CHEMOTHERAPY INDUCED CARDIOMYOPATHY: WHAT PRIMARY CARE PROVIDERS SHOULD KNOW

By

JANE JAYVENA NARAYAN

Bachelor of Science, University of British Columbia, 2007
Bachelor of Science in Nursing, British Columbia Institute of Technology, 2010

A CULMINATING PROJECT SUBMITTED IN PARTIAL
FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF NURSING-NURSE PRACTITIONER

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(School of Nursing)

THE UNIVERSITY OF BRITISH COLUMBIA

Vancouver

April/2017

Table of Contents

Abstract

As the efficacy of cancer treatments improve, the number of long-term cancer survivors have increased. The concept of cancer survivorship exacerbates the need for primary care providers (PCPs) to identify and treat the potential long-term sequela of chemotoxicity. Amid numerous long-term complications of chemotherapeutic agents, cardiovascular toxicities have been extensively documented in the literature with chemotherapy induced cardiomyopathy (CIC) as one of the leading cardiovascular complications. Guidelines and recommendations are inconsistent regarding the long-term care of this specialized population, yet consensus does exist that if detected early, morbidity and mortality resulting from cardiomyopathy within this population can be improved. This literature review provides PCPs with knowledge in 5 main areas: 1. the clinical definition of CIC and inducing agents, 2. populations at risk, 3. methods and frequency for surveillance, 4. essential clinical assessments and education to provide to patients, and 5. appropriate referral and treatment options. The information obtained from guidelines and research studies was developed into an informational poster and presented at the British Columbia Nurse Practitioner Association's (BCNPA) annual conference to disseminate evidence-based knowledge regarding the awareness CIC. With increased awareness of this complication it is anticipated that PCPs will be able to promptly identify at-risk patients, provide effective screening and initiate prompt consultations to the appropriate specialty in attempts to improve overall outcomes in cancer survivors.

Chemotherapy-Induced Cardiomyopathy: What Primary Care Providers Should Know

As the efficacy of anticancer treatments progress, research reveals that long-term outcomes such as cardiotoxicity are associated with a poorer prognosis than the underlying malignancy itself (Higgins, O'Halloran, & Chang, 2015). Among cancer survivors, cardiotoxicity is now acknowledged as a prominent cause of long-term morbidity and mortality (Lenneman & Sawyer, 2016; Nolan, Lowenthal, Venn, & Marwick, 2014; Virani et al., 2016). Cancer is the leading cause of mortality among Canadians, and the Canadian Cancer Society (CCS) estimates that 202, 400 new cases of cancer were diagnosed in 2016 and 78, 800 Canadians died from cancer in the same year (CCS, 2016). In 2009, statistics indicate that 810, 000 people were living with cancer and among those diagnosed, 29% were diagnosed within the last 2 years, 32% within the last 3-5 years and 38% within the last 5-10 years (CCS). Additionally, the CCS predicts that the overall 5-year survival rate of cancer patients is 60% within Canada (CCS). This is important to note because within the first few years of diagnosis, most individuals receive and recover from active therapy and are followed by a specialist, however, 3 to10 years post diagnosis most survivors have completed their therapy and have returned back to the care of their primary care provider (PCP).

Cardiotoxicity can present in many forms including arrhythmias, hypertension, pericardial disease, myocardial ischemia, valvular dysfunction, arterial thrombosis and commonly cardiomyopathy (Cross et al., 2014; Herrmann, Lerman, Sandhu, Villarraga, Mulvagh, & Kohli, 2014; Higgins et al., 2015; Lipshultz, Cochran, Franco & Miller, 2013; Virani et al., 2016). Chemotherapy-induced cardiomyopathy (CIC) can occur in an acute manner (immediately or shortly after starting active chemotherapy), early (less than one year), or late (greater than one year, but most commonly several years) after chemotherapy has been

completed (Carver, Szalda, & Ky, 2013; Raj, Franco, Lipshultz, 2014). The reported estimate of CIC in cancer survivors is approximately 10% with 2% to 4% of these survivors going on to develop end-staged heart failure (Lenneman & Sawyer, 2016). Furthermore, heart transplantation data analysed from the United Network of Organ Sharing revealed the incidence of heart transplants as a result of CIC are rising (Lenneman & Sawyer). Thus, it is imperative for long-term cancer survivors to be monitored closely post-active cancer therapy to decrease the incidence of CIC and its complications.

Various practitioners make up health care systems within different countries and each have their own clinical expertise and scope of practice. Since survivors are living much longer, it has become common practice for PCPs to provide long-term care to cancer survivors. PCP's can be composed of General Practitioners (GPs) or Nurse Practitioners (NPs). A GP is a medical doctor who is trained to practice general medicine in a primary care context (College of Family Physicians of Canada, 2016). A Nurse Practitioner (NP) is a registered nurse who has accomplished a masters degree and is able to legally diagnose conditions, prescribe medications and manage care throughout the life span (BCNPA, 2015). While both of these practitioners serve as vital components within the healthcare system, for the purpose of this literature review NPs will be the primary focus.

Rationale and Scope of Project

As therapies improve and patients survive acute complications of chemotherapy, we must focus on the long-term consequences of these pharmacological interventions. NP's must understand the pathophysiology of the disease, recognize pharmacological agents involved, identify at risk populations, understand surveillance methods and their frequencies, and have access to a comprehensive plan of care to approach CIC in order to improve overall morbidity

and reduce mortality. The purpose of this culminating project is to improve CIC awareness among novice NP's in the primary care setting by synthesizing current practice recommendations based on pertinent articles and clinical practice guidelines.

The concept I will analyze in this project is the early detection and intervention of CIC and how this can improve overall morbidity and mortality in cancer survivors. First, I will explore the background of cardiovascular disease in relation to cancer survivorship and focus on major themes and concepts such as cardio-oncology, cardiomyopathy, CIC and agents involved. Next, I will present literature that discusses surveillance of CIC among at-risk populations, the advantages and disadvantages of surveillance modalities and screening recommendations. I will then explore essential clinical assessments that PCPs must conduct and outline education that should be routinely provided to survivors. Finally, if CIC is detected, I will explore a plan of care including sources to promptly refer patients to for appropriate care.

Based on the extensive literature review, a poster was created that incorporated the pathophysiology, pharmacological agents, patient presentation, diagnositic criteria, screening tests, and treatment options for patients suffering from CIC (refer to appendix B). To create this poster, a UBC branded poster template was used from UBC's Information Technology website. This project was presented at the BCNPA's annual conference in June 2017.

Search Strategy

Literature reviews should be unbiased and current (Cronin, Ryan, & Coughlin, 2008). In an attempt to determine whether the early detection and intervention of CIC can improve overall morbidity and mortality in long-term cancer survivors, a literature review of publications from three databases: MEDLINE with Full Text, PubMed, and CINAHL with Full Text was conducted. The search was limited to peer-reviewed articles published in 2010 and beyond. The

keywords: cardio-oncology, cardiomyopathy, post-chemotherapy induced cardiomyopathy, chemotherapy, cancer survivorship, primary care, nurse practitioner, physician, were used in all possible combinations with mappings to subject headings (i.e.: MeSH terms). Abstracts were reviewed for content application and retain or rejected, a total of 62 articles were reviewed for this literature review. In addition, the reference lists of pertinent articles and guidelines were also reviewed for content applicability and were utilized as references if content application and relevance was deemed.

Background

Cancer Survivorship

A report conducted by the Institute of Medicine and the National Research Council of the National Academies explored the transition between a cancer patient to a survivor, this report first introduced the theme of 'cancer survivorship' in the management of cancer patients (Hewitt, Greenfield & Stovall, 2006). The components of cancer survivor care should include detection of recurrent or new cancers, surveillance for long-term side effects, prevention strategies, interventions and coordination between PCPs and specialists (Cooper, Loeb, & Smith, 2010; Grunfeld & Earle, 2010).

A systematic review consisting of 15 studies assessed the health care needs of cancer survivors in primary care practice, it revealed that cancer survivors have diverse needs which are not met by current PCPs (Hoeskstra, Heins & Korevaar, 2014). It was found that majority of PCPs monitored chronic conditions, provided routine preventative exams, and had limited knowledge of acute and chronic co-morbid conditions that could arise from cancer treatments; vise-versa was found among oncologists causing frustration among cancer survivors (Grunfeld & Earle, 2010).

A study by Nekhlyudov, Aziz, Lerro, and Virgo (2014) explored awareness of long-term chemotherapy effects between PCPs and oncologists. A survey was sent out to 1, 130 oncologists and 1, 072 PCPs, which asked participants to identify long-term chemotherapy effects that they had observed or had knowledge of for five chemotherapeutic agents used to treat colon or breast cancer. Results found that oncologists were extremely confident in the knowledge of long-term side effects for cancer therapies (76-77%) versus PCPs (23-31%). 95% of oncologists observed or reported familiarity with long-term cardiac effects of doxorubicin in comparison to 55% of PCPs (Nekhlyudov et al., 2014). Furthermore, it was found that knowledge of other agents resulted in even poorer outcomes. Although PCPs are willing to care for cancer survivors, this study clearly displayed a knowledge gap between PCPs and oncologists highlighting a need for further education among this group of providers with respect to long-term recognition and management of cancer induced side effects.

Cancer and Cardiovascular Disease (CVD)

Some of the best statistics on cancer survivorship and long-term complications of treatments is derived from pediatric cancer survivors (Armenian et al., 2015; Nolan et al., 2014; Oeffinger et al., 2006). Oeffinger et al's retrospective study compared pediatric cancer survivors (average 17.5 years post chemotherapy) to their non-cancer treated siblings, and found they had a 3 times increased risk for the development of a chronic health condition and a 15 times increased risk for the development of chronic heart failure (2006). This finding highlighted a substantial correlation between cancer survivorship and CVD.

Patnaik, Byers, DiGuiseppi, Dabelea & Denberg's study followed a total of 63, 566 women diagnosed with breast cancer for an average of 9 years in the United States (2011). This study looked at women who were diagnosed at age 66 or older. They utilized the Surveillance,

Epidemiology, and End Results (SEER) Medicare linked database which tracks cancer incidence and survival in the US. In this study, CVD was the leading cause of death, it accounted for 15.9% of the study population compared to breast cancer, which accounted for 15.1% of deaths (Patniak et al.). CV effects are multifactorial and can have various overlapping risk factors, however, cardiotoxic effects of modern-day chemotherapy also contribute to these complications (Nolan et al., 2014).

