A Novel Comparative Analysis Approach to Personalize Chemotherapy Dose Calculation in Early Breast Cancer

by

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Abstract

Background

Worldwide, body surface area [BSA] is used to calculate chemotherapy dose. The BSA formula was originally developed in 1916, derived from height and weight, with no consideration of other patient characteristics. Most chemotherapy agents have a narrow therapeutic index and are distributed in lean body mass [LBM], leading to under- or over-dosing and deleterious effects to major organs, including the cardiovascular system, when body composition is not considered. While experts worldwide acknowledge the limitations and risks of BSA dosing, no practical approach to personalizing chemotherapy dose has been developed to this date. Ideally, body composition would be assessed by tests already routinely performed, avoiding unnecessary radiation exposure, clinic visits, discomfort to the patient, and cost. For example, most breast cancer patients undergo cardiac imaging prior to chemotherapy as per our clinical guidelines. We hypothesized that clinical parameters routinely performed prior to chemotherapy could predict LBM in early breast cancer patients.

Method

Early stage breast cancer patients (n = 45) enrolled in the Multidisciplinary Team Intervention in Cardio-Oncology (TITAN) study underwent pre-treatment cardiac MRI, body composition (iDEXA) and laboratory (complete blood cell count and chemistry). Cardiac MRI and iDEXA are considered 'gold standard' imaging modalities. The Pearson correlation was calculated to find the relationship between cardiac MRI values, total lean body mass, and routine chemistry. Our modeling approach, which is novel in this area, aimed to select the best combination of

parameters with the most predictive ability of total lean mass (iDEXA). The parameters included in this study were: cardiac MRI metrics (Left Ventricle (LV) mass, cardiac output), and laboratory parameters associated with major organ function (albumin, creatinine, bilirubin). All parameters were tested using univariate, multivariate and subset selection approach. Akaike's Information Criterion (AIC) was used to measure model quality, with lower AIC values indicating closer prediction.

Results

The univariate analysis of each parameter independently showed LV mass is most predictive with AIC 857.8, while combination of all parameter in multivariate fashion show improvement in prediction with AIC 851. The subset selection approach shows, Adjusted R2 with 4 parameters had AIC 849.14, Schwartz's information criterion (BIC) with 2 parameters had AIC 849.66 and Mallows' C Selection (Cp) model with 3 parameters had the least AIC 848.71 value ($P < 0.001$).

Conclusion

Our comparative analysis showed that the Cp model with 3 parameters (LV mass, cardiac output and bilirubin) has high prediction ability of LBM. This model can form the basis of a personalized formula for chemotherapy dose calculation. We expect this work to result in optimal cancer-specific outcomes while reducing short and long-term toxicities associated with necessary.

Preface

The TITAN study has undergone full ethics review and approval by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-16-1041) and the trainee has been added to the research team.

Chapter three of this thesis has been presented at the 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017 as M D Perri, S Singhal, K Hegadoren, C Norris, J Mackey, I Paterson and E Pituskin, "Abstract P6-13-08: A novel comparative analysis approach to personalize chemotherapy dose in early breast cancer". I was responsible for data entry and analysis as well as the abstract composition. S Singhal assisted with data analysis as well as abstract composition. K Hegadoren, C Norris, J Mackey, I Paterson were involved in concept formation. E Pituskin was the supervisory author and was involved with the concept formation and abstract composition. The manuscript that appears in Appendix A is a review paper that looks at the impact of cancer treatment on women`s health will be submitted for publication to *Journal of Women`s Health* as co-authored by Melissa Perri. Appenidx B is a manuscript that has been accepted by the Seminars in Oncology Nursing as co-authored by Dr. Edith Pituskin, Dr. Ian Paterson, Nanette Cox-Kennett, Derek Rothe, Melissa Perri, and Dr. Harald Becher.

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Chapter 1: Understanding Early Breast Cancer and Chemotherapy Treatment

Introduction

Cancer is the number one cause of death of Canadians. However, because of advances in cancer treatment more patients are living longer after their cancer diagnosis and treatment. This longevity has consequences, most notably the short and long-term toxic side effects of anticancer therapy on multiple major organ systems. Currently, Body Surface Area (BSA) is used to calculate patient's chemotherapy dose. BSA is not reliable as it uses only the patient's total weight and does not account for the patient's body composition, renal or hepatic function. Lean Body Mass (LBM) is known to correlate with renal and hepatic function and can currently be determined using Dual Energy X-Ray Absorptiometry (DEXA) scans or calculated after a clinical MRI or CT scan of the third lumbar region (Prado, Birdsell, & Baracos, 2009). We hypothesize that Left Ventricular (LV) muscle undergoes similar muscle changes as the skeletal muscle. In this study, we will assess if there is a correlation between LV muscle mass and total LBM. If our hypothesis is correct, LV muscle mass may predict lean body mass and may be used to calculate the dose of chemotherapy.

Background

Early Breast Cancer

In Alberta, breast cancer is the most common form of female cancer (Alberta Health Services [AHS], 2015). One in eight women will be diagnosed with breast cancer in their lifetime, equating to 25,700 women in 2016 (AHS, 2015; Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2016). Screening and early detection has improved substantially

over the years, resulting in 80% of breast cancer patients being diagnosed with early and curable stage one or two breast cancer (AHS, 2015). The ability to diagnosis breast cancer earlier and improvements in anticancer therapies have decreased breast cancer mortality since the 1990s (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2016).

In Alberta, there are standard guidelines for breast cancer diagnosis and treatment (AHS, 2012). Early breast cancer diagnosis is established through bilateral mammography or breast ultrasound and biopsy confirming malignant histology. Whole-body scans such as Computed Tomography (CT), Positron Emission Tomography (PET), or nuclear bone scans are not indicated until there is clinical suspicion of metastatic breast cancer (Chintamani, Tandon, Mishra, Agarwal, & Saxena, 2011; Tan, Goh, Fook-Chong, Khin, Wong, & Yong, 2011).

The treatment for early stage breast cancer is considered curative in nature. In Alberta, the survival rate at three years for stage one breast cancer is 100%, stage two is 98%, and stage three is 86% (AHS, 2015). However, most anticancer therapies are considered to be toxic to multiple organ systems with associated short and long-term debilitating side effects. A large portion of breast cancer patients will have multiple comorbid conditions and cardiovascular risk factors at the time of their cancer diagnosis therefore increasing their risk for organ dysfunction (Patnaik, Byers, DiGuiseppi, Denberg, & Dabelea, 2011).

Cardiac toxicity in early breast cancer treatment

Cardiotoxicity is an example of a major organ toxicity associated with cancer treatment (Jones et al., 2007). Cardiotoxicity is defined as the clinical findings of heart failure, such as shortness of breath on exertion, fatigue and peripheral edema or Left Ventricular Ejection Fraction (LVEF) <53% (Marwick, 2016; Plana et al., 2014; Virani et al., 2016). Patients with

lymph node positive breast cancer are commonly treated with a class of drugs called 'anthracyclines', well known to cause cardiomyopathies and cardiac dysfunction, leading to permanent myocardial damage (Feund, Grover, & Durst, 1978). Anthracycline drugs cause direct myocyte damage, with swelling of the cells leading to cell death (Friedman, Bozdech, Billingham, & Rider, 1978). Because cell death occurs, the damage caused by anthracyclines is irreversible (Plana et al., 2014). Anthracycline-related cardiomyopathies are thought to be dose dependent (Prana et al., 2014). However, cardiotoxicity has been frequently observed in cancer survivors who received standard, low dose anthracycline regimens, particularly pediatric, elderly, or those with cardiovascular risk factors (Hequet et al., 2004).

Another standard agent in the treatment of human epidermal growth factor receptor two (HER2+) overexpressing breast cancer patients is trastuzumab, an antibody specifically developed to block the HER2 receptor. It was not until trastuzumab was developed and tested that it was discovered that HER2 receptors also existed on cardiomyocytes. Cardiomyocyte HER2 receptor activities are thought to regulate adaptation to physiologic (and possibly psychologic) stress and protective from heart failure (Crone et al., 2002; Özcelik et al., 2002). In a Cochrane review of trastuzumab-based chemotherapy regimens in early breast cancer, (8 studies, n = 11,991 patients) trastuzumab increased the risk of congestive heart failure fivefold (Moja et al., 2012). Taken together, cardiotoxic effects of anthracycline and trastuzumab can have short and long term deleterious cardiovascular consequences, leading breast cancer survivors to be three times more likely to die from cardiac disease compared to age-matched controls (Hanrahan et al., 2007; Thavendirathan et al., 2016).

How is cardiotoxicity detected?

