Cardiovascular complications are a leading cause of therapy-related morbidity and mortality in long-term survivors of childhood cancer. The research of Saro Armenian, at the City of Hope, California, focuses on understanding the pathophysiology and risk factors for these cardiovascular complications which include heart failure, coronary artery disease, and stroke. Taking a dual approach, he is exploring ways to prevent these complications and investigating early screening tools to identify individuals most at risk.

**A two-pronged approach to reduce heart failure in childhood cancer survivors**

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**IMPROVED SURVIVAL IS COMPLICATED**

Although improved survival rates are a major step forward for childhood cancer, treatment-associated complications are a growing concern. While children generally tolerate the acute effects of chemotherapy relatively well compared to adults, exposure to chemotherapy, radiation, and/or surgery during childhood can contribute to serious complications that may not manifest until years after the completion of therapy. Recent studies revealed that two out of three childhood cancer survivors will develop a chronic health condition such as subsequent malignant tumours, cardiovascular problems, endocrine diseases, and musculoskeletal disorders. Of these, anthracycline-associated cardiovascular complications remain a leading cause of late mortality and morbidity in childhood cancer survivors. Today, those that survive childhood cancer have a five-fold greater risk of developing heart failure (HF) compared to age-matched controls, and the overall survival rate following these complications is less than 50%.

**ANTHRACYCLINES AND HEART FAILURE**

Cardiotoxicity resulting from anthracycline exposure occurs along a continuum from asymptomatic cardiac dysfunction characterised by abnormalities of cardiac function and structure detected via imaging studies, to clinically evident HF. Heart failure is initiated by the formation of free radicals, which leads to remodelling and weakening of the cardiac muscle, eventually impairing the heart's ability to pump blood efficiently. The link between childhood anthracycline exposure and HF risk is dose-dependent. In other words, the greater the exposure to anthracyclines during childhood, the greater the risk of HF later in life. As well as anthracycline exposure, other factors contribute to the increased risk of HF in childhood cancer survivors. These include younger age (less than five years) at exposure, female gender, preexisting heart disease, and simultaneous irradiation of the mediastinum (the central thoracic cavity). The overall lifetime risk for developing HF is further exaggerated by the fact that childhood cancer survivors are also at a higher

An innovative mHealth platform can be used to monitor cardiac function in survivors at risk for developing heart failure. Individuals may check their heart health as often as they like and relay the information back to their doctors in real time.

**Childhood cancer survivors have a greater than five-fold risk of developing heart failure compared to age-matched controls**
Do genetics play a role in the increased risk of heart failure among childhood cancer survivors? It is well-established that there is marked variability in the prevalence and severity of therapy-related HF that is not explained exclusively by clinical and treatment factors such as age at exposure, sex, and cumulative anthracycline dose. Studies are under way to examine how an individual’s genetic make-up could explain the variability in risk. The information obtained from these studies could set the stage for the development of accurate and personalised risk-prediction models, providing physicians and patients with knowledge about HF risk even before administration of therapy. This would allow them to avoid certain exposures, if a comparable alternative exists, or closely monitor patients during and after therapy is initiated.

Is the HF risk greater after certain types of cancer than others? HF is more prevalent in individuals with certain cancers because of the intense treatment for cure, not because of the cancer itself. Given the toxicity associated with anthracyclines and its large impact, it makes more sense to intensify efforts to avoid their use altogether, rather than finding ways to circumvent or counteract their toxicity. It is important to note that the development of anthracyclines contributed to the tremendous cure rates we see today, and that the vast majority of children treated with anthracyclines do not develop HF. For many types of cancers, there are no alternatives to anthracyclines. As such, it is imperative to develop novel strategies for personalised delivery of these drugs, taking into consideration the genetic factors as well as the physical health of the patient at the time of treatment. Efforts are underway to develop less toxic therapies for both paediatric and adult cancer patients. It is the responsibility of the oncology community to translate the knowledge gained from our survivorship studies today towards better cures for tomorrow.

How accurate do you expect the mHealth-based platform to be in detecting cardiac dysfunction? Our initial study of approximately 200 patients showed that the handheld mHealth platform was as accurate as cardiac magnetic resonance imaging (MRI), which is the gold standard measure of heart function. Additional validation studies are under way in both paediatric and adult populations, and should shed more light on the accuracy of this platform in oncology and non-oncology settings.

What’s next for your research? With the advent of new integrative electronic health record systems, we have the opportunity to utilise advances in computer sciences (e.g., natural language processing) to study health outcomes in hundreds of thousands of patients at a fraction of the time it takes to study them today. This has the potential to not only capture health information more rapidly, but to share this knowledge with researchers and practitioners who are developing the next generation of therapeutic clinical trials. The challenge facing clinicians and researchers alike is how to integrate genomics, personalised medicine, and risk prediction into real-time decision making for our patients and families. These decisions have to be balanced by very real concerns such as the cost-effectiveness of our screening and treatment approaches. As such, we have a number of studies examining new paradigms in care delivery for our most vulnerable patients. As paediatric oncologists, we have to ensure that our patients not only survive their treatment, but thrive for decades afterwards, recognising that their best days are ahead of them.