The *Multiple Hit Hypothesis* emerges in the literature as a mechanism to understand the phenomenon of cancer therapy-provoked myocardial dysfunction (Virani et al., 2016). This hypothesis proposes that customary risk factors associated with heart disease such as increased lipids, sedentary lifestyle, smoking combined with cardiotoxic cancer therapies overpower the myocardium leading to overall cardiac dysfunction (Cardinale, Bacchiani, Beggiato, Colombo, & Cipolla, 2013).

Cardio-Oncology

Amid long-term cardiotoxic complications that may arise with chemotherapy treatments, cardio-oncology services have started to emerge globally in an attempt to lead treatment and management of this complex population (Herrmann et al., 2014). Prior to cardio-oncology, patients who experienced acute cardiovascular complications during cancer treatment were referred to regular cardiology services. Cardio-oncology is a new discipline that has been created with the intention to examine new strategies and establish clinical expertise in risk stratification, prevention, prompt diagnosis, and treatment of cardiotoxicity in cancer patients (Carter & Clark, 2015; Ghosh & Walker, 2017; Virani et al., 2016). Cardio-oncology services serve two areas of practice: acute and chronic. In an acute situation, patients actively undergoing treatment with known agents are monitored and managed for cardiovascular complications. In chronic

situations, cardio-oncology services apply to survivors who now exude late-onset cardiotoxic symptoms (Carter & Clark, 2015). In 2016, the Canadian Cardiovascular Society (CCS) published a guideline by a panel of experts from across Canada that outlines best practices for cardiovascular complications of cancer therapy (Virani et al., 2016). Applicable aspects of this guideline have been incorporated into this review.

Cardiomyopathy

Cardiomyopathy refers to disease of the heart muscle causing reduced ability of the myocardium (heart) to pump blood to rest of the body (Heart and Stroke Foundation of Canada, 2017). This literature review focuses on the cardiotoxic effect of cardiomyopathy that occurs as a result of treatment, therefore, it is very important to have an adequate understanding of the various types of cardiomyopathy that are seen in clinical practice. Furthermore, cardiomyopathy may result without symptoms and progress later to different forms of heart failure (Carter & Clark, 2015; Curigliano et al., 2016). There are 5 main types of cardiomyopathy: ischemic, dilated (congestive), hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathy (ARVC) or arrhythmogenic right ventricular dysplasia (AVAD).

Ischemic cardiomyopathy is most common form of cardiomyopathy. It results due to a lack of blood flow to the myocardium, in the form of a narrowed or blocked artery. When a blockage occurs, there is a lack of oxygenated blood reaching the myocardium causing a loss or weakening of the muscle of the myocardial tissue. It most commonly occurs as a result of heart attacks or coronary artery disease (Heart and Stroke Foundation of Canada, 2017).

Dilated or Congestive cardiomyopathy is a form of cardiomyopathy that occurs as a result of the weakening of the chambers or walls of the myocardium decreasing the overall ability of the myocardium to pump blood to the rest of the body. It is usually caused by viral

infections, excessive alcohol consumption or cocaine use (Heart and Stroke Foundation of Canada, 2017). This form of cardiomyopathy is seen as a result of chemotherapeutic agents in the adult population (Lipshultz et al., 2013).

Hypertrophic cardiomyopathy (HCM) is caused by a thickening of the walls of the myocardium making it difficult to pump blood. The most common type of HCM occurs when there is an enlargement between the bottom chambers causing blockage of blood flow. This form of cardiomyopathy is very uncommon and may lead to abnormal rhythms potentially resulting in sudden death in some individuals (Heart and Stroke Foundation of Canada, 2017).

Restrictive cardiomyopathy is a form of cardiomyopathy that occurs in which the myocardium is unable to stretch properly limiting the amount of blood that fills that chambers causing an overall restriction in the blood flow (Heart and Stroke Foundation of Canada, 2017). This form of cardiomyopathy is seen in pediatric survivors of cancer (Lipshultz et al., 2013).

ARVC/ AVAD is extremely rare form of cardiomyopathy that results when the right ventricle muscle develops scar tissue causing a disruption in the hearts normal rhythm. Research reveals that it is the leading cause of sudden cardiac death in athletes and younger population and is caused by genetic mutations (Heart and Stroke Foundation of Canada, 2017).

Literature Review: Chemotherapy-Induced Cardiotoxicity (CIC)

Types of CIC

Literature reveals that there are two distinctly different pathophysiological mechanisms that illicit cardiotoxic effects: Type 1 cardiotoxicity (involving death of the myocardium cells) and Type 2 cardiotoxicity (reversible impairment to the myocardial cells) (Cross et al., 2015; Herrmann, et al., 2014; Higgins et al., 2015; Moudgil & Yeh, 2016; Nolan et al., 2014). It is essential for PCPs to understand the type of agent used during active chemotherapy either alone

or in combination with another agent or radiation because each path has its own set of associated risk factors. There are several classes of chemotherapeutic agents, however, this review will focus solely on anthracycline and monoclonal antibody type agents as those are seen in the long-term CIC setting. Alkylating agents (cyclophosphamide, Ifosfamide) and Protein kinase inhibitors (Sunitinib, Sorafenib, Lapatinib, and Imatinib) also emerge in the literature as agents that cause CIC but primarily in an acute setting (days to weeks) and rarely in the long-term setting (Cross et al.; Higgins et al.).

Type 1 Cardiotoxicity- Anthracyclines- Type one cardiotoxicity involves the destruction of myocytes resulting in non-reversible cardiomyopathy (Cross et al., 2015; Herrmann et al., 2014; Higgins et al., 2015). Anthracyclines are the primary class of medications that are responsible for this form of cardiomyopathy. They were first introduced in the 1970's and are a class of chemotherapy medications that stem from Streptomyces bacterium *Streptomyces peucetius var* (Nolan et al., 2014). Examples of anthracyclines agents include epirubicin, idarubicin, daunorubicin, mitoxantrone, and most commonly doxorubicin. These agents are commonly used for treatment of breast cancer, osteosarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and acute leukemia (Cross et al.; Groake, Tong, Khambhati, Cheng, & Moslehi, 2012).

The cardiotoxic side effect profile of this chemotherapeutic class has been extensively documented. The iron and free radial hypothesis emerges in the literature as a means to explain cardiotoxic effects that arise with this class of medications. It is proposed that "anthyracyclines form a complex with iron, which in turn catalysts free radical production. The free radials then act within the cell to cause membrane disruption and cellular dysfunction, cells of the myocardium are particularly vulnerable" (Nolan et al., 2014, p. 940).

The effect of anthyracyclines can be seen in two different mechanisms. Firstly, it can occur as an early acute mechanism (during active therapy) or a later chronic mechanism, which presents as asymptomatic cardiomyopathy and has the potential to progress to active chronic heart failure (Curigliano et al., 2016; Groarke et al., 2012). Specialists commonly monitor acute effects during therapy, yet chronic manifestations occur years later in the community therefore it is vital for PCPs to recognize.

The earliest study outlining cardiotoxic effects of doxorubicin (DOX) was published in 1979. This study was a retrospective analysis that looked at 4018 records of patients treated with DOX and found that there were 88 cases (2.2%) of chronic heart failure (CHF)/cardiomyopathy with a 28-60% rate of mortality within this population (Von Hoff, Layard, Basa, Davis, Von Hoff, Rozencweig & Muggia, 1979). In this study, it was found that patients who had a cumulative dose of DOX > 400 mg/m^2 had an incidence of CHF of 3%, >550 mg/m^2 had an incidence of 5%, and 700 mg/m^2 had an incidence of 18% (Von Hoff et al.). Since this study, there have been numerous studies that have solidified the connection between cardiomyopathy and anthracycline treatment (Swain, Whaley & Ewer, 2003; Cross et al., 2016). Swain et al. (2003) studied the effect of DOX on 360 patients who were treated for small cell carcinoma or breast cancer. It was found that 32 patients had a diagnosis of CHF, but that 149 patients fit the criteria for a cardiac event. The incidence of cardiotoxicity was deemed to be much higher in this study compared to that of Von Hoff et al. and overall patients who had a cumulative dose of > 400 mg/m^2 had an incidence of CIC of 5%, >550 mg/m^2 had an incidence of 26%, and >700 mg/m^2 had a incidence of 48% (Swain et al.). These studies clearly support that there is a dose dependent correlation between the use of anthracyclines and incidence of CIC.

Interestingly, more recent studies reveal that even with small doses of anthracycline therapy (375mg/m^2) silent changes to myocardial function can be seen on MRI imaging within 6 months of therapy cessation (Drafts et al., 2013). Another study with an anthracycline cumulative dose of 240 mg/m^2 revealed that changes were seen at a microscopic level in endomyocardial biopsies taken from patients (Moudgil & Yeh, 2016). Therefore, these studies in combination with patients receiving multi-agent therapy or adjuvant use of chest radiation have promoted some researchers to caution clinicians that there may be no potentially safe dose of anthracyclines (Higgins et al., 2015).

Type 2 Cardiotoxicity- Monoclonal Antibodies - Type 2 cardiotoxicity is characterized by the lack of myocyte structural abnormalities and can be reversed once therapy is stopped (Herrmann et al., 2014). Monoclonal antibodies are one of the primary classes of medications that are responsible for type 2 cardiotoxicity (Cross et al., 2015; Mougdil & Yeh, 2016). They are molecules that are laboratory engineered that function as substitute antibodies that imitate the immune systems attack on cancer cells (Groake et al., 2012). The most common monoclonal antibodies in cancer treatment are trastuzumab (Herceptin) and Bevacizumab. Trastuzumab is mainly used in breast cancer treatment and targets the HER2 cells (Nolan et al., 2014). The mechanism of cardiotoxicity continues to be unclear, however, it is believed that "the cardiac dysfunction associated with trastuzumab is a direct consequence of ErbB2 inhibition in cardiomyocytes" (Curigliano et al., 2016, p. 312). In studies with mice, it was found that when the ErbB2 receptor was deleted, it resulted in systolic dysfunction and dilated cardiomyopathy that indicates that this receptor is crucial in sustaining function within the myocardium (Curigliano et al.).

Studies reveal that adjunctive treatment with trastuzumab for HER2 type of breast cancers result in a 33% reduction in mortality rate (Patnaik et al., 2011). Furthermore, Dahabreh et al. conducted a meta-analysis of five randomized control trials that explored the outcome of breast cancer treatment with and without trastuzumab in approximately 13 500 women and found that women who received trastuzumab as part of their therapy had a 34% lower risk of mortality with its use and a 40% lower risk of reoccurrence (2008).