Since the standard treatment for breast cancer has been associated with cardiac dysfunction, provincial and national guidelines recommend that these patients routinely undergo cardiac monitoring before and/or during treatment, depending on the chemotherapy regimen (AHS, 2012). Several imaging modalities can evaluate cardiac function with availability generally dictating which test is performed, such as Multigated Radionuclide Angiography (MUGA), echocardiogram, and cardiac MRI (Kiluk, Kaur, Meade, Ramos, Morelli, King et al. 2010; Reitsamer, Menzel, Glueck, Rettenbacher, Weismann, & Hutarew, 2010). Cardiac MRI is the gold standard of cardiac imaging, providing highly reproducible measures of LV function and mass, however limited in terms of accessibility and expertise (Bellenger & Pennell, 1999).

How is chemotherapy dose determined?

It is intuitive that chemotherapy drug dosing should be individualized as much as possible to the patient, with the goal of curing the cancer with as few side effects as possible. Since chemotherapy agents have a narrow therapeutic index, accurate dosing of the agents is required (Felici, Verweiji, Sparreboom, 2002; Gurney 1996). This means a specific drug level is required to ensure that the medication is effective against the cancer while at the same time not causing undesired toxic effects (Felici et al.; Gurney). To understand the effects of medications used in cancer treatment the pharmacokinetics (absorption, distribution, metabolism and clearance) of each drug needs to be explicated. The chemotherapy agents used to treat early stage breast cancer are given via an intravenous route, therefore this means 100% of the medication will be absorbed. When a medication is given, it must be distributed to the site of action for it to have its effect (Edmunds & Mayhew, 2013). Factors that affect a drug's apparent volume of distribution includes plasma protein binding, obesity, edema, and tissue binding. As one

example, the anthracycline epirubicin has 77% protein binding, predominantly albumin, with a steady-state volume of distribution of 21 to 27 L/kg (Lexicomp, 2017). Any changes to the fat: muscle ratio will affect a drug's distribution (Edmunds & Mayhew). Therefore, patient's age, gender, disease and body composition affect the drugs distribution (Edmunds & Mayhew). Furthermore, patients have different abilities to metabolize and eliminate medications. Drug metabolism occurs in the liver using the cytochrome P450 enzyme system and/or through conjugate reactions (Edmunds & Mayhew, 2013). Each patient's cytochrome P450 system differs due to their gender, genetics and race, and this process is currently not well understood (Edmunds & Mayhew). The liver and kidneys are responsible for the elimination process where the drug and its metabolites are removed from the body (Edmunds & Mayhew). Renal elimination occurs by glomerular filtration, or active carrier mediated tubular secretion (Edmunds & Mayhew). Glomerular filtration rate is critical for the filtration of the medication, if the rate is reduced there will be decrease clearance and prolonged systemic exposure (Edmunds & Mayhew). The current practice globally, attempts to individualize chemotherapy treatment by using BSA to calculate the drug dose, which does not take into account any of these important factors (Gurney).

What is Body Surface Area?

BSA is the total surface area the body would occupy if it was cut into little pieces that would lay flat (Sawyer & Ratain, 2001). However, one cannot practically measure BSA this way, so BSA is calculated using the patient's height and weight with a formula created by DuBois and DuBois: (Du Bois & Du Bois, 1916 as cited in Sawyer & Ratain; Sawyer & Ratain).

$$BSA= BSA= (W^{0.425} \times H^{0.725}) \times 0.007184$$

BSA aims to provide individualized doses, while decreasing interpatient variability (Felici et al.; Gurney, 1996), In the literature BSA was initially used to determine the safe starting dose of chemotherapy agents in phase I trials and was never intended to be used to determine the routine dosage for patient's chemotherapy (Sawyer & Ratain). Pinkel (1958) studied the use of BSA in calculating the dose for five chemotherapy agents (mechlorethamine, methotrexate, 6-mercaptopurine, actinomycin, and triethylenethiophosphoramide) for adults and children. However, in this study the pharmacokinetic properties of the drugs were not studied and therefore the anticancer effects could not be compared with the toxic effects. With the exception of methotrexate, the medications tested in Pinkel's study are not listed on the Alberta Health formulary list for cancer treatment, therefore are not used in current practice. After Pinkel's study, the use of BSA to determine the dose of chemotherapy agents became common practice globally, without any further studies considering the relationship between the dose of the chemotherapy, BSA or other potentially important parameters of body composition or organ function (Baker et al.; Gurney; Felici et al., 2002).

Since then, multiple authors have critiqued BSA in chemotherapy treatment. Grochow, Baraldi, and Noe (1990) studied the relationship of pharmacokinetics with height, weight and BSA, showing that BSA did not predict pharmacokinetics of the drugs studied. Baker et al. (2002) reviewed 33 anticancer agents to determine if variability of interpatient drug clearance could be explained with BSA. Their study showed that BSA dosed drugs only decreased interpatient variability in 5 out of 33 agents. Renal clearance variability was reduced in 15% to 35% of the drugs, meaning that only one third of the variability can be explained by BSA. The studies that have suggested the presence of a relationship between renal function and BSA have established this relationship using urea clearance (Sawyer & Ratain). Urea clearance provides

information on renal tubular function and not Glomerular Filtration Rate (GFR). GFR is demonstrated through the calculation of creatinine clearance. Renal drug clearance is a function of the glomerulus and therefore creatinine clearance is a better indicator of drug clearance. Liver function is important for drug metabolism, however, a relationship between liver function and BSA has never been established (Felici et al., 2002).

A comprehensive review by Sawyer et al., summarized the limitations of BSA, strongly recommending that investigators develop a formula that considers organ function and drug pharmacokinetics. Taken together BSA has been adopted worldwide as a chemotherapy dosing approach even though a relationship has never been shown between BSA and drug pharmacokinetics and clearance (Prado et al., 2007).

Lean Body Mass

If BSA should not be used to dose chemotherapy, what other measurement can be used? As explained previously, organ function is vital to drug metabolism, but to date has not been considered in drug prescribing practices. A relationship between organ function and Lean Body Mass (LBM) has been demonstrated and may represent the optimal approach for prescribing drugs distributed and metabolized in lean tissues (Prado et al., 2009; Sawyer & Ratain, 2001). LBM includes metabolic tissues such as the liver and kidneys, intracellular and extracellular fluid, and skeletal muscle (Prado et al.). In studying liver and kidney volume and function with drug clearance, Nawaratne et al. (1998) found a strong correlation between kidney volume and LBM and univariate analysis confirmed that LBM was related to renal function ($p=0.005$). However, there was only a weak correlation between liver volume and LBM ($r^2=0.21$ $p=0.04$) and there was no correlation found between liver volume and hepatic clearance ($p=0.497$). This finding may be explained by the fact that drug metabolism is also affected by hepatic enzymes

and not just liver volume (Nawaratne et al., 1998). In addition, depending on which specific P450 is involved saturability is not routinely observed.

Two items need to be considered with LBM to calculate drug dosage. First, one must consider the body composition of the patients receiving chemotherapy. In patients with metastatic breast cancer receiving the anticancer drug capecitabine, Prado et al. (2009) showed that 25% of the patients were classified as being sarcopenic. Sarcopenia is defined as having low muscle mass and may be present in patients who are normal weight, overweight or obese (Prado et al.). Prado et al., assessed body composition using mathematical formulas from clinically performed MRI or CT scans at the third lumbar vertebra. In these patients, toxicity was experienced by 50% of sarcopenic patients versus 20% of nonsarcopenic patients ($p=0.03$). An important study by Guenancia et al. (2016) showed that being overweight or obese increased risk for developing cardiotoxicity after treatment with anthracyclines and trastuzumab in early breast cancer. In this study, the cardiac risk factors of obese and overweight patients did not differ from the normal weight patients. Taken together body composition of normal weight, overweight, and obese patients differ significantly, and this may in turn influence treatment-related toxicity. Accordingly, the importance of body composition to individualize chemotherapy drug dosage cannot be understated.

The consideration with LBM to calculate drug dosage is how the patient's lean body mass may be readily determined. Currently body composition is measured using commercially available body composition machines (DEXA) or extrapolated by mathematical formulas from clinically performed MRI or CT scans (Mourtzakis et al., 2008; Prado, Birdsell, & Baracos, 2009). Limitations of these methods include poor access to specialized imaging equipment, cost, exposure to radiation doses as well as limitations of mathematical formulas. Furthermore,

patients with early stage breast cancer do not routinely have CTs performed, given their low risk for metastatic disease, in contrast to Prado's study populations with advanced disease. The addition of a CT scan to quantify tissues at the third lumbar vertebra would require the patient to undergo extra diagnostic imaging (and radiation exposure) that is not currently required for their treatment nor are readily available prior to treatment.

