite 5209, Nashville, TN 37232.
e-mail: daniel.lenihan@vanderbilt.edu

Next, Dr Saro Armenian, at City of Hope in Duarte, CA, presented a description and review of the data regarding *Screening and intervention for cardiomyopathy.* Early pharmacologic intervention, in the asymptomatic setting, has been shown to improve long-term cardiac outcomes in adults following myocardial infarction, or in children with progressive neuromuscular disorders at high risk for cardiac dysfunction such as Duchene muscular dystrophy [8–11]. As a result, a number of clinical care Guidelines [12, 13] have recommend routine echocardiographic screening for cardiac dysfunction in asymptomatic childhood cancer survivors after completion of anthracycline-based therapy. However, there are gaps in knowledge pertaining to: how long should echocardiographic screening continue after completion of therapy, the reproducibility and validity of abnormal echocardiographic findings, and the utility of early intervention in childhood cancer survivors with asymptomatic cardiac dysfunction.

Two recently published cost-effectiveness analyses [14, 15] have utilized Markov modeling to demonstrate that screening for asymptomatic cardiac dysfunction can be cost-effective. However, the utility of screening is largely dependent on the relative effect size of the intervention. Co-administration of anthracyclines with dexrazoxane can ameliorate the acute cardiotoxicity associated with anthracyclines [16, 17], but the long term efficacy of this approach has yet to be determined. Importantly, the growing numbers of childhood cancer survivors who have not been treated with dexrazoxane make it imperative that new approaches be investigated for long-term heart failure risk reduction. For this population, early initiation of an angiotensin-converting enzyme inhibitor or β-blocker may prevent the progression of chronic cardiac remodeling. This strategy is currently being investigated in an ongoing NCI-funded multi-institutional randomized double-blinded placebo controlled trial (NCT02717507) of low dose carvedilol in childhood cancer survivors at highest risk for developing heart failure. In the meantime, healthcare providers are asked to educate and counsel all survivors of childhood cancer about the importance of maintaining a heart-healthy lifestyle, and to aggressively screen for and manage modifiable cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia [12].



## Acknowledgements

The presented report is the summary of the session 4th of the **Global Cardio-Oncology Summit**, organized in Nashville, Tennessee, US (October 15-16th, 2015).

## References

1. Armstrong GT, Kawashima T, Leisenring W et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 2014; 32: 1218-1227.
2. Armstrong GT, Oeffinger KC, Chen Y et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013; 31: 3673-3680.
3. Armstrong GT, Plana JC, Zhang N et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. J Clin Oncol 2012; 30: 2876-2884.
4. Armstrong GT, Joshi VM, Zhu L et al. Increased tricuspid regurgitant jet velocity by Doppler echocardiography in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. J Clin Oncol 2013; 31: 774-781.
5. Armstrong GT, Chen Y, Yasui Y et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. N Engl J Med 2016; 374: 833-842.
6. Wang X, Sun CL, Quinones-Lombrana A et al. CELF4 Variant and Anthracycline-Related Cardiomyopathy: A Children's Oncology Group Genome-Wide Association Study. J Clin Oncol 2016; 34: 863-870.
7. Armenian SH, Xu L, Ky B et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. J Clin Oncol 2016; 34: 1122-1130.
8. Hunt SA, Abraham WT, Chin MH et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112: e154-e235.
9. Connuck DM, Sleeper LA, Colan SD et al. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. Am Heart J 2008; 155: 998-1005.
10. Duboc D, Meune C, Pierre B et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. Am Heart J 2007; 154: 596-602.

11. Rhodes J, Margossian R, Darras BT et al. Safety and efficacy of carvedilol therapy for patients with dilated cardiomyopathy secondary to muscular dystrophy. Pediatr Cardiol 2008; 29: 343-351.
12. Armenian SH, Hudson MM, Mulder RL et al. Recommendations for Cardiomyopathy Surveillance for Survivors of Childhood Cancer: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2015; 16: e123-e136.
13. Shankar SM, Marina N, Hudson MM et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. Pediatrics 2008; 121: e387-e396.
14. Wong FL, Bhatia S, Landier W et al. Cost-effectiveness of the children's oncology group long-term follow-up screening guidelines for childhood cancer survivors at risk for treatment-related heart failure. Ann Intern Med 2014; 160: 672-683.
15. Yeh JM, Nohria A, Diller L. Routine echocardiography screening for asymptomatic left ventricular dysfunction in childhood cancer survivors: a model-based estimation of the clinical and economic effects. Ann Intern Med 2014; 160: 661-671.
16. Lipshultz SE, Rifai N, Dalton VM et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med 2004; 351: 145-153.
17. Lipshultz SE, Adams MJ, Colan SD et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. Circulation 2013; 128: 1927-1295.



**Authors' contributions:**
Both authors equally contributed to idea & design of the article, clinical data collection, analysis and writing the manuscript.