Although trastuzumab has been proven to lower mortality rates, it also has the ability to cause asymptomatic declines in myocardial function and acute symptomatic failure, however, it is widely accepted that these effects are reversible with cessation of therapy (Groarke et al., 2012). In a study by Ewer et al. of 38 patients treated for HER2 positive breast cancer, it was found that prior to the start of trastuzumab therapy the mean left ventricular ejection fraction (LVEF) of the group was 0.61 +/- 0.13 (it is important to note that patients in this group had already been treated with anthracycline therapy) (2005). As trastuzumab therapy continued at 4.5 months, it was found that the LVEF dropped to 0.43 +/- 0.16, using paired t-tests as a statistical measure. 37 out of 38 patients had their therapy stopped due to the decline in function. At that time, 31 patients were treated according to heart failure guidelines and 6 patients were observed. In all 37 patients, the LVEF recovered back to 0.55 +/- 0.11 after 1.5 months, reinforcing the reversibility factor associated with trastuzumab treatment (Ewer et al., 2005). Several other bodies of literature support that cessation of trastuzumab therapy for 4-8 weeks results in LVEF recovery (Lenneman & Sawyer, 2016; Virani et al., 2016). Trastuzumab-induced cardiomyopathy is not dose dependent (as in anthracyclines); however, when combined with anthracycline therapy it has been found to have an increased incidence of CIC by up to 27% compared to 3% with treatment of trastuzumab alone (Seidman et al., 2002).

Furthermore, it is documented that the combination of different chemotherapeutic agents with or without trastuzumab to the treatment regime has blurred the concept of type one and two toxicities in that although trastuzumab is considered a reversible agent, but when given with a non-reversible agent more damage can be seen (Higgins et al., 2015).

Literature Review: Surveillance of CIC

CIC has the potential to progress to end-stage heart failure within 2-4%of cancer survivors (Lenneman & Sawyer, 2016). It is important for PCP's to identify patients at risk, conduct ongoing surveillance in attempts for early diagnosis and once identified initiate appropriate treatment to hinder further development of the condition.

Who needs surveillance?

Everyone who has received cancer treatment with a chemotherapeutic drug known to increase the incidence of cardiomyopathy requires long-term follow up by a PCP, however, it is essential for PCP's to be able to identify individuals that are at greatest risk for developing CIC in order to mitigate harm as these survivors have a rapid incidence of deterioration compared to low or moderate risk groups (Armenian et al., 2015). The following section has been divided into pediatric population, adult population and pregnant population as each category has distinct considerations.

Pediatric Population- Children and adolescents treated for childhood cancers are at increased risk for developing cardiomyopathy later in adulthood as evidenced by several long-term follow-up studies (Henson et al., 2016; Lipshultz et al., 2013; Mulrooney et al., 2016). Mulrooney et al. (2016) conducted a cross sectional study of 1853 adult survivors of childhood cancer. The average age of the cohort was 31 years and average age at diagnosis of cancer was 8 years. Evaluation of the population was done through a medical history, physical examination

and imaging (echocardiography, ECG and walking test). It was found that 7.4% of survivors had cardiomyopathy (with 4.6% as a new diagnosis) and that majority of the survivors were asymptomatic at the time of evaluation. It was concluded that age was correlated with incidence of CIC because abnormalities were found in 3-24% of survivors in the age group of 30-39, whereas incidence jumped to 10-37% in survivors who were 40 years and above (Mulrooney et al.). This study highlights the importance of early screening in pediatric cancer patients because many remain asymptomatic for years. Another study out of England followed 200, 945 cancer patients and evaluated them at the 5-year mark (Henson et al., 2016). It was found that 2, 016 of these survivors died related to cardiac disease, although this study looked at all forms of cardiac disease not just cardiomyopathy, it did conclude that the age at which diagnosis was made was the greatest determinant of future cardiac mortality risk, with younger age of diagnosis increasing overall risk (Henson et al.).

Guidelines for management of pediatric patients deemed at highest risk stem from the Children's Oncology Group (COG). It is the world's leading organization dedicated to research of childhood and adolescent cancers. The COG has set forth Long-Term Follow-up (LTFU), which identify patients at increased risk for CIC because once treatment is completed there is often an asymptomatic period of cardiomyopathy that precedes the development of overt symptoms (Armenian et al., 2015).

The COG identifies patients who have had their cancers treated with the following as high risk patients warranted for ongoing monitoring: patients treated with a total dose of 300mg/m^2 or more of anthracyclines (DOX, daunorubicin, idarubicin, mitoxantrone, or epirubicin) therapy at less than 18 years of age, total cumulative anthracycline dose of 550mg/m^2 or greater at older than 18 years of age, overall age of treatment less than 5 years of age, female

gender, African descent, treatment with Amsarcrine or any other known cardiotoxic chemotherapeutic agent, or a high dose of Cytoxan prior to a stem cell or bone marrow transplant (COG, 2013; Lipshultz et al., 2013). Additionally, radiation therapy with a dose of 20Gy or more to areas affecting the heart or nearby tissues (such as lungs, spine, total body) also put the child at increased risk for developing CIC due to the combination of the two treatment modalities (COG). It is recommended that pediatric cancer survivors who have had over 40 Gy of radiation involving the myocardium or surrounding tissues or a combination of anthracycline therapy (at any dose) and radiation treatment greater than 30 Gy undergo a stress test 5-10 years after completion of radiation therapy and referral to a cardiologist if warranted (COG, 2013).

Girls are susceptible to cardiotoxic complications as evidenced in animal studies, which reveal that anthracyclines are not well absorbed by fat. Girls naturally have a higher percentage of body fat thus by basing dosing of medications on overall body mass this results in a higher concentration of medication exposed to cardiomyocytes then males (Lipshultz et al., 2013).

It is crucial to identify and continue to monitor pediatric patients at highest risk during their asymptomatic phase and intervene early in order to decrease morbidity and mortality. Armenian et al. (2015) set out to harmonize clinical practice guidelines from 4 leading international oncology bodies related to pediatric cancer survivorship: the UK Children's Cancer and Leukemia Group (UKCCLG), North American Children's Oncology Group (COG), the Dutch Childhood Oncology Group (DCOG), and the Scottish Intercollegiate Guidelines Network (SIGN). Each organization had slightly variable alterations in guidelines. COG and DCOG recommendations are the same, however, the UKCCKG and SIGN recommend that survivors whom a cumulative dose of anthracyclines of 250mg/m^2 or more are at higher risk as opposed to 300mg/m^2 (Armenian et al.). These differences prompted Armenian et al. to put forth

harmonized recommendations based on an expert panel of pediatric cardiologists, pediatric oncologists and other cancer care disciplines. Although not yet adapted by the COG, this harmonization initiative establishes a platform for international collaboration (Armenian et al.).

Adult Population- Unfortunately, guidelines in the adult population are not as concrete as the pediatric population. However, consensus among adult researchers lies in identification of at risk patients and prompt surveillance of these groups.

The use of trastuzumab is associated with reversible injury mainly in an acute capacity and studies have been conducted which reveal that after completion of trastuzumab therapy there are rarely any long-term cardiomyopathy effects discouraging long-term cardiac surveillance on patients treated with this medication alone (Herrrmann et al., 2014). However, if additional risk factors or pre-existing disease occur within the patient then a tailored plan of care should be developed and followed. Literature identifies that adults who have been treated with anthracycline therapy or radiation involving the myocardium or surrounding tissues are crucial candidates for long-term monitoring (Herrmann et al.; Swain et al., 2003). As described earlier, the highest risk of anthracycline documented cardiomyopathy occur with cumulative doses over 700 mg/m^2 however literature identifies survivors treated with greater than 400mg/m^2 deemed the threshold for increased vigilance (Higgins et al., 2015; Swain et al.).

In the adult population the following groups of cancer survivors as considered at high risk: those who have received a cumulative dose of anthracycline greater then 400 mg/m^2, age of patient at exposure (greater than 65), concomitant administration of trastuzumab, female gender, African race, concurrent or prior use of radiation greater than 35Gy, elevated troponin and/or NT-pro-BNP biomarkers early (one month) following exposure to therapy or pre-existing

cardiovascular risk factors such as hypertension, diabetes mellitus or hyperlipidemia (Curigliano et al., 2016; Groke et al., 2012; Virani et al., 2016).

Pregnant Women- Pediatric cancer survivorship studies reveal that PCPs must identify and refer young women who are pregnant or wanting to become pregnant and have them evaluated by a cardiologist (COG, 2013). COG have identified the following as increased risk warranting a consultation: anthracycline dose of greater than 300 mg/m^2, radiation at any dose if anthracycline therapy was also used, radiation at 30 Gy or greater to the heart or tissues surrounding that area, or total body irradiation (2013).

During pregnancy overall plasma volume is increased by up to 50% potentially putting a women who has unidentified cardiomyopathy at risk for deterioration either in pregnancy or during delivery (Armenian et al., 2015). These women must be evaluated by cardiologists to ensure that there is no new development of cardiomyopathy during pregnancy potentially causing harm to the patient and fetus. Additionally, PCPs must be vigilant with their differential diagnoses because symptoms related to cardiomyopathy such as fatigue; ankle swelling and shortness of breath can mimic common pregnancy symptoms (Armenian et al.).

What Surveillance Modality Should Be Used?

Once the PCP has identified patients that require surveillance based on risk factors it is then important to accurately document this information using a reliable modality (for example through the use of an online charting system tickler) to ensure follow-up is not missed during subsequent office visits. Extensive research exists that explores various modalities available for ongoing surveillance to identify CIC. It is essential for the PCP to understand the modalities available and how they differ from one another. This section will outline the main forms utilized

in practice and current recommendations so that the PCP can make an informed decision regarding the best modality method for each patient.