An ideal approach to determine body composition would be represented by a test that is: routinely performed prior to chemotherapy and this avoids unnecessary radiation exposure, clinic visits, discomfort to the patient, and cost. As per the Alberta clinical practice guideline, early stage breast cancer patients scheduled to receive anthracycline and/or trastuzumab treatment undergo cardiac imaging to assess LV function (Kiluk et al., 2010; Reitsamer et al., 2010). Animal studies have shown that cardiac muscle evolves similar to skeletal muscles during cancer cachexia process (Cosper & Leinwand, 2011; Xu et al., 2011). To date, no research has been performed to assess the relationship between cardiac muscle mass and body composition in cancer patients undergoing curative intent treatment.

Hypothesis

The LV undergoes similar evolution of muscle mass as that of skeletal muscle in early breast cancer patients.

Research Question #1

Is there a correlation between LV muscle mass and LBM in early breast cancer patients?

Research Question #2

Can the LV muscle mass be used to predict LBM in early breast cancer patients?

Method

Participants

Study participants were participants in the actively enrolling Multidisciplinary Team Intervention in Cardio-Oncology (TITAN) study (Pituskin et al., 2016). The participants were all over the age of 18 years old, had confirmed early stage breast cancer with curative treatment plan (including anthracycline and trastuzumab therapy), and were all able to complete study-related assessments. The participants had no known cardiac dysfunction, were treatment naïve [defined as no prior anthracycline or trastuzumab therapy or previous radiation to the thorax]. There were 44 participants enrolled with the larger TITAN study at the time of data collection for this study.

Ethics Approval

The TITAN study had undergone full ethics review and approval by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-16-1041) and the trainee has been added to the research team.

Data Collection Method

Recruitment of the study participants was initiated in 2015. All cardiac MRIs were non-contrast and completed on the 1.5T Siemens Syngo Argus at the Elko MRI of the Mazankowski Alberta Heart Institute. Standard reportage included: quantitative and indexed LV mass, LVEF, LV end diastolic volume, LV end systolic volume, LV stroke volume. Body composition data was collected via the General Electric iDxa at the Cross Cancer Institute. The iDxa scans standard acquisitions included total skeletal muscle mass, total lean mass, and gynoid versus android distribution. Cardiac MRI and iDxa scans were chosen for the TITAN study as they

represent the gold standard of each modality (Bellenger &Pennell, 1999; Bellenger, Davies, Francis, Coats & Pennell 2000; Fan et al., 2014). The following data were collected for each participant: patient and treatment characteristics, routine laboratory results, cardiac MRI metrics and iDEXA body composition metrics (See Table 1.1 for complete list of data fields).

Analysis

Descriptive analysis of patient characteristics and demographics was performed. Correlation wasperformed to assess if there was a linear relationship between the LV mass and LBM and the strength of the relationship if present. All parameters were be tested using univariate, multivariate and subset selection approach to see if there was a stronger ability to predict LBM by using the parameters collected in the study. Akaike's Information Criterion (AIC) was used to measure the model's quality, with lower AIC values indicating closer prediction of LBM.

Feasibility

This project received ethics approval for the research team (HREBA.CC-16-1041) and my research question was added to the study. Dr. Pituskin has an established area of research, experience working with and mentoring thesis students. Dr. Pituskin was available for guidance in understanding the data, patient population relevant literature, and research process. The data for the project was available for data entry and analysis only baseline data was needed. An on-site statistician was available at the Cross Cancer Institute if further statistical analysis was required. Timely completion of the project is required to satisfy the Faculty of Graduate Study

and Research (FGSR) thesis requirement. This is required for the trainee to complete the national nurse practitioner licensing exam upon graduation.

Limitations

This study was a prospective study where secondary analysis was completed on the baseline data collected in the TITAN study. The study participants were all female with early stage breast cancer undergoing baseline cardiac assessment prior to their chemotherapy. Therefore, further research may be needed to extend the research findings to male patients and different cancer patients, including pediatric oncology patients.

Implications to Nursing

Breast cancer is a common female cancer that affects one in eight females (AHS, 2015). This research will potentially allow us to help change the way chemotherapy is dosed. The dose of chemotherapy agents influences the outcome of cancer therapy therefore it is important that the dose is appropriate for the patient and drug (Gurney, 1996). With more patients surviving breast cancer it is important that we reduce their risk of short and long term effects of anti-cancer therapy toxicities by ensuring individualized doses. Nurse Practitioners (NPs), as prescribers of chemotherapy, need to be cognizant of risks. As well registered nurses are involved in all aspects of oncology treatment, and by being involved in ongoing research and knowledge transfer to clinical practice will allow more opportunities to be proactive in minimizing potential adverse events rather than managing such event as they arise.

Significance

To our knowledge, no team in the world has examined LV mass as a surrogate for skeletal muscle mass with the potential for a single imaging test to not only evaluate cardiac function but inform appropriate and safe dosing of chemotherapy agents. If our hypothesis is correct, this project will provide fundamental knowledge to change cancer treatment globally. Our team also expect our findings to inform research in other patient populations with devastating sarcopenia, such as heart and kidney failure or acquired immune deficiency syndrome

Table 1.1 Data Collected for Thesis

Patient Characteristics	Date of Birth Gender Height Weight Comorbid conditions
MRI Data	MRI Body Surface Area Left Ventricle Ejection Fraction Left Ventricle End Diastolic Volume Left Ventricle End Diastolic Volume index Left Ventricle End Systolic Volume Left Ventricle End Systolic Volume index Left Ventricle Mass Left Ventricle Mass index Left Ventricle Stroke Volume Left Ventricle Stroke Volume index Cardiac Output
DEXA Data	Total body mass Total body fat Total body lean Total body BMC Total Trunk mass Total Trunk fat Total Trunk lean Total Trunk BMC
ARIA data	Height Weight Body surface area Baseline serum creatinine Heart rate Blood pressure Chemotherapy cycle 1 total dose each drug Cycle 1 Toxicity (if any): Febrile neutropenia, GI toxicity, cardiac toxicity

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Chapter Two: Literature Review

Background

Vogenberg, Barash, and Pursel (2010) define personalized medicine as "[treatment that has] the potential to tailor therapy with the best response and highest safety margin to ensure better patient care." (p. 560). The current practice to individualize one's chemotherapy is to use body surface area (BSA) to calculate the drug dose (Gurney, 1996). Using BSA has been the standard of practice since Pinkel's 1958 study, where dosing of chemotherapy agents based on BSA was studied in the pediatric and adult population. This study did not assess the drugs' pharmacokinetics and therefore could not compare the anticancer effects to the toxicities caused by the chemotherapy agents. After Pinkel's study, there were no further studies that considered the relationship between chemotherapy dose, BSA or other parameters of body composition (Baker et al., 2002; Gurney; Felici et al. 2002). BSA remains the standard of practise worldwide, however, experts recognize serious limitations. Grochow, Baraldi, and Noe (1990) conducted a study looking at the relationship between drug clearance and pharmacokinetics with height, weight, and BSA. In their study, they found using BSA to calculate drug doses did not explain the pharmacokinetics of the drugs studied. Accordingly, even though there are no studies that demonstrate a convincing relationship between BSA, drug clearance and pharmacokinetics, using BSA to dose chemotherapy remains the current standard of practice (Prado et al., 2007).

Lean Body Mass

Hydrophilic medications are distributed to the lean body mass (LBM) and the LBM is responsible for 99% of the bodies metabolic processes (Roubenoff & Kehayias, 1991). LBM is

made up of metabolic tissues such as the liver and kidneys, intracellular and extracellular fluid, and skeletal muscle (Prado et al., 2009a). A relationship between organ function and LBM has been convincingly demonstrated and may represent the optimal measure for normalizing doses of drugs that are distributed and metabolized in lean tissues (Prado et al., 2009b; Sawyer & Ratain, 2001). Nawaratne et al. (1998) showed that kidney volume was strongly correlated with LBM and through univariant analysis, LBM was related with renal function ($p=0.005$). Their study also indicated that LBM was the only variable that was significantly correlated with drug antipyrine clearance. Even though the study showed a correlation between the liver volume and BSA, there was no correlation between BSA and drug hepatic clearance. Finally, LBM has been a precise measurement that can potentially be utilized to determine a drug's pharmacokinetics (Sawyer & Ratain, 2001). Having a lower amount of LBM has been associated worse cancer outcomes, and one could postulate that body composition influences cancer treatment toxicities (Shachar et al., 2017).