Diagnosis

The measurement of left-ventricular ejection fraction (LVEF) is the most commonly used marker of reference irrespective of the type of modality used to screen for cardiotoxicity (Virani et al., 2016). A concrete definition of CIC lacks in the literature however, two references are commonly sited in literature and used as endpoints in studies. One definition is adapted from the independent Cardiac Review and Evaluation Committee on trastuzumab trials that involves the presence of one or more of the following for a definitive diagnosis of CIC: 1. An overall decrease in the LVEF either affecting the entire myocardium or the severe in the septal region, 2. Presence of any clinical CHF features, 3. Signs of CHF such as an S3 or tachycardia, or 4. A reduction of 5% from baseline to an overall LVEF of less than 55% in symptomatic patients or a reduction of 10% from baseline to an overall LVEF of 55% in asymptomatic patients (Carter & Clarke, 2015; Higgins et al., 2015). The second commonly used reference adapted from the American Society of Echocardiography and the European Association of Cardiovascular Imaging defines cancer related cardiac dysfunction as a reduction in LVEF of > 10% to a value of <53% (Plana et al., 2014; Virani et al., 2016). It is important to note that these definitions are often used during active chemotherapy. For long-term CIC there is no concrete definition and literature guides clinicians to heart failure guidelines for diagnosis (these will be discussed later) (Virani et al., 2016).

MUGA Scan (Mult-acquisition Gated Scintigraphy)- MUGA scans have been widely used in practice to detect LVEF. They reveal precise and reproducible measurements of LVEF however they expose the patient to radiation. MUGA scans do not provide information on heart

structures or inflammatory conditions which are alternative common complications of cancer treatments (Curigliano et al., 2016; Groarke et al., 2012).

Echocardiography -Echocardiography utilizes ultrasound technology to analyze structures of the heart muscle. It has emerged in the literature as the preferred method of surveillance because it is widely available, inexpensive, and does not expose the patient to any radiation (Groarke et al., 2012; Nolan et al., 2014). There are two types of echocardiograms that are used, 2- dimensional (2D) or three-dimensional (3D).

Often, the diagnosis of cardiotoxicity relies on early detection thus subtle differences in LVEF must be detected. 2D echocardiograms have been widely used, however, for a reliable difference to be detected there must be a greater than 10% difference from the previous image. Furthermore, 2D quality for patients who are obese or those who suffer from musculoskeletal deformities may be impaired (Nolan et al, 2014). In the long-term setting, guidelines recommend echocardiography as the gold standard for imaging (BC Guideline, 2015).

3D echocardiograms have become the preferred form to detect cardiotoxicity during active chemotherapy treatment (Plana et al., 2014). It has the ability to measure the actual volume of ejection fraction as oppose to estimated measurements (as in 2D). Additionally, the results are more reproducible between different technicians that are conducting the scans. Furthermore, literature reveals a strong correlation between 3D echocardiogram results and cardiac MRI measurements (Plana et al.)

Strain Imaging (global longitudinal strain imaging)- Strain imaging is a novel imaging technique that measures the strain on the myocardium which can be used to detect differences in active cancer treatment, it has not been explored in long-term survivors (Thavendiranathan, Poulin, Lim, Plana, Woo, 2014). It does this through a speckle tracking technique by measuring

global longitudinal strain (GLS) on the myocardium. Changes in strain (subtle abnormalities) to the wall of the myocardium are seen earlier then changes with LVEF (Plana et al., 2014). A systematic review by Thavendiranathan et al. discovered that there was a greater than 10-15% reduction in GLS as quickly as 3 cycles into the scheduled chemotherapy treatment, and these same patients went on to display significant impairments in their LVEF post therapy (2014). Using this form of imaging, it has been found that a difference of measurement from baseline greater than 15% symbolizes an abnormal result (Virani et al., 2016). This imaging technique is quite new however proves to offer promising potential in even earlier detection of CIC in acute patients.

Cardiac MRI (CMR)- CMR is the gold standard for the measurement of myocardial masses and volumes. Of note, echocardiography is the gold standard for imaging modality in diagnosis of heart failure (BC Guidelines, 2015). MRI has the best image quality and can detect subtle differences in myocardial volumes with excellent spatial resolution (Toro-Salazer, Gillan, et al., 2013). These subtle differences in myocardial volumes make this imaging modality ideal for active cancer treatment screening because early detection is key (Carter & Clark, 2015). However, cost and limited access emerge as frequent barriers to obtaining this form of imaging (Nolan et al., 2014).

Biomarkers -Biomarkers such as troponin and natriuretic peptides have been studied extensively in the detection of cardiotoxicity. Elevation of biomarkers during acute treatment or shortly after have been correlated with development of late-onset CIC (Plana et al., 2014).

Troponins are released when acute damage is done to the myocardium as early as 2-3 hours post injury. Cardinale et al. have conducted two studies exploring the role of troponins in cancer therapy. The first study in 2000 involved 204 patients, which measured release of

troponin after each dose of chemotherapy. 65 participants experienced a raise in troponin whereas 139 did not. In the troponin positive group there was a marked reduction in LVEF, which persisted at the end of the study, this was not evident in the troponin negative group (Cardinale et al., 2000). Next, the same group of researchers followed 703 cancer patients and obtained troponin levels: One immediately after chemotherapy and then one month later. Results revealed that participants whose troponin were <0.08ng/mL had a 1% cumulative rate of cardiac events. Whereas, participants whose troponin were >0.08ng/mL had an 84% rate of cardiac events. Another trial with 81 participants that suffered from HER2+ breast cancer found that a 25% of the participants developed cardiomyopathy but levels of troponin drawn during active treatment were unable to confirm this (Sawaya et al., 2011). Therefore, although some studies do show correlation between acute raise of troponin and later onset of CIC, critics have challenged the ideal timing of these biomarkers thus further research is needed (Ky & Craver, 2011).

Serum levels of natriuretic peptides include brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP). It is important to note that there is a substantial difference in calculation of the two measurements therefore they cannot be interchanged. Elevation in these measurements are seen with impairment to filling pressures in the myocardium. The use of these values in a predictive nature in the context of CIC remains conflicting and inconclusive (Plana et al., 2014; Virani et al., 2016). Alternatively, Carver et al. reveal that a major strength for the use of BNP can be in a non-existent capacity, in that when a patient does not have a rise in BNP during post therapy screening despite questionable symptoms then it can be confidently concluded that the symptoms are a result of a non-cardiac origin (2013; BC Guideline, 2015).

Overall Recommendation-Screening - The Canadian Cardiovascular Society recently published a guideline for the evaluation and management of cardiovascular complications during

cancer therapy (Virani et al., 2016). Within this guideline, there are three major recommendations with regard to detection of cardiotoxicity, two with regard to acute treatment detection and one that is applicable in the long-term setting. It is recommended that regardless of the imaging modality, the patient should have their LVEF assessed before, during, and after completion of therapy (Virani et al.). This is particularly important because when PCPs reimage patients post therapy they must be able to directly compare images in order to determine if overall LVEF abnormalities are present. Different modalities are not interchangeable therefore cannot be compared even though they all measuring LVEF (Bellenger et al., 2000). Additionally, their recommendation is the use of 3D echocardiography when feasible (Virani et al., 2016). In an acute detection capacity, the guideline suggests the use of GLS and biomarkers to monitor for early cardiotoxic effects (Virani et al., 2016).

What Frequency Should Surveillance Be Performed?

After a PCP picks an appropriate method of surveillance, they then must determine the frequency at which surveillance must be performed. Again, Canada does not have distinct guidelines that can be generalized to all at risk individuals, instead, we must look at the population being cared for.

Pediatric Population- In British Columbia (BC) overall recommendations from the COG are followed with respect to frequency of screening in the pediatric population. As discussed above, a younger age of onset and cumulative dose of anthracyclines serve as substantial risk factors within this population. Therefore, the COG has set out guidelines which breakdown the frequency of screening according to age at which treatment was given and dose of anthracycline therapy. Refer to appendix A for a breakdown of these guidelines (COG, 2013). Frequency of surveillance should be started no later than 2 years after treatment completion and

should be continued life long (Armenian et al., 2015; COG, 2013). Once surveillance frequency is determined, it is essential for the PCP to have a method in place to ensure accurate follow-up and screening is completed on an ongoing basis. There are several cancer treatment tools available online (ie: BC Children's Hospital Oncology website) to aid PCPs in the documentation of cancer therapies and complications of patients while undergoing treatment. PCPs can download these forms, complete the information and include them in the patients chart for quick reference.

Adult Population- Of the two groups of agents that cause cardiotoxicity: anthracycline and trastuzumab, different principles guide each path for long-term follow-up. Trastuzumab has no long-term cardiac complications as its effects are reversed once the medication is stopped therefore if there are no complications during treatment and shortly after, no further long-term follow-up is needed (Higgins et al., 2015).

On the other hand, anthracycline therapy posse's long-term effects that are irreversible due to the death of myocardial cells. Anthracyclines along with radiation therapy put these patients at risk for long-term complications qualifying them for long-term surveillance (Herrmann et al., 2014). In 2013, the European Association of Cardiovascular Imaging and the American Society of Echocardiography published recommendations for surveillance frequency related to radiation. It is recommended that a screening echocardiogram be completed 5 years post radiation treatment in asymptotic patients that are at high risk and 10 years in all other patients; after initial screening re-assessment with an echocardiogram should be completed every 5 years (Lancellotti et al., 2013; Herrmann et al.). If a patient had radiation as part of their treatment regime then the above guidelines can be followed, unfortunately, there are no such consensus guidelines for anthracycline only therapy. However, a recent article by Carter and

Clarke in the Canadian Journal of Cardiology does state that it is "reasonable to reassess LVEF 6 months after completion of therapy, annually for 2-3 years, and then every 3-5 years for life" (2015, p.1491). This recommendation was for detection of anthracycline-induced cardiomyopathy that presents as late onset.

The BC guidelines on chronic heart failure (CHF) discourage routine screening of asymptomatic patients but do state that the choice to screen high-risk patients should be considered on an individual basis (BC Guidelines, 2015). Therefore, it would be prudent for PCPs to identify low to high-risk patients and continue to monitor them yearly on a clinical basis and if abnormalities arise then echocardiograph evaluation would be warranted. Once symptoms arise PCPs must follow the CHF guideline on screening (Herrmann et al., 2014; Virani et al., 2016).

What Assessments and Education Should the PCP Routinely Provide?

Assessments- Once active chemotherapy treatments are complete, PCPs become the primary point of contact for many patients once again. Along with education, it is crucial for the PCP to perform annual assessments on asymptomatic cancer survivors that include: medical history and physical examination (BC Guidelines, 2015; CCS, 2014; COG, 2013). When conducting a medical history the PCP must inquire about prudent comorbidities or potential risk factors that can attribute to the development of cardiomyopathy such as hypertension, sleep apnea, diabetes, atrial fibrillation, coronary heart disease, thyroid dysfunction, chronic obstructive pulmonary disease, anemia, chronic kidney disease, alcohol use and smoking (BC Guideline; CCS). It is also essential to inquire about past or current symptoms of heart failure such as fatigue, breathlessness, swelling in the lower extremities, nocturnal dyspnea, confusion, orthopnea, swelling around the abdomen, reduced appetite, or decreased exercise capacity (BC

Guideline, CCS). The physical examination consists of assessment for signs of fluid overload, decreased cardiac output, and functional limitation. Signs of fluid overload include weight gain (2 kilograms over two days or 2.5 kilograms over one week), peripheral edema, extra heart sounds (S3/S4), elevated jugular venous pressure, pulmonary crackles, reduced oxygen saturation, or ascites (BC Guideline, CCS). Features that signify decreased cardiac output include pallor or cyanosis particularly around the lips or nail beds, elevated heart rate, or decreased blood pressure (BC Guideline, CCS).

Once both of these assessments are completed, findings can then be used to determine the patients overall functional assessment based on the New York Heart Associations (NYHA) functional classifications. Class 1 indicates that the patient does not have any symptoms with ordinary physical activity and no overt restrictions. Class 2 indicates that symptoms are present with ordinary activity resulting in minor modifications in overall activity. Class 3 indicates that minor activity creates symptoms and overall limitations are present. Class 4 indicates that there are symptoms present at rest and the patient is unable to do activity (BC Guideline, 2015; CCS, 2014). Herrmann et al. (2014) explain that LV dysfunction initially occurs are a result of stress on the myocardium despite an identifiable injury therefore patients who have been treated with cardiotoxic treatments can be classified as Class 1 or asymptomatic however this is not stated in the BC Guidelines for CHF.

If there are no abnormalities or concerning findings during the medical history or physical examination then re-evaluation should be completed annually (COG, 2013, Lancellotti et al., 2013). However, if abnormalities or concerns arise then PCPs can proceed with standard cardiomyopathy/CHF investigations such as imaging (echocardiogram- considered the gold

standard), laboratory values (BNP, kidney function, TSH, CBC), and 12-lead ECG (to look for any arrhythmias, evidence of myocardial infarction, or hypertrophy) (BC Guideline, 2015).

Physical Activity- Exercise should be promoted in all patients before, during and after cancer treatment (Armenian et al., 2015; Johnson, Davis, Law & Sulpher, 2016; Lipshultz et al., 2013; Virani et al., 2016). Physical inactivity is a major contributor of overall cardiovascular (CV) disease and one of the most common modifiable risk factors. Children aged 6-17 should engage in a minimum of 60 minutes of physical activity daily whereas adults (greater than 18) should engage in a minimum of 150 minutes of moderate-intensity physically activity per week (Center for Disease Control and Prevention, 2011). It has been found that engaging in 150 minutes of activity can decrease CV mortality by 14% and 300 minutes can decrease CV morality by 20% if engaged weekly (Johnson et al., 2016). Literature relating heart failure to exercise indicates that patients who engage in the highest category of exercise (greater than 2000 MET/week) had the largest reduction in heart failure risk by up to 36.4% (Pandey et al., 2015). This dose-dependent relationship between heart failure and physical activity serves as the basis for encouraging patients at risk for CIC to engage in ongoing exercise. Of note, PCPs must educate patients who have impaired EFs to refrain from excessive weight training or activities such as wrestling because these activities can result in an increased strain on the heart potentially increasing overall damage (COG, 2013).

Smoking Cessation- Smoking has many adverse side effects including the development of atherosclerotic plaque accumulation creating blockages and increased strain on the heart leading to potential or further deterioration of LVEF (Johnson et al., 2016). There is an overall 2 to 3 times increase in death from a CV or cancer cause in smokers than non-smokers (Johnson et

al.). Therefore, it is crucial for PCPs to identify patients who continue to smoke and strongly advocate for smoking cessation. Resources such as Quitnow can be used by PCPs.

Weight Loss/Obesity- In Canada, it estimated that roughly 1 in 7 children and 1 in 4 adults are obese (Bancej et al., 2015). An obese state creates an increased overall blood volume and cardiac output due to the high metabolic activity of excessive fat (Aplert, 2011). This excess volume for prolonged periods can lead to ventricular dilation and wall stress leading to worsening cardiomyopathy. The incidence of overweight and obese adults is increasing dramatically Canada-wide and is positively correlated with CV disease, diabetes, hypertension and chronic illnesses such as cancer (BC Guideline, 2011; Johnson et al., 2016).

According to the World Health Organization, overweight is classified as a body mass index (BMI) of greater than 25 kg/m^2 whereas obese is classified as a BMI greater than 30 kg/m^2 (WHO, 2003). It is estimated that every $1kg/m^2$ of additional weight, the risk of acquiring cancer increases by 21% (Johnson et al., 2016). Therefore, prompt identification and subsequent counseling regarding healthy weight maintenance must be initiated by the PCP among obese patients. This counseling can include a 500-1000kcal/day deficit in diet pattern, regular physical exercise, weight loss goal of 5-10% of original weight and regular monthly follow-up (BC Guideline, 2011). If the patient falls into the obese class 2 or 3 (greater than a BMI of 35 kg/m^2) category then pharmacological management with the use of Xenical or surgical intervention may be considered to reduce the chance for additional comorbidity development (BC Guideline, 2011). For patients who are not obese, it is still essential to counsel them to maintain healthy weight in order to avoid adverse effects associated with an elevated BMI.

Diet- In a meta-analysis of 16 studies Wang et al. found that all cause mortality was the lowest in the group that consumed the highest amount of fruits and vegetables (2014). This was

determined to be 5 servings of fruits and vegetables, and there was no additional benefit in mortality data if additional servings were consumed (Wang et al.). In western civilizations, diets consist of high levels of carbohydrates, red meat, and saturated fat contributing to increased CV risk (Johnson et al., 2016). Numerous studies have been conducted on various diets and the Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean diet are associated with the best overall reduction in CV outcomes and incidence of cancer (Johnson et al.). These diets consist of unsaturated fat, high quantities of fruits and vegetables and whole grains. At risk patients should also be counseled to restrict overall sodium consumption in the diet to less than 2000 milligrams daily and alcohol consumption to one drink per day (BC Guidelines, 2015). Furthermore, if a patient has symptoms of fluid overload then the PCP should begin education regarding the restriction of fluids to 1.5-2 liters per day (BC Guidelines, 2015).

Cardiomyopathy Detected: Plan of Care for the PCP

Patients who experience cardiotoxic complications such as cardiomyopathy post treatment (either symptomatic or asymptomatic decline in LVEF) must be treated according to widely established evidence based heart failure guidelines (Carter & Clark, 2015; Herrmann et al., 2014; Higgins et al., 2015; Lenneman & Sawyer, 2016; Virani et al., 2016).

Treatment- Treatment of heart failure (HF) consists of clinical systems and classification of LVEF into two categories: HF with preserved EF greater than 40% (HF-pEF) or HF with reduced EF < 40% (HF-rEF). Once an identified abnormality is discovered, it is crucial to consider alternative possible differential diagnoses that could contribute to the findings prior to concluding that the abnormality is related to chemotherapeutic treatment (Carter & Clark, 2015). These diagnoses may stem from either a cardiac or non-cardiac origin such as ischemia, inflammation, infection, alcohol, drugs, nutritional deficiencies, or inherited disorders (Carter &

Clark). Once all other causes are ruled out and CIC is the sole contributor of dysfunction, the PCP must then determine the types of chemotherapeutic agents used, doses, timing of treatments, preventative measures or surveillance during treatment (if any) (Carter & Clark).

For patients who have HF-rEF, CCS guidelines advise the clinician to initiate triple therapy with the use of a beta-blocker (BB), angiotensin-converting enzyme inhibitor (ACEi) and mineralocorticoid receptor antagonists (MRA) (CCS, 2014). According to the conventional algorithm, medications should be up titrated to maximal tolerated doses by patients within 6 months of initiation to achieve maximal benefit (CCS, 2014; Howlett et al., 2016). Consensus among experts reveals that patients with HF-rEF will remain on indefinite treatment, however, in the context of CIC patients who EFs have recovered this may be individualized on a case basis particularly if it occurred during acute treatment as opposed to late onset (Howlett et al., 2016). The use of triple therapy is widely studied in the heart failure population but there is limited data from CIC populations because classically this population have been excluded from randomized clinical trials used to obtain efficacy data for HF therapies (Curigliano et al., 2016). However, several small trials have been conducted showing promising results. In a study by Cardinale et al. consisting of 201 participants who developed anthracycline related cardiomyopathy were started on enalapril (ACEi) with the addition of carvedilol (BB) (if possible) upon identification of impaired LVEF (2010). EF was measured routinely for an average of 36 months and it was found that benefit from therapy depended on time to treatment for the recovery of LVEF. When treatment was started in the time frame of 2 months following therapy, 64% of participants LVEF had fully recovered, however, 6 months after completion of treatment resulted in no LVEF recovery (Cardinale et al.).

For people with HF-rEF, there are no routine therapies that have been proven to show mortality benefit, therefore, symptomatic treatment and control of other comorbidities with the use of diuretics, MRAs, BBs, or ACEi is indicated (BC Guidelines, 2015; CCS, 2014). However, Carter and Clark acknowledge that in patients who have potential anthracycline induced cardiomyopathy with an LVEF of 40-50%, an ACEi and BB should be considered due to the benefits from small trial data as a result of prompt initiation (2015). Virani et al. reveal that this combination of treatment may be considered in patients who have asymptomatic declines during cancer therapy as well (2016). Furthermore, PCPs must ensure that they optimally treat blood pressure according to the Canadian Hypertension Education Program (CHEP) guidelines to a target of less than 140/90 mmHg for all patients excluding patients with diabetes for whom a target of 130/80 mmHg must be attained (BC Guideline, 2015; Virani et al., 2016).

Consultation- If all other causes of cardiomyopathy are ruled out and cancer treatment is related to either symptomatic or asymptomatic LVEF decline, it would be warranted to send the patient to a cardio-oncology clinic for evaluation (Carter & Clark, 2015). The mandate of these clinics is to cultivate evidence-based recommendations for detection, prevention and treatment of cardiotoxicity in cancer patients in attempts to decrease overall mortality (Carter & Clark). A cardio-oncology clinic exists at Vancouver General Hospital which services the lower mainland. If the diagnosis of CIC is not well established (ie: other potential causes such as ischemia have not been ruled out) then a cardiology consult may be warranted. Furthermore, newly diagnosed HF patients can be referred to HF clinics. These clinics will see all newly diagnosed patients with NYHA I classification within 6-12 weeks and NYHA II-IV on a more urgent basis given individualized cases (Howlett et al., 2016).