Method

The purpose of this literature review was to explore research on the relationship between body composition and toxicities related to breast cancer chemotherapy. Whittemore and Knafl (2005) integrative review process was used to guide this integrative review. MEDLINE and EMBASE databases were searched between May 2017 and June 2017. An expert librarian from the John W. Scott Library, University of Alberta, aided with search terms for each database. The terms included in this search are: antineoplastic agents, adverse reactions, adverse effects, toxicities, taxanes, anthracycline, trastuzumab, body composition, body fat, adipose, skeletal muscles, body mass, obese, overweight, lean mass, breast neoplasm, breast tumor, malignancy,

and carcinoma. This search resulted in 656 articles. The search was narrowed using: English language, peer reviewed articles and specific toxicities monitored for were identified. The toxicities of specific interest included: cardiovascular toxicities, febrile neutropenia, neuropathy, hematological toxicities, and grade two or higher hand foot syndrome and gastrointestinal side effects. Articles were excluded: no specific toxicities were studied, if capped chemotherapy doses were used, if the article focused on the changes to body weight from cancer disease process or cancer treatment, if body composition or BMI were not used as a study variable, and if the primary outcome was mortality and progression free survival.

After reviewing all articles, based on the above inclusion and exclusion criteria, 11 articles were identified as eligible for inclusion in the review.. Each articles' references were hand searched which revealed no new articles for inclusion. Two review articles were included and the articles used for those reviews revealed an additional 9 articles. A total of 20 articles were included in the integrative review.

Results

Table 2.1 Summary of Studies Included in Integrative Review

Title	Author/ Year	Study Design	Type of Breast Cancer/Main chemotherapy treatment	Weight/body size variable	Type of Toxicity	Key Findings regarding relationship between weight/BMI/body composition and toxicity	Consideration
Cardiac safety of the adjuvant Trastuzumab in a Moroccan population: observational monocentric study of about 100 patients	Aitelhaj et al., 2013	Retrospective observational N=100	Localized breast cancer HER 2+	BMI – overweight (25-30 $kg/m^{2)}$ Obese (>30 kh/m^2)	Cardiotoxicity	38 participants developed cardiotoxicity 31.57% of those pts were considered overweight developed cardiotoxicity (p=0.61) 42.1% of those pts considered to be obese developed cardiotoxicity (p=0.57)	small sample size limited follow up
Long-Term Cardiac Follow-Up in Relapse-Free Patients	Bonneterre et al., 2004	Prospective Study N=150	Node positive operable breast cancer	BMI	LV dysfunction	BMI was higher in the patients who had LV	Small sample size

After Six Courses of Fluorouracil, Epirubicin, and Cyclophosphamide, With Either 50 or 100 mg of Epirubicin, As Adjuvant Therapy for Node-Positive Breast Cancer: French Adjuvant Study Group						dysfunction however this was not statistically significant p =0.1	
Doxorubicin-induced cardiac dysfunction in unselected patients with a history of early-stage breast cancer	Caram et al., 2015	Prospective study N=269	Stage I, II, III breast cancer treated with neoadjuvant/adjuvant treatment	BMI	Cardiotoxicity	BMI was not statistically significantly associated with reduced LVEF (p=0.57)	They did not perform LVEF assessment on all participants Only included pts who survived their cancer treatment
Incidence of febrile neutropenia among early-stage breast	Chan, Chen, Chiang, Huey Tan, & Ng, 2012	observational retrospective cohort	Early stage BC (stages I-IIIa) adjuvant	BMI-Healthy weight BMI <23 kg/m2 and	febrile neutropenia	BMI and body surface area (BSA) significantly associated with	Overweight pts had a lower plasma concentrati

cancer patients receiving anthracycline-based chemotherapy		study N=189		Overweight – BMI > 23 kg/m2		febrile neutropenia (p=0.02) Pts with BMI < 23 had 3.6 times more likely to develop febrile neutropenia compared to BMI >23 (p=0.006).	on due to increase volume of distribution Small sample size All patients were of Asian ethnicity The cohort had a young median age with only 14 pts being considered elderly
Trastuzumab-induced cardiotoxicity in early breast cancer patients: a retrospective study of possible risk and protective factors	Farolfi et al., 2012	Retrospective N=179	Early breast cancer, Adjuvant trastuzumab	BMI	Cardiotoxicity	BMI was not associated with development of cardiotoxicity. P=0.323	Small sample size Short period of follow up
Long-term	Fumoleau et	Retrospecti	Early breast cancer	BMI	Cardiotoxicit	BMI greater	

cardiac toxicity after adjuvant epirubicin-based chemotherapy in early breast cancer: French Adjuvant Study Group Results	al., 2006	ve study N=3778	Adjuvant treatment	(BMI < 27 kg/m^2 vs BMI > 27 kg/m^2)	y	than 27 was associated with increased risk for developing cardiotoxicity (p=0.03)	
Cardiac Safety of (Neo)Adjuvant Trastuzumab in the Community Setting: A Single-Center Experience	Gomes da Fonseca et al., 2014	Retrospecti ve study N=237	Non-metastatic HER 2 positive breast cancer patients Treated with adjuvant and adjuvant treatment	BMI	Cardiotoxicit y	BMI was found to not be significantly associated with development of cardiotoxicity p= 0.236	Small sample size Long term follow up was not completed.
BMI, Lifestyle factors and taxane-induced neuropathy in breast cancer patients: the pathway study	Greenlee et al., 2017	Prospective cohort study N= 1327	Invasive breast cancer Taxane chemotherapy	BMI	Neuropathy	Increase risk for developing chemotherapy induced peripheral neuropathy Overweight vs normal weight OR=2.37 CI=1.19-4.88 p=0.02 Obese vs normal	Self-report of peripheral neuropathy

						OR=3.21 CI= 1.52-7.02 p=0.03	
Alcohol and HER2 Polymorphisms as Risk Factor for Cardiotoxicity in Breast Cancer Treated with Trastuzumab	Lemieux et al., 2013	Retrospecti ve cohort study N=237	Non-metastatic breast cancer trastuzumab	BMI	Cardiotoxicit y – LVEF drop by 10% from baseline or an EF < 45%	Odds ratio for the BMI of 25-29 was 1.33 (CI 0.59-3) p= 0.49 Odds ratio for BMI >30 was 0.41 (CI 0.11-1.53) p= 0.19	Small sample size LVEF was assessed using MUGA scans, and 2D echos No baseline LVEF available for 35.9% of participants
Effect of Obesity on the Leukocyte Nadir in Women Treated with Adjuvant Cyclophosphami de, Methotrexate, and Fluorouracil Dosed According to Body Surface Area	Poikonen, Blomqvist, & Joensuu, 2001	N=340	Adjuvant chemotherapy Node positive without distant metastasis	BSA BMI (mildly obese if BMI > 25, Obese if BMI >30)	Hematologic al toxicities	BMI and leukocyte nadir were significantly related Pts with higher BMI had higher leukocyte nadir (Spearman correlation 0.3 p<0.001)	Pts with BMI <22 kg/m2 received higher dose in relation to BMI, weight

Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment	Prado et al., 2009	Prospectively N=55	Metastatic breast cancer Anthracycline and or taxane treatment	Body composition using CT scan for LBM	Grade 2 or higher: Hand foot syndrome Diarrhea Stomatitis Nausea Vomit Neutropenia	Prevalence of toxicity was significantly higher in the sarcopenic patient p=0.03 (20% of nonsarcopenic patient vs 50% of sarcopenic patient)	Small sample size
An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity	Prado et al., 2010	Prospective study N= 24	Stage II and III Adjuvant (5FU, epirubicin, cyclophosphamide)	BSA CT scan at L3 BMI	Neutropenia Leucopenia NCI-CTEP Common Toxicity Criteria version 2.0	Pts with same BSA presented with large variations in LBM and liver mass The mean LBM in toxicity absent group (56.2 kg) was statistically higher than the toxicity group (41.6 kg) with p=0.002 LBM was correlated with neutrophil	Small sample size

						nadir (r=0.5 with p=0.023)	
Trastuzumab induced cardiotoxicity in HER2 positive breast cancer patients attended in a tertiary hospital	Rocha Ayres et al., 2015	Retrospective descriptive study N=79	Breast cancer without distant metastasis adjuvant/neoadjuvant chemotherapy	BMI	Cardiotoxicity	No association found between BMI and cardiotoxicity	Small sample size No long term follow up No baseline EF measured on some participants
Diastolic Dysfunction Following Anthracycline-Based Chemotherapy in Breast Cancer Patients: Incidence and Predictors.	Serrano et al., 2015	Analytical prospective Observational cohort study N=85	Anthracycline based chemotherapy	BMI	Cardiotoxicity Diastolic dysfunction	Odds ratio for obese (7.6 p=0.001) and overweight (2.8 p=0.004) patients to develop diastolic dysfunction Age (over the age of 50) was found to be a risk factor for developing diastolic dysfunction (OR=4.1 p=0.001)	Single center study Low number of clinical cardiotoxicity due to the short surveillance (12 months)