Primary prevention strategies- In an effort to decrease cardiotoxic complications that arise with cancer treatment researchers have started to investigate potential primary prevention strategies that could be used to decrease the incidence of CV complications such as cardiomyopathy (Curigliano et al., 2016; Davis & Virani, 2016; Herrmann et al., 2014; Madonna et al., 2015; Virani et al., 2016). Clinical trials have found no significant benefits from a cardio-protective standpoint with use of probucol, vitamin E, and N-acetyl cysteine (Madonna et al.). However, promising cardio-protective effects have been seen with several small and moderate size clinical trials with the use of statins, dexrazoxane , beta-blockers (BB), and angiotensin-converting enzyme inhibitors (ACEi) (Madonna et al.).

Statins - There is promising research being conducted regarding cardio-protective effects of statin use and CIC. In a study of 40 patients undergoing chemotherapy, patients were randomized to a statin group that was treated with 40mg of atorvastatin daily and a placebo group (Acar et al., 2011). Each group received chemotherapy one time per month for 6 months duration. All patients had their LVEF measured through the use of echocardiography at baseline and 6 months into therapy. Aside from showing an expected overall decrease in cholesterol levels, it was also found that the placebo group had an overall decrease in LVEF (62.9% +/- 7.0 vs. 55.0% +/- 9.5%) when compared to the statin group. This result revealed that statins might have potential to exert cardioprotective effects from an antioxidative and inflammatory standpoint (Acar et al.). Furthermore, another observational study of 628 women with breast cancer who underwent anthracycline chemotherapy researched the effects of continuous uninterrupted statin therapy vs. no statin therapy (Seicean, Plana, Budd, & Marwick, 2012). It was found that the group with continuous statin use had an overall decreased incidence of heart failure (Seicean et al.).

Dexrazoxane- Dexrazoxane (DRZ) is an iron chelator that prevents formation of anthracycline-iron complexes that contribute to oxidative stress (Madonna et al., 2015). It has been approved for use in metastatic breast cancer patients who have received a doxorubicin dose of greater than 300mg/m^2 (Higgins et al., 2015). Mixed results from studies have contributed to the lack of widespread use of this agent (Ky & Carver, 2011).

Angiotensin-Converting-Enzyme Inhibitors (ACEi) -The effects of enalapril (ACEi) were explored in a randomized control trial consisting of 473 patients who were treated with high-dose anthracycline therapy (Cardinale et al., 2006). 114 patients had a rise in troponin levels and were subsequently randomized to treatment with enalapril or not. The medication was started approximately one month after completion of therapy and sustained for one year. It was found at the one-year follow-up that the treatment group had a substantially lower occurrence of cardiac events 2% and no change to LVEF whereas patients in the non-treatment group had an 52% occurrence of cardiac events and decline in LVEF (Cardinale et al.; Curigliano et al., 2016).

Beta-Adrenergic Blockers (BB)-The OVERCOME trial looked at 90 patients with acute leukemia who had treatment with anthracyclines. It attempted to determine if there could be the prevention of LV dysfunction by using enalapril (ACE-i) and carvedilol (BB). The overall results reveal that the intervention group had a lower rate of cardiomyopathy and death (6.7% vs. 22%) indicating that this combination therapy has the ability to prevent changes in LV dysfunction (Bosch et al., 2013). Since then there have been more trials that are underway to determine the large-scale generalizability of such interventions. The MANTICORE (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial is being conducted in HER2+ cancer participants to determine the effectiveness of bisoprolol versus perindopril (Curigliano et al., 2016). Furthermore, the PRADA (Prevention of Cardiac Dysfunction During

Adjuvant Breast Cancer Therapy) trial is looking at the use of metoprolol, candesartan or combination and its impact on patients receiving anthracycline and trastuzumab therapy. This study showed that the use of candesartan is protective in early decline (Curigliano et al.). Although these are preliminary findings, it is hopeful that results of these studies will provide direction regarding primary prevention strategies for cancer patients but for now Davis and Virani discourage the use of these medications as a routine primary prevention strategy in all patients receiving cardiotoxic treatments (2016). This is based on the premise that routine use of medications may subject patients to alternative side effects of the medications in the context of no defined benefit (Virani et al., 2016).

Conclusion

As medical advancements improve the efficacy of cancer treatments, patients have outlived acute complications and lead longer lives (Higgins et al., 2015). A gap in knowledge regarding long-term cardiotoxic effects exists among PCPs due to the complexity associated with post-oncology management (Nekhlyudov et al., 2014). Initial presentation of CIC typically occurs in an asymptomatic manner with LVEF decline seen once a substantial amount of damage to the myocardium has occurred resulting in end-staged HF symptoms in up to 4% of survivors (Lenneman & Sawyer, 2016). Guidelines, research studies and clinical trials were reviewed in an effort to provide novice PCPs with knowledge to identify at-risk patients, employ effective screening, promptly engage in treatment according to CCS's HF guidelines or refer to a specialist (Armenian et al., 2015; Curigliano et al., 2016; Madonna et al., 2015; Moudgil & Yeh, 2016); Virani et al., 2016). The information was then created into a poster (refer to appendix B) and presented at the BCNPA's annual conference. It is anticipation that with in-depth knowledge

of CIC, PCPs will be better equipped to cease negative outcomes and promote continued longevity among cancer survivors.

References

Acar, Z., Kale, A., Turgut, M., Demircan, S., Durna, K., Demir, S., & Agac, M. (2011). Efficiency of Atorvastatin in the protection of anthracycline-induced cardiomyopathy. *Journal of the American College of Cardiology,* 58(9), 988-989. doi: 10.1016/j.jacc.2011.05.025.

Armenian, S., Hudson, M., Mulder, R., Chen, M., Constine, L., Dwyer, M., . . . Kremer, L. (2015). Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: A report form the international late effects of children cancer guideline harmonization group. *The Lancet Oncology,* 116(3), 123-136. doi: 10.1016/S1470-2045(14)70409-7

Bancej, C., Jayabalasingham., Wall, R., Rao, D., Do, T., Groh, M., & Jayaraman. (2015). Trends and projections of obesity among Canadians. *Health Promotion Chronic Disease Prevention Canada,* 35, 109-112. Retrieved on March 1, 2017 from http://www.phac-aspc.gc.ca/publicat/hpcdp-pspmc/35-7/assets/pdf/ar-02-eng.pdf

Bellinger, A. M., Arteaga, C. L., Force, T., Humphreys, B. D., Demetri, G. D., Druker, B. J., & Moslehi, J. J. (2015). Cardio-oncology: How new targeted cancer therapies and precision medicine can inform cardiovascular discovery. *Circulation, 132*(23), 2248-2258. doi:10.1161/CIRCULATIONAHA.115.010484

Bosch, X., Rovira, M., Sitges, M., Domenech, A., Ortiz-Perez, J., Caralt, T., . . Esteve, J. (2013). Enalapril and Carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies. *Journal of the American College of Cardiology,* 61(23), 2355-2362. doi: http://dx.doi.org/10.1016/j.jacc.2013.02.072

British Columbia Guideline. (2011). *Obesity.* Retrieved on March 1, 2017 from http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/obesity.pdf

British Columbia Guidelines. (2015). *Chronic Heart Failure*. Retrieved on March 1, 2017 from http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/heart-failure-chronic

British Columbia Nurse Practitioner Association (BCNPA). (2015). *NP's in BC.* Retrieved from https://bcnpa.org/npsinbc/

Canadian Cardiovascular Society (2014). *Heart Failure Compendium*. Retrieved on March 1, 2017 from https://www.ccs.ca/index.php/en/resources/heart-failure-compendium

Canadian Cancer Society (2016). *Canadian Cancer Statistics 2016.* Retrieved from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%2001/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2016-EN.pdf?la=en

Cardinale, D., Bacchiani, M., Colombo, A., Beggiato, M., & Cipolla, C. (2013). Strategies to prevent and treat cardiovascular risk in cancer patients. *Seminal Oncology,* 40, 186-98. doi: http://dx.doi.org/10.1053/j.seminoncol.2013.01.008

Cardinale, D., Colombo, A., Lamanti, G., Colombo, N., Civelli, M., Giacomi, G., . . . Cipolla, C. (2010). Anthracycline-Induced Cardiomyopathy. *Journal of the American Journal of Cardiology,* 55(3), 213-220. doi: 10.1016/j.jacc.2009.03.095

Cardinale, D., Colombo, A., Sandri, M., Lamantia, G., Colombo, N., Civelli, M., . . . Cipolla, C. (2006). Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation-AHA,* 114(23). doi: https://doi.org/10.1161/CIRCULATIONAHA.106.635144

Cardinale, D., Sandri, M., Martinoni, A., Tricca, A., Civelli, M., Lamantia, G., . . . Fiorentini, C. (2000). Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. Journal of American College of Cardiology, 36(2), 517-522. doi: 10.1016/S0735-1097(00)

Cardinale, D., Sandri, N., Colombo, A., Boeri, M., Lamantia, G., Civelli, M., . . . Cipolla, C. (2004). Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Journal of American College of Cardiology,* 109(22). doi: https://doi.org/10.1161/01.CIR.0000130926.51766.CC

Carter, L., & Clarke, B. (2015). A practical approach to the oncology patient with heart failure. *Canadian Journal of Cardiology,* 31(12), 1489-1492. doi: http://dx.doi.org/10.1016/j.cjca.2015.05.002

Carver, J., Szalda, D., & Ky, B. (2013). Asymptomatic cardiac toxicity in long-term cancer survivors: Recommendations for surveillance. *Seminars in Oncology,* 40(2), 229-238. doi: 10.1053/j.seminoncol.2013.01.005.

Centers for Disease Control and Prevention (CDC). (2011). How much physical activity do children need? *Centers for Disease Control and Prevention* [online], http://www.cdc.gov/physicalactivity/everyone/ guidelines/children.html

Children's Oncology Group (COG). (2013). Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Retrieved on March 1, 2017 from

College of Family Physicians of Canada. (2016). *What Is Family Medicine?* Retrieved from http://www.cfpc.ca/faq/

Cooper, J., Loeb, S., & Smith, C. (2010). The primary care nurse practitioner and cancer survivorship care. *Journal of the American Association of Nurse Practitioners,*

22(8), 394-402. doi: 10.1111/j.1745-7599.2010.00528.x

Cronin, P., Ryan, F. & Coughlin, M. (2008). Undertaking a literature review: a step-by-step approach. *British Journal of Nursing, 17*(1), 38-43. Retrieved from http://www.cin.ufpe.br/~in1002/leituras/2008-undertaking-a-literature-review-a-step-by-step-approach.pdf

Cross, M., Berridge, B., Clements, P., Cove-Smith, L., Force, T., Hoffmann, P., . . . Park, B. (2014). Physiological, pharmacological and toxicological considerations of drug-induced structural cardiac injury. *British Journal of Pharmacology,* 172, 957-974. doi: 10.1111/bph.12979

Curigliano, G., Cardinale, D., Dent, S., Criscitiello, C., Aseyev, O., Lenihan, D., & Cipolla, C. (2016). Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. *CA: A Cancer Journal for Clinicians,* 66(4), 309-325. doi: 10.3322/caac.21341

Dahabreh, I., Linardou, H., Siannis, F., Fountzilas, G., & Murray, S. (2008). Trastuzumab in the adjuvant treatment of early-stage breast cancer: A systematic review and meta-analysis of randomized controlled trials. *Oncologist,* 13(6), 620-30. doi: 10.1634/theoncologist.2008-0001

Davis, M., & Virani, S. (2015). Routine prophylactic cardioprotective therapy should not be given to all recipients of potentially cardiotoxic cancer chemotherapy. *Canadian Journal of Cardiology,* 32(7), 926-930. doi: http://dx.doi.org/10.1016/j.cjca.2016.02.061

Drafts, B., Twomley, K., D'Agostino, R., Lawrence, J., Avis, N., Thohan, J., . . . Hundley, W. (2013). Low to moderate dose anthracycline-based chemotherapy is associated with non-invasive imaging evidence of subclinical cardiovascular disease. *JACC. Cardiovascular Imaging,* 6(8), 877-885. doi:

10.1016/j.jcmg.2012.11.017

Ewer, M., Vooletich, M., Durrand, J., Woods, M., Davis, J., Valero, V., & Lenihan, D. (2005). Reversibility of Trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment. *Journal of Clinical Oncology,* 22(31), 7820-7826. doi: 10.1200/JCO.2005.13.300

Ghosh, A., & Walker, M. (2017). Cardio-oncology. *British Journal of Hospital Medicine,* 78(1), 11-13. doi: 10.12968/hmed.2017.78.1.C11

Groarke, J., Tong, D., Khambhati, J., Cheng, S., & Moslehi, J. (2012). Breast cancer therapies and cardiomyopathy. *Medical Clinics of North America, 96*(5), 1001-1019. doi:10.1016/j.mcna.2012.07.008

Grunfeld, E., & Earle, C. (2010). The interface between primary and oncology speciality care: Treatment through survivorship. *Journal of the National Cancer Institute,* 40, 25-30. doi: 10.1093/jncimonographs/lgq002

Heart and Stroke Foundation. (2017). *Cardiomyopathy.* Retrieved on March 1, 2017 from http://www.heartandstroke.ca/heart/conditions/cardiomyopathy

Henson, K., Reulen, R., Winter, D., Bright, C., Fidler, M., Frobisher, C., . . . Hawkins, D. (2016). Cardiac mortality among 200,000 five-year survivors of cancer diagnosed aged 15-39 years: The teenage and young adult cancer survivor study. *Circulation -AHA,* 135(18), 1521-1533. doi: https://doi.org/10.1161/CIRCULATIONAHA.116.022514

Herrmann, J., Lerman, A., Sandhu, N. P., Villarraga, H. R., Mulvagh, S. L., & Kohli, M. (2014). Evaluation and management of patients with heart disease and cancer: Cardio-oncology. *Mayo Clinic Proceedings, 89*(9), 1287-1306. doi:10.1016/j.mayocp.2014.05.013

Hewitt, M., Greenfield, S., Stovall. (2006). From Cancer Patient to Cancer Survivor- Lost in Transition. Washington, DC: The National Academies Press. doi:https://doi.org/10.17226/11468.

Higgins, A., O'Halloran, T., & Chang, J. (2015). Chemotherapy-induced cardiomyopathy. *Heart Failure Review,* 20 (1), 721-730. doi: 10.1007/s10741-015-9502-y

Hoekstra, R., Heins, M., Korevaar, J. (2014). Health care needs of cancer survivors in general practice: A systematic review. *BMC Family Practice,* 15(94), 1-6. doi: 10.1186/1471-2296-15-94

Howlett, J., Chan, M., Ezekowitz, J., Harkness, K., Heckman, G., Kouz, S., . . .Zieroth, S. (2016). The Canadian cardiovascular society heart failure companion: Bridging guidelines to your practice. *Canadian Journal of Cardiology,* 32(3), 296-310. doi: 10.1016/j.cjca.2015.06.019.

Johnson, C., Davis, M., Law, A., & Sulpher, J. (2016). Shared risk factors for cardiovascular disease and implications for preventive health and clinical oncology patients. *Canadian Journal of Cardiology,* 32, 900-907. doi: http://dx.doi.org/10.1016/j.cjca.2016.04.008

Ky B., & Carver J. R. (2011). Biomarker approach to the detection and cardioprotective strategies during anthracycline chemotherapy. Heart Fail. Clin. 7, 323–33110.1016/j.hfc.2011.03.002

Lancellotti, P., Nkomo, N., Badano, P., Bergler-Klein, J., Bogaert, J., Davin, L., . . . Yang, P. (2013). Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the

European Association of Cardiovascular Imaging and the American Society of Echocardiography. *European Heart Journal of Cardiovascular Imaging,*14, 721-40. doi: https://doi.org/10.1093/ehjci/jet123

Lenneman, C., & Sawyer, D. (2016). Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. *Circulation Research,* 118, 1008–1020. doi: 10.1161/CIRCRESAHA.115.303633

Lipshultz, S., Cochran, T., Franco, V., & Miller, L. (2013). Treatment-related cardiotoxicity in survivors of childhood cancer. *Clinical Oncology,* 10, 697-710. doi:10.1038/nrclinonc.2013.195

Madonna, R., Cadeddu, C., Deidda, M., Mele, D., Monte, I., Novo, G., . . . Mercuro, G. (2015). Improving the preclinical models for the study of chemotherapy-induced cardiomyopathy: A position paper of the Italian working group on drug cardiotoxicity and cardioprotection. *Heart Failure Rev,* 20(5), 621-631. doi: 10.1007/s10741-015-9497-4

Moudgil, R., & Yeh, E. (2016). Mechanisms of cardiotoxicity of cancer chemotherapeutic agents: Cardiomyopathy and beyond. *Canadian Journal of Cardiology,* 32(7), 8630870. doi: 10.1016/j.cjca.2016.01.027

Mulrooney, D., Armstrong, G., Huang, S., Ness, K., Ehrhardt, M., Joshi, V., . . . Hudson, M. (2016). Cardiac outcomes in adult survivors of childhood cancer exposed to cardiotoxic therapy: A cross-sectional study. *Annals of Internal Medicine,* 164(2), 93-101. doi: 10.7326/M15-0424

Nekhlyudov, L., Aziz, N., Lerro, C., & Virgo, K. (2014). Oncologists' and primary care physicians awareness of late and long-term effects of chemotherapy: implications for care of the growing population of survivors. *Journal of Oncology Practice,*

10(2), 29-36. doi: 10.1200/JOP.2013.001121

Nolan, M., Lowenthal, R., Venn, A., & Marwick, T. (2014). Chemotherapy-related cardiomyopathy: a neglected aspect of cancer survivorship. *Internal Medicine Journal,* 44(1), 939-950. Doi: 10.1111/imj.12532

Oeffinger, K., Mertens, A., Sklar, C., Kawashisma, T., Hudson, M., Meadows, A., . . . Robison, L. (2006). Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine,* 355(15), 1572-82. doi: 10.1056/NEJMsa060185

Pandey, A., Garg, S., Khunger, M., Darden., D., Ayers, C., Kumbhani, D., . . . Berry, J. (2015). Dose–Response Relationship Between Physical Activity and Risk of Heart Failure. *Circulation-AHA,* 132, 1786-1794. doi: 10.1161/CIRCULATIONAHA.115.015853

Patnaik, J., Byers, T., DiGuiseppi, C., Dabelea, D., & Denberg, T. (2011). Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: A retrospective cohort study. *Breast Cancer Research,* 13(3), 1-9. doi: 10.1186/bcr2901

Plana, J., Galderisi, M., Barac, A., Ewer, M., Ky, B., Scherrer-Crosbie, . . . Lancellotti, P. (2014). Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: A report from the American Society of Echocardiography and the European Association of cardiovascular imagine. *European Heart Journal,* 15, 1063-1093. doi: doi:10.1093/ehjci/jeu192

Raj, S., Franco, V., & Lipshultz, S. (2014). Anthracycline-induced cardiomyopathy: A review of pathophysiology, diagnosis, and treatment. *Current Treatment Options*

in Cardiovascular Medicine, 16(6), 315-329. doi: 10.1007/s11936-014-0315-4.

Sawaya, H., Plana, S., Januzzi, B., Ky, V., Cohen., S., Gosavi, J., . . . Kuter, I. (2011). Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *American Journal of Cardiology,* 107, 1375-1380. doi: http://dx.doi.org/10.1016/j.jjcc.2012.06.007

Seicean, S., Plana, C., Budd, T., & Marwick, T. (2012). Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy. *Journal of the American College of Cardiology,* 60(23), 2384-2390.