Risk factors for chemotherapy-induced neutropenia occurrence in breast cancer patients: data from the INC-EU Prospective Observational European Neutropenia Study	Schwenkglenks et al. 2011	Prospective study N=444	adjuvant or neoadjuvant chemotherapy grade I–III breast cancer,	Weight	Chemotherapy induced neutropenia	Older age and lower weight were significantly associated with chemotherapy induced neutropenia. Weight per additional 10 kg (OR 0.67, CI 0.57-0.79 p=0.000) Age per additional 10 years (OR 1.35, CI 1.06-1.73, p=0.016) Highly significant negative correlation between BSA and dose/kg	
Skeletal Muscle Measures as Predictors of Toxicity, Hospitalization, and Survival in	Shachar et al., 2016	Retrospective N= 40	Metastatic breast cancer Taxane based chemotherapy	Body composition using CT scans at the L3	Grade 3-4 National Cancer Institute common toxicity	Sarcopenia was significantly associated with experiencing more grade 3-4	Small sample size Pts could have received

Patients with Metastatic Breast Cancer Receiving Taxane-Based Chemotherapy.					criteria for adverse events (NCI-CTCAE): Hematologic, Febrile neutropenia, WBC growth factor usage, Neurotoxicity, Gastrointestinal toxicities	toxicities (57% of sarcopenic vs 18% normal body composition p=0.02) Lower skeletal muscle gauge (SMG) [p=0.04] and lower skeletal muscle density (SMD) [p=0.01] was significantly associated with developing grade 3-4 toxicities within treatment cycles 1-3 All patients admitted to hospital due to their toxicities were considered sarcopenic. Low lean body mass (LBM) p=0.003, SMD	biologic agents at the same time as taxanes therefore affecting toxicities found in the study Different mechanisms of actions of the different taxanes could have affected the results

						p=0.03, and low SMG p=0.01 were significantly associated with hospitalizations.	
Body Composition as a Predictor of Toxicity in Patients Receiving Anthracycline and Taxane-Based Chemotherapy for Early-Stage Breast Cancer.	Shachar et al., 2017	Retrospective N= 151	Early breast cancer (stage 1-3) Doxorubicin-cyclosphosphamide, taxane based chemotherapy	Body composition using CT scan at the L3	Grade 3-4 National Cancer Institute common toxicity criteria for adverse events (NCI-CTCAE): Hematologic, Febrile neutropenia, WBC growth factor usage, Neurotoxicity, Gastrointestinal toxicities, CHF, DVT, PE, leukemia	Every 5 kg decrease in LBM significantly increased risk of any toxicity by 36% (p=0.002) Every 5 unit decrease in Skeletal muscle index (SMI) increase the risk of toxicity by 27% (p=0.002) Every 100 AU decrease in SMG the risk of toxicity increased by 8% (p=0.006)	Sample included only n=9 over the age of 65
Association	Wang et al.,	Retrospecti	Stage I-IV	BMI	Cardiotoxicit	Multivariate	Small

between obesity and trastuzumab-related cardiac toxicity in elderly patients with breast cancer	2017	ve N=133	Trastuzumab		y	regression showed that obesity was significantly related to adverse cardiac event (OR= 4.706, CI=1.984-10.147, p=0.002)	sample size Short duration of follow up
Body fat composition impacts the hematologic toxicities and pharmacokinetics of doxorubicin in Asian breast cancer patients	Wong et al., 2014	Prospective N=84	Metastatic breast cancer	BMI BSA Body composition done with CT scan at L3	Grade 4 hematological toxicities	Significant relationship found between the underweight/ overweight pts and grade 4 leukopenia	Small sample size
Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer	Yu et al., 2015	Retrospective chart review for pt. information and observational study N=608	Early breast cancer Adjuvant trastuzumab	BMI	Cardiotoxicity	Pts who required interruption in therapy were statistically older (Age 55 vs 50 years, p < 0.0001) and had higher BMIs (BMI 28.2 vs 26.9 kg/m^2, p=0.036)	Assessment of EF was based on physician preference and therefore differed for all patients The EF that resulted in the

						Interruption in therapy occurred due to treatment induced cardiotoxicity	interruption in treatment was pre-defined and therefore differed per pt.

Body Composition. Body composition and weight were captured using BMI, CT scan at the third lumbar region, BSA, or body weight. Five studies used CT scans at the third lumbar region, however the majority (3 out 5) of these studies included metastatic breast cancer patients. The remainder of the studies used BMI (n=13) or weight (n=1) to assess the body composition. The World Health Organization (WHO, 2017) defines BMI "as a person's weight in kilograms divided by the square of his height in meters (kg/m2)". As well the WHO also defines being overweight as having a BMI greater than or equal to 25 kg/m2 and being obese as having an BMI greater than or equal to 30 kg/m2 (WHO). The use of these definitions was inconsistent in the studies reviewed. In the literature review not all of the studies defined being overweight and obese as per the WHO's criteria. For example, one article looked at body weight and age as a determinant for body composition as increased age is associated with decreased muscle mass and density (Weinberg et al., as cited in Shachar et al., 2017).

Relationship between sarcopenia and toxicities. Five studies used CT scans at the third lumbar region to assess participant's muscle mass, skeletal muscle gauge and density (Prado et al., 2009; Prado et al., 2010; Shachar et al., 2016; Shachar et al., 2017; Wong et al., 2014) . These studies consistently demonstrated a significant relationship between decreased LB< measurements and measured toxicities.

Relationship between increase BMI and toxicities. Fourteen studies used BMI to classify their participants' body composition (Aitelhaj et al., 2013; Bonneterre et al. 2004; Caram et al. 2015; Chan, Chen, Chiang, Huey Tan, & Ng, 2012; Farolfi et al., 2012; Fumoleau et al., 2006; Gomes da Fonseca et al., 2014; Greenlee et al., 2017; Lemieux et al., 2013; Poikonen, Blomqvist, & Joensuu, 2001; Rocha Ayres et al., 2015; Serrano et al., 2015; Wang et al., 2017; Yu et al., 2015). Seven of these studies demonstrated a relation between increased BMI and

increased rates of toxicities (Chan, Chen, Chiang, Huey Tan, & Ng, 2012; Fumoleau et al., 2006; Greenlee et al., 2017; Poikonen, Blomqvist, & Joensuu, 2001; Serrano et al., 2015; Wang et al., 2017; Yu et al., 2015). Seven of the studies either showed no relationship between body size and toxicities or their results were non significant (Aitelhaj et al., 2013; Bonneterre et al. 2004; Caram et al. 2015; Farolfi et al., 2012; Gomes da Fonseca et al., 2014; Lemieux et al., 2013; Rocha Ayres et al., 2015;). These studies had small samples sizes ([Range N=79-237] Median 149) and short period of toxicity surveillance, therefore longer term toxicities such as cardiotoxicity may have been missed.

Relationship between increase age and toxicities. Two articles demonstrated that increasing age was associated with increased chemotherapy toxicities (Serrano et al., 2015 & Schwenkglenks et al., 2011). One of the articles studied lower weight with increase age led to increased toxicities (Schwenkglenks et al., 2011). The other study showed that increased age and BMI were associated with increasing rates of toxicities (Serrano et al., 2015) . These studies suggested changes to body composition (decrease muscle mass) that occurs with normal aging can lead to increased toxicities.

Discussion

Being able to prescribe personalized chemotherapy holds the potential to reduce the short and long term toxicities of anticancer therapies while maintaining optimal cancer-specific outcomes. Current practice of using BSA to individualize chemotherapy doses has failed to account for a large amount of interpatient variability (Baker et al., 2002; Gurney, 1996). This literature review has highlighted an association between body composition or BMI and toxicities associated with chemotherapy. This finding can be explained by increases in body mass size,

altering the volume of distribution of hydrophilic drugs therefore affecting their metabolism and clearance (Abernethy & Greenblatt as cited in (Poikonen, Blomqvist, & Joensuu, 2001).

Most of the studies used in this literature review were retrospective chart reviews. Therefore, the patients' body composition could not be prospectively assessed using modern approaches such as DEXA scans or CT scans at the 3rd lumbar region. Rather, these studies relied on measurements routinely performed during cancer care (i.e. height and weight) to classify if the patient is underweight, normal weight, overweight, or obese. Overall these studies showed that there is a relationship between body size (increased body size) and the amount of chemotherapy toxicities the participants experienced.

The five remaining studies specifically assessed participants' body composition using CT scans at the third lumbar region. The majority of participants in these studies had metastatic breast cancer and therefore had clinical CT scans performed to monitor tumor response as part of routine care. These studies demonstrated a convincing relationship between the amount of lean body tissue and the amount of grade two to four toxicities (including hematological, febrile neutropenia, neurotoxicity, gastrointestinal, cardiovascular, hand/foot syndrome) that will be experienced. Having a lower amount of lean body tissue is strongly associated with increased risk of chemotherapy-related toxicities in advanced breast cancer patients.

As per clinical guidelines CT scans are not routinely performed in early stage breast cancer patients until metastatic disease is suspected (AHS, 2012). This is important to consider as 80% of breast cancer patients will be diagnosed with stage I or II cancer (AHS, 2015). As such, a major gap in the literature exists regarding how to assess body composition for patients who have curable, early stage breast cancer. Body composition cannot be determined by looking at an individual's height and weight as sarcopenia is present in underweight, normal weight,

overweight and obese patients (Prado et al., 2009). The ideal approach to determining early breast cancer patients body composition would be to use a test that is; done routinely prior to starting breast cancer treatment, doesn't expose patients to unnecessary additional scans that will expose them to radiation, additional hospital visits, discomfort, or increase health care cost.

Early breast cancer patients undergoing anthracycline and/or trastuzumab treatment have cardiac imaging done to assess the LV function prior to starting treatment (Kiluk et al., 2010; Reitsamer et al., 2010). Animal models have demonstrated that the myocardial muscle evolves similar to the lean muscle mass during cancer cachexia process (Cosper & Leinwand, 2011; Xu et al., 2011). However, to date no one has studied changes to the myocardial mass in humans and if myocardial mass may be used as predictor to a patient's LBM. If this relationship exists, then myocardial muscle mass could be used to predict LBM, allowing the prescription of personalized chemotherapy that would help to reduce the short and long term toxicities.

Lean body compartment and body composition should be considered when personalizing chemotherapy doses. Currently BSA is used to individualize chemotherapy doses, this method has several limitations, most notably, it does not consider the patient's body composition. The literature reviewed demonstrates how increased BMI, and low LBM, are related to increased toxicities experienced by breast cancer patients. There is a gap in the literature on how to concurrently assess the LBM of early stage breast cancer patients without exposure to additional imaging that is not clinically relevant. One way this gap can be addressed would be studying to see if the clinically required cardiac assessment performed prior to chemotherapy shows a relationship between left ventricle (LV) mass and LBM and if there was a relationship, could LV mass be used to predict one's LBM.

References for Chapter Two

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Chapter Three: A Novel Comparative Analysis Approach to Personalize Chemotherapy Dose Calculation in Early Breast Cancer

Background

Cancer is the number one cause of death of Canadians. The most common form of cancer for females is breast cancer, with one in eight women diagnosed in their lifetime (Canadian Cancer Society Advisory Committee on Cancer Statistics, 2016). Breast cancer screening and detection have improved considerably, meaning that 80% of breast cancer cases are diagnosed at early stage, and improvements in therapies have substantially decreased breast cancer mortality since the 1990s (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2016; Alberta Health Services [AHS], 2015).

However, chemotherapy is well known to be toxic to major organ systems, causing short and long-term side effects. Cardiotoxicity is an example of a major and potentially deadly organ toxicity associated with cancer treatment, defined as clinical findings of heart failure, such as shortness of breath on exertion, fatigue and peripheral edema or left ventricular ejection fraction (LVEF) <53% (Marwick, 2016; Plana et al., 2014; Virani et al., 2016). Common breast cancer treatment regimens include ‘anthracyclines’, well known to cause cardiomyopathies and cardiac dysfunction, leading to permanent myocardial damage (Feund, Grover, & Durst, 1978), and in HER2-overexpressing breast cancer, trastuzumab, an antibody specifically developed to block the HER2 receptor. Cardiomyocyte HER2 receptor activities are thought to regulate adaptation to physiologic (and possibly psychologic) stress and protective from heart failure (Crone et al., 2002; Özcelik et al., 2002). In a Cochrane review of trastuzumab-based chemotherapy regimens in early breast cancer (8 studies, n = 11,991 patients) trastuzumab increased the risk of congestive heart failure fivefold (Moja et al., 2012). Thavendirathan et al. (2016) recently

showed that cardiotoxic effects of combination of anthracycline and trastuzumab, anthracycline alone and non-anthracycline occur rapidly after treatment, with breast cancer survivors three times more likely to have cardiac event or heart failure diagnosis compared to age-matched controls.

It is intuitive that chemotherapy drug dosing should be individualized as much as possible to the patient, with the goal of cure with as few side effects as possible. Body surface area (BSA) is a formula originally developed in 1916, however since then many authors have argued that BSA fails to individualize chemotherapy dose, not accounting for factors well known to be important to drug distribution, metabolism and excretion. A comprehensive review by Sawyer et al. (2001), summarized the multiple limitations of BSA, strongly recommending that investigators develop a formula that considers lean body mass (LBM) and organ function.

An important study by Guenancia et al. (2016) showed that being overweight or obese increased risk for developing cardiotoxicity after treatment with anthracyclines and trastuzumab in early breast cancer. Here, the cardiac risk factors of obese and overweight patients did not differ from those of normal weight patients. Chemotherapy agents are hydrophilic, and accordingly, body composition influences treatment-related toxicity (Prado et al., 2009; Prado et al., 2011). Currently body composition is measured by body composition machines (DEXA) or extrapolated by mathematical formulas from clinically performed MRI or CT scans not routinely available(Mourtzakis et al., 2008; Prado, Birdsell, & Baracos, 2009). An ideal approach to determine body composition would be represented by a test that is; routinely performed prior to chemotherapy and avoids unnecessary radiation exposure, clinic visits, discomfort to the patient, and cost. Early stage breast cancer patients routinely undergo cardiac imaging to assess LV function (Kiluk et al., 2010; Reitsamer et al., 2010). Animal studies have shown that cardiac

muscle evolves similar to skeletal muscles during cancer cachexia process as cardiac muscle is a striated muscle and similar in nature to the skeletal muscle (Cosper & Leinwand, 2011; Xu et al., 2011). Decrease in cardiac muscle in cancer patients is caused by decrease cardiac myocyte size from reduced amounts of sarcomeric proteins (Cosper & Leinwand). To date, no research has been performed to assess the relationship between left ventricle (LV) mass and LBM in cancer patients undergoing curative intent treatment.

Hypothesis/Research questions

We hypothesized that LV muscle undergoes similar evolution as the total LBM.

Research Question #1

Is there a correlation between LV muscle mass and LBM in early breast cancer patients?

Research Question #2

Can the LV muscle mass be used to predict LBM in early breast cancer patients?

Method

Participants. Study participants were actively enrolled in the Multidisciplinary Team Intervention in Cardio-Oncology (TITAN) study (Pituskin et al., 2016). The participants were all over the age of 18 years old, confirmed early stage breast cancer with a curative treatment plan, can exercise and complete DEXA scans. The participants had no known cardiac dysfunction, and were treatment naïve (no prior anthracycline or trastuzumab or previous radiation to the thorax).

Data Collection. Baseline data for the 44 participants were collected. All cardiac MRIs were non-contrast and completed on the 1.5T Siemens Syngo Argus at the Elko MRI of the Mazankowski Alberta Heart Institute. Standard MRI metrics included: quantitative, and indexed LV mass, LV ejection fraction, LV end-diastolic volume, LV end systolic volume, LV stroke

volume. Body composition data was collected via the General Electric iDxa at the Cross Cancer Institute. Standard acquisitions included: total skeletal muscle mass, total lean mass, and gynoid versus android distribution. Cardiac MRI and iDxa scans were chosen for the TITAN study as they represent the gold standard of each imaging modality (Bellenger &Pennell, 1999; Bellenger, Davies, Francis, Coats &Pennell 2000; Fan et al., 2014). Cardiac MRI was also selected as it allows for a more a precise measurement of all metrics, therefore reduces the sample size required to demonstrate a relationship (Bellenger et al., 2000). Standard patient characteristics (demographics, hormone and HER2+ status, past medical history and cardiac risk factors) and routine laboratory work including general chemistry, renal function, liver function were collected.