Seidman, A., Hudis, C., Pierri, M., Shak, S., Paton, V., Ashby, M., . . . Keefe, D. (2002). Cardiac dysfunction in the trastuzumab clinical trials experience. *Journal of Clinical Oncology,* 20, 215-21. doi: 10.1200/JCO.2002.20.5.1215

Swain, S., Whaley, F., & Ewer, M. (2003). Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trails. *Cancer, 97(11), 2869-2879. Doi:* 10.1002/cncr.11407

Thavendiranathan, O., Poulin, P., Lim, K., Plana, J., & Woo, A. (2014). Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after chemotherapy. *Journal of American Cardiology,* 63, 2751-2768. doi: http://dx.doi.org/10.1016/j.jacc.2014.01.073

Virani, S. , Dent, S., Brezden-Masley, C., Clark, B., Davis, M., Jassal, D., . . . Straatman, L. (2016). Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy. *Canadian Journal of Cardiology,* 32(7), 831-841. doi:

http://dx.doi.org/10.1016/j.cjca.2016.02.078

Von Hoff, D., Layard, M., Basa, P., Davis, H., Von Hoff, A., Rozencweig, M., & Muggia, F. (1979). Risk factors for Doxorubicin-induced congestive heart failure. *Annals of Internal Medicine,* 91(5), 710-717. doi: 10.7326/0003-4819-91-5-710

Wang, X., Ouyang, Y., Liu, J., Zhu., M., Zhao, G., Bao, W., & Hu., F. (2014). Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *British Medical Journal,* 349. doi: https://doi.org/10.1136/bmj.g4490

World Health Organization. Obesity and overweight. Geneva: World Health Organization; 2003. Available from: http://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf

Appendix A

Frequency of Echocardiogram Surveillance in Pediatric Population - COG (COG, 2013)

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM (or comparable cardiac imaging)			
Age at Treatment*	Radiation with Potential Impact to the Heart§	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	< 200 mg/m²	Every 2 years
		≥ 200 mg/m²	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m²	Every 5 years
		≥100 to <300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
≥5 years old	Yes	<300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
	No	<200 mg/m²	Every 5 years
		≥200 to <300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
Any age with decrease in serial function			Every year
*Age at time of first cardiotoxic therapy (anthracycline or radiation [see Section 80], whichever was given first)			

Appendix B

Culminating Project: Poster Presentation for BCNPA

Chemotherapy Induced Cardiomyopathy: What PCPs Should Know

Jane Narayan, BSc, BSN, RN; Supervisors: Jennifer Krist, MN-NP, NP(F); Marlene Burrows, MN-NP,NP(F)
University of British Columbia, School of Nursing, Vancouver, Canada

BACKGROUND

In 2016, it was estimated that the overall 5-year survival rate of cancer patients was 60%. With improved cancer treatments, long-term cancer survivors are increasing. Cancer survivorship exacerbates the need for primary care providers (PCPs) to identify and treat the potential long-term sequela of chemotoxicity. Amid numerous long-term complications of chemotherapeutic agents chemotherapy induced cardiomyopathy (CIC) emerges as one of the leading long-term cardiovascular complications. It can occur in up to 10% of cancer survivors, and proceed to end-stage HF in 2-4%. This poses substantial implications for survivors as they compound the effects of aging along with cancer therapy, however, early detection and treatment can reduce morbidity and mortality. Research studies and guidelines were explored and synthesized into an informational poster for knowledge translation among PCPs.

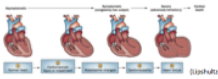
(Canadian Cancer Society, 2016; Cooper, Loeb, & Smith, 2010; Curigliano et al., 2016; Higgins, O'Halloran, & Chang, 2015; Lenneman & Sawyer, 2016; Virani et al., 2016)

CHEMOTHERAPY INDUCED CARDIOMYOPATHY: WHAT IS IT?

Cardiotoxicity: Cancer therapy effects can present as: arrhythmias, hypertension, pericardial disease, myocardial ischemia, valvular dysfunction, arterial thrombosis and cardiomyopathy.

Cardiomyopathy: Disease of heart muscle causing reduced ability of the myocardium to pump blood to rest of the body. Types: Ischemic, dilated (congestive), hypertrophic, restrictive, and arrhythmogenic right ventricular.

CIC: Cardiomyopathy (symptomatic or asymptomatic) induced by chemotherapeutic agents can result in acute, early, or late effects. Common agents: Anthracyclines, Monoclonal antibodies, Tyrosine Kinase Inhibitors



(Lipshultz et al., 2013)

MOST COMMON INDUCING AGENTS

	EXAMPLES	ONSET	PROGNOSIS	USED IN	PATIENT RF
ANTHRACYCLINES	Doxorubicin (Incidence increases with cumulative dose) Epirubicin Idarubicin Daunorubicin Mitoxantrone	Acute or Early (<1y) or Late (>1 y)	Classically Not Reversible (Type 1 cardiotoxicity)	Breast CA Osteo-sacroma Hodgkin's/ Non-Hodgkin's Lymphoma ALL	Extreme age: <5 or >65 Radiation Pre-existing CVD Females Smoking Black Race Trisomy 21
MONOCLONAL ANTIBODIES	Trastuzumb Bevacizumb	Acute or Early (<1y)	Reversible (Type 2 cardiotoxicity)	HER2+ Breast CA	Advanced age >50 Pre-existing CVD EF: 55% or lower Anthracycline use

(Cross et al., 2014; Mougidi et al., 2016; Virani et al., 2016)

POPULATIONS AT RISK

Pediatric Population: Increased risk for developing CIC in adulthood. The North American Children's Oncology Group (COG) reveals the greatest risk factors include: Younger age at treatment, >300mg/m^2 anthracycline dose, >30Gy Radiation (engaging heart), combination of anthracycline and radiation, or pregnancy

Adult Population: Cumulative dose of anthracycline greater then 400mg/m^2,>65 age, concomitant use of trastuzumab, female gender, black race, concurrent or prior use of radiation greater than 35Gy, elevation of biomarkers or pre-existing CV risk factors such as hypertension, diabetes mellitus or hyperlipidemia.

Pregnant Women: Women treated with anthracyclines or radiation. During pregnancy overall plasma volume is increased by up to 50% potentially putting a women who has unidentified cardiomyopathy at risk for deterioration either in pregnancy or during delivery. (Armenian et al.; COG, 2013; Curigliano et al., 2016)

SURVEILLENCE METHODS

Echocardiography (2D/3D):
- Easily accessible, inexpensive, no radiation exposure
- **2D:** Routinely used- reliable difference greater than 10% from previous image Impaired in obese patients
- **3D:** Preferred form to detect cardiotoxicity (measures actual volume)

MUGA Scan:
- Reproducible & accurate measurements of LVEF
- Exposes patient to radiation
- No information on heart structures

LEFT VENTRICULAR EJECTION FRACTION (LVEF)

Cardiac MRI (CMR):
- Can detect subtle differences in myocardial volume- best used in acute treatment
- Best image quality
- Cost and access= barriers

Strain Imaging (GLS):
- Measures strain on the myocardium
- Speckle tracking echo technique
- Changes in strain seen prior to LVEF decline on 2/3D echo
- Promising

Biomarkers: Troponin and BNP- Used in acute treatment for evidence of myocardial damage. Elevation during treatment predicts future LV dysfunction, helps with risk stratification post therapy, helps clinician determine if patient is a candidate for cardioprotective therapy; Elevated BNP=positive in HF

DIAGNOSIS:
Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD)= a decrease in LVEF > 10%, to a value <53%.

Frequency: Pediatric: Refer to GOC guidelines- Usually lifelong, based on cumulative anthracycline dose +/- radiation. **Adult:** Limited Evidence. If treated with anthracycline + Trastuzumab +/- radiation research reveals reasonable to monitor annually 2-3 years post therapy then every 3-5 years for life **altered if symptoms appear**
*Always use same modality to measure LVEF (different modalities are not interchangeable even though same measurement)
(Carter & Clark, 2015; Curigliano et al., 2016; Plana et al., 2014; Toro-Salazer et al., 2013; Thavendiranathan et al., 2014)

PLAN OF CARE: EDUCATION/ASSESSMENT/REFERRAL

ONGOING PATIENT EDUCATION:

Smoking Cessation:
-Encourage smoking cessation (Quit Now)
-2-3x increase in death related to CA/CVD in smokers compared to nonsmokers
-encourages atherosclerotic plaque accumulation ↑ strain

Physical Activity:
-Has protective effect particularly in patients at risk for cardiomyopathy/HF (dose-dependent relationship_
-150 min/week ↓mortality by 14%
-300min/week ↓ mortality by 20% (up to 30% in HF patients)
-Women benefit more then men

Well-Balanced Diet:
Increased CV risk with diet's high in saturated fat, sugar, red meat
-Encourage Mediterranean Diet (↓ cardiac events by 1/3)
-Alcohol consumption: 1 drink/day

Obesity/Healthy Weight:
-In Canada-1 in 7 children; 1 in 4 adults
-Each 1Kg/m2 of excess weight ↑ CA risk by 21%
-at risk for ↓ cardiac reserve therefore risk for ↑CIC risk
-Encourage healthy weight
-Refer to BC Guidelines on obesity for management

(Barnett et al., 2015; Johnston et al., 2016)

PATIENT ASSESSMENT:

Medical History	• HPI: Fatigue, swelling in lower extremities, SOB, Confusion, reduced appetite, abdominal swelling, nocturnal dyspnea • Assess for PMx or ongoing: HTN, Diabetes, Sleep Apnea, CVD (valvular disease, CAD, ARb), Smoking, COPD, CKD, anemia, alcohol or substance abuse
PHYSICAL EXAM	• Elevated JVP, peripheral edema, extra heart sounds (S3/S4), pulmonary crackles, ascites, displaced apex, reduced oxygen saturation, Low BP, HR >100
INVESTIGATIONS	• Echo (if warranted), CXR, ECG, BNP, TSH, CBC, Lytes, Cr • Ensure optimal BP control (CHEP guidelines); Diabetes and hyperlipidemia control (BC Guidelines, 2015; CCS, 2015)

MANAGEMENT:
Primary Prevention: Small scale studies show positive effects with the use of statins, ACE-I, BB however it is discouraged to use these medications in a prevention capacity until larger studies with generalizable data is produced
Treatment: If a patient presents with clinical signs of HF then the PCP must follow the CCS Guidelines for CHF (either preserved EF>40% or reduced EF<40) and initiate prompt treatment based on these evidence based guidelines
Consultation: Referral to a Cardiac Oncology Clinic (For known or suspected CV disease in survivors; CV risk modification related to previous oncology treatment); or Cardiologist if further management is needed (Davis & Virani, 2016; CCS, 2014)

RESOURCES

- Canadian Cardiovascular Society Guidelines- Heart Failure (2014) and Management of Cardiovascular Complications of Cancer Therapy (2016)
- Children's Oncology Group- Long-term Follow-up Guidelines (2013)

a place of mind THE UNIVERSITY OF BRITISH COLUMBIA