Data analysis. All parameters were tested using univariate, multivariate and subset selection approach. Akaike's Information Criterion (AIC) was used to measure model quality, with lower AIC values indicating closer prediction.

Results

Baseline data for 44 TITAN participants were assessed. (Table 1) The average age of the participants was 52.3 years old (range 28-68 years old) on the date of their cardiac MRI.

Table 3.1- Participants characteristics

Total participants	N=44
Average age	52.4 years old
Minimum age	28 years old
Maximum age	68 years old
Estrogen Positive	N=38 (86%)
Estrogen Negative	N= 6 (14%)
Human Epidermal Growth Factor Receptor 2 (HER2+) positive	N=13 (30%)
HER 2+ negative	N=31 (70%)

History of Hypertension	N=5 (11%)
History of Hyperlipidemia	N=3 (6%)
Smoking	Current N=2 (5%) Smoking history N=11 (25%) Non-smoker N=27 (61%) Unknown smoking history N=4 (9%)
Diabetes	N=6 (12%) Type 1- N= 1 (2%) Type 2- N= 5 (11%)
Chronic Renal Failure	N=0
ETOH abuse	N=1 (2%)
Current ETOH	No use N= 10 (22%) Occasional N= 27 (61%) 1-2 drinks/day N= 2 (4.5%) >2 drinks/day N= 1 (2%) Unknown use N= 4 (9%)

Body composition data was collected from the DEXA scan, height, and weight entered into the electronic medical record (table 2).

Table 3.2 Body Composition Data

	Mean (range)
BSA (m^2)	Mean: 1.84 (1.44 - 2.37)
BMI (kg/m^2)	Mean 28.44 (17.46 - 45.41)
Total body mass (kg)	Mean:75.13 (46.2 - 144.4)
Total body fat (kg)	Mean: 30.2 (16.9 - 67.7)
Total lean body (kg)	Mean: 41.9 (41.9 - 56.7)
Total body bone mass (kg)	Mean: 2.365 (1.67 - 3.03)
Total trunk mass (kg)	Mean: 37.35 (21.3 - 62.4)
Trunk fat (kg)	Mean: 15.8 (3.64 - 35.46)
Trunk lean (kg)	Mean: 20.66 (16.54 - 26.53)
Trunk bone mass (grams)	Mean: 692 (415 – 964)

BSA=Body Surface Area, m=meter, kg=kilogram
Baseline cardiac assessment was completed using cardiac MRI prior to the initiation of chemotherapy (table 3). Cardiac output was calculated using LV stroke volume and baseline heart rate.

Table 3.3 Cardiac MRI Parameters

LV Ejection Fraction (%)	Average: 61.75 (47 - 70)
LV stroke volume (ml)	Average: 78.98 (49 - 131)
LV mass (grams)	Average: 87.86 (48 - 118)
LV end diastolic volume (ml)	Average: 128.7 (72 - 200)
LV end systole volume (ml)	Average: 49.66 (23 - 84)
Cardiac output (L/min)	Average: 5.33 (2.97 - 7.68)

ml=millilitre, L=liter

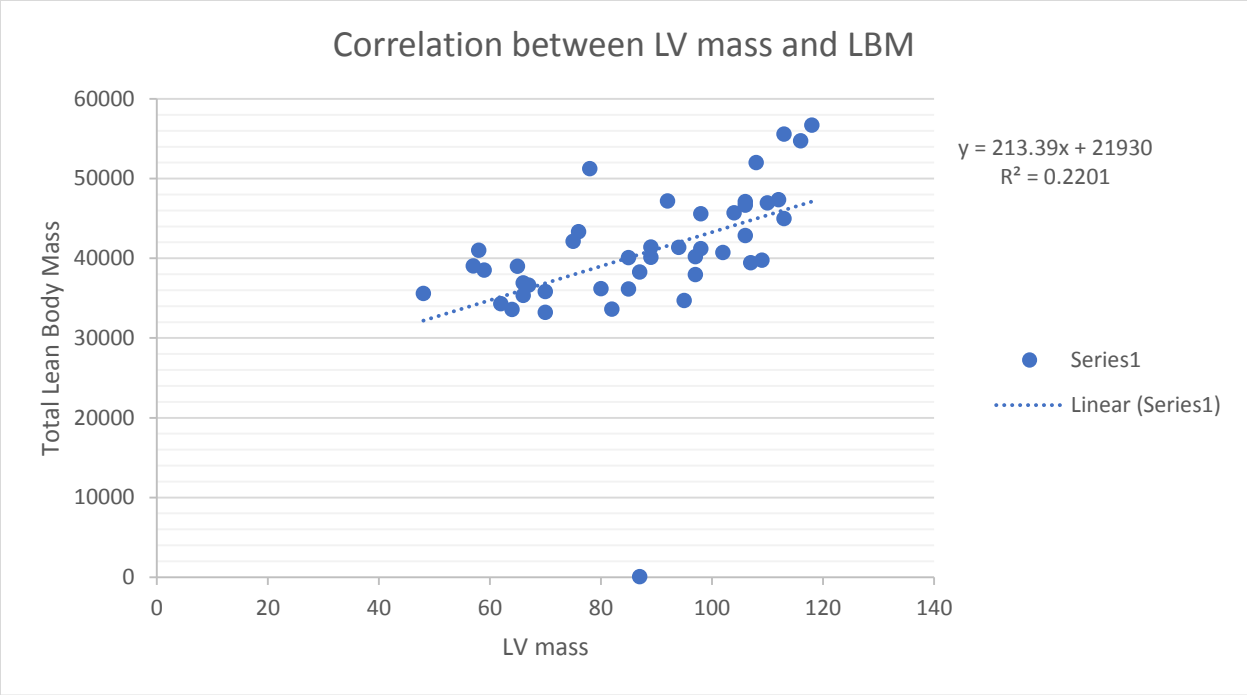
Baseline laboratory data was also collected for patients prior to starting chemotherapy (table 4).

Table 3.4 Baseline Laboratory Values

Serum creatine (normal 50-90 mmol/L)	Average: 67.7 (45 – 90)
Creatinine clearance	Average: 1.77 (0.91 – 3.48)
Total protein	Average: 74.59 (65 – 83)
Total bilirubin (normal 4-20)	Average: 9.36 (4 – 22)
ALT	Average: 28.03 (12 – 66)
AST	Average: 25.16 (16 - 46)
Alk Phos	Average: 72.64 (35 – 12)
LDH	Average: 158.84 (86 - 210)
Albumin	Average: 44 (38 – 49)

The Pearson correlation for LV mass to lean body tissue is 0.47 implying a moderate positive correlation. See Figure 3.1.

Figure 3.1 Correlation between LV mass and LBM



Given that organ function evaluates drug metabolism and excretion Akaike's Information Criterion (AIC) was used to assess if multiple variables increased the strength of the relationship between lean total muscle mass and LV mass and to measure quality of multiple models, with lower AIC values indicating closer prediction (Sawyer & Ratain, 2001) Univariate analysis of each parameter independently showed LV mass is predictive with an AIC value of 857.8. while a combination of all parameters in multivariate fashion show improvement in prediction with AIC= 851. The subset selection approach showed Adjusted R2 with four parameters had AIC=849.14, Schwartz's information criterion (BIC) with two parameters had AIC = 849.66, and Mallows' C Selection (Cp) model with three parameters (LV mass, cardiac output, and total bilirubin) having the least AIC = 848.71 value ($P < 0.001$).

Discussion

Early breast cancer, in spite of improvements in detection and treatment, remains a difficult and burdensome survivorship issue due to large population, multimodality treatment complexity and high level of disability after necessary treatments. We are the first to show that routine clinical assessments performed prior to chemotherapy can predict LBM. This data will inform a new chemotherapy calculation formula, the first improvement since the original 1916 BSA formula.

In 1916 DuBois and DuBois developed the BSA formula, at that time aiming to individualize dose in phase I trials. BSA was never intended to be used to determine the routine dosage for patient's chemotherapy (Sawyer & Ratain). Pinkel (1958) studied BSA in calculating chemotherapy dose, however, the pharmacokinetic properties of the drugs were never studied, and anticancer effects could not be compared with the toxic effects. Nonetheless, after Pinkel's study, BSA remained common practice. Since that time, multiple authors have critiqued BSA in chemotherapy treatment. Grochow, Baraldi, and Noe (1990) studied the relationship of pharmacokinetics with height, weight and BSA, showing that BSA did not predict pharmacokinetics of the drugs studied. Baker et al. (2002) reviewed 33 studies which included 1650 patients to determine if variability interpatient drug clearance could be explained with BSA. Their study showed that BSA dosed drugs only decreased interpatient variability in five agents. Renal clearance variability was reduced in 15% to 35% of the drugs, meaning that only one third of the variability can be explained by BSA. Liver function is important for drug metabolism, however, a relationship between liver function and BSA has never been established (Felici et al., 2002).

A comprehensive review by Sawyer et al., summarized the limitations of BSA, strongly recommending that investigators develop a formula that considers organ function and drug pharmacokinetics. None of the authors provided a practical, patient-specific alternative to BSA.

LV mass. Cardiac muscle is a striated muscle and undergoes atrophy caused by anorexia, HIV, bedrest, LV assist devices (Cosper & Leinwand, 2011; Hill & Olson, 2008; Pruznak et al, 2008; Gottidiener, Gross, Henry, Borer, & Ebert, 1978). Cosper and Leinwand assessed the effects that cancer has on LV mass in mice, showing a decreased LV mass within 27 days of tumor cells inoculum. Female mice initially gained LV mass and loss less LV mass compared to male mice with cancer. They gave the female mice fulvestrant an estrogen receptor antagonist to assess if estrogen protect LV mass. Post fulvestrant they found that the tumor bearing female mice had similar LV and body mass loss as tumor bearing male mice. Cosper and Leinward mice study also demonstrated that LV mass loss was due to decrease size in myocytes and not due to cell death. This study demonstrates that there is a relationship between LV mass and LBM as they undergo similar atrophy during the cancer process.

Cardiac Output. CO was one of the first parameters to be studied using BSA (Sawyer & Ratian, 2001). De Simone et al. (1997) study which included 970 adult and children demonstrated that there is relationship between BSA and CO.

Bilirubin. Despite there being established correlations between BSA and liver volume there has been no relationship found between BSA and liver oxidative metabolism (Sawyer & Ratian, 2001). Nawarante et al. (1998) showed that liver volume only had a modest correlation with LBM however LBM was the only parameter to be significantly correlated to hepatic clearance of antipyrine. Prado et al. (2011) study demonstrated that aspartate aminotransferase and LBM explained 33% of the variation in epirubicin clearance. One may postulate that this

relationship previously found between hepatic clearance of antipyrine and LBM maybe be the reason that total bilirubin was found to be predictive of LV mass.

Cancer treatment is known to have short and long-term toxic effects to all organ systems. Cardiotoxicity is life-threatening, even in the short-term. Guenancia et al. (2016) showed that being overweight or obese increased risk for developing cardiotoxicity after treatment with anthracyclines and trastuzumab in early breast cancer. Here, the cardiac risk factors of obese and overweight patients did not differ from the normal weight patients. Given that chemotherapy is hydrophilic and distributed to the LBM, which includes the cardiopulmonary, renal and skeletal muscle, using BSA may lead to the patient and their organ systems being ‘overdosed' with standard BSA chemotherapy dose calculation. Guenancia et al. (2016) literature reviewed pool results from 15 studies and demonstrated that being overweight or obese increased the risk for development of cardiotoxicity. The pooled odds ratio for overweight or obese breast cancer patients to develop cardiotoxicity following anthracycline or combination of anthracycline and trastuzumab was 1.38 (95% CI, 1.06 to 1.80 N= 8745). Prado et al. (2011) demonstrated that reduced LBM lead to greater incidence of toxicities and lower absolute neutrophil nadir in early breast cancer patients being treated with epirubicin. Prado et al. (2011) showed that lower LBM (41.6 kg vs. 56.2 kg) was associated with higher rates of grade one to four NCI common toxicities ($p=0.002$). Post cancer treatment, cancer survivors have 30% lower peak oxygen consumption than age and sex matched sedentary adults with no history of cancer (Haykowsky, et al., 2009; Jones, et al., 2007). One theory to explain why cancer patients have decrease peak oxygen consumption is that cancer patients may have developed cardiotoxicity and other treatment related toxicities including skeletal muscle that affect their exercise tolerance

(Adamsen, 2009), leading to cardiopulmonary dysfunction and fatigue, highly prevalent in breast cancer survivors.

Important research has previously been performed examining LBM and toxicity. Prado et al., (2009) showed that sarcopenia is evident in 25% of metastatic breast cancer patients, including those with normal weight. Grade two or higher toxicity (hand and foot syndrome, diarrhea, stomatitis, nausea, vomiting, neutropenia) was experienced by 50% of sarcopenic patients versus 20% of nonsarcopenic patients ($p=0.03$). However, outside of research-based body composition scan or calculated CT /MRI prior to our work, no practical approach for assessing LBM had been developed (Mourtzakis et al., 2008; Prado et al., 2009b).

Strengths

We have shown that LBM can be closely approximated with using clinically available parameters of LV mass, cardiac output and bilirubin. Cardiac MRI and iDxa scans were chosen for the TITAN study as they represent the gold standard of each imaging modality (Bellenger &Pennell, 1999; Bellenger, Davies, Francis, Coats &Pennell 2000; Fan et al., 2014). Cardiac MRI was also selected as it allows for a more a precise measurement of all metrics, therefore reduces the sample size required to demonstrate a relationship (Bellenger et al., 2000).

A strength of our study also represents a limitation, for cardiac MRI is not widely available. Next steps will validate the correlation observed in this study with 3D cardiac echocardiograms.

Limitations

This study was a prospective study where secondary analysis was completed on the baseline data collected in the TITAN study. The study participants were all female with early

stage breast cancer undergoing baseline cardiac assessment prior to their chemotherapy. Therefore, further research may be needed to extend the research findings to male patients and different cancer patients, including pediatric oncology patients.

Implications to Nursing

Breast cancer is a common female cancer that affects one in eight females (AHS, 2015). This research will potentially allow us to help change the way chemotherapy is dosed. The dose of chemotherapy agents influences the outcome of cancer therapy therefore it is important that the dose is appropriate for the patient and drug (Gurney, 1996). With more patients surviving breast cancer it is important that we reduce their risk of short and long term effects of anti-cancer therapy toxicities by ensuring individualized doses. Nurse Practitioners (NPs), as prescribers of chemotherapy, need to be cognizant of risks. As well registered nurses are involved in all aspects of oncology treatment, and by being involved in ongoing research and knowledge transfer to clinical practice will allow more opportunities to be proactive in minimizing potential adverse events rather than managing such event as they arise.

Conclusion

Cancer treatment has evolved over the last 50 years, and due to advances in screening, detection and treatment breast cancer patients have an increased five-year survival rate. Nonetheless, toxic treatment effects leading to organ dysfunction including cardiotoxicity are now leading to 3x risk of cardiac death within three years of treatment completion. We have demonstrated a strong relationship between LBM and LV mass, CO, and bilirubin with LBM, and that clinically relevant and available tests hold the potential to inform precise chemotherapy dose calculation. These findings may not only benefit cancer patients, but also inform treatment

of other major patient populations with devastating sarcopenia such as pediatric oncology, heart and kidney failure, and acquired immune deficiency.

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Chapter Four: Conclusion

This chapter serves as the conclusion for the information presented in this thesis. The purpose of this thesis was to explore the current practice of using BSA to dose chemotherapies, and the pitfalls associated with using BSA to dose chemotherapy and assess the current literature on how LBM can be used dose chemotherapy. In this study we examined 44 early stage breast cancer patients from the Cross Cancer Institute in Edmonton Alberta between 1 January 2015 and 31 March 2017 and assessed whether there was a relationship between LBM and LV mass and if LV mass could predict LBM. The results demonstrated that there is a moderate correlation between LBM and LV mass. With advanced statistical analysis we were able to demonstrate that the relationship between LBM and LV mass improved when multivariable analysis was completed. The AIC value was the strongest when LV mass, CO, total bilirubin was used to predict LBM.

Major discussion points

1. Breast cancer affects one in eight women and this equates to 25 700 women in 2016 being diagnosed with breast cancer in Alberta.
2. Currently chemotherapy is weight based and the dose is calculated using the patient's BSA. The goal of using BSA to dose chemotherapy is to provide personalized medicine and reduce interpatient variability.
3. However, the current literature demonstrates that there is a large amount of interpatient variability in regard to drug clearance and toxicities that is not accounted for by BSA.

4. The integrative review presented that patients with decrease weight, body size, or LBM experienced more short and long-term side effects from their breast cancer treatment. The studies that used body composition scans to determine a patient's body composition showed that there was a relationship between the amount of lean body tissue and the toxicities associated with breast cancer treatment.
5. Chemotherapy drugs are hydrophilic meaning they are distributed to the LBM, and LBM has been shown to predict drug clearance. The current literature shows that LBM maybe a better metric to use when dosing chemotherapy and may lead to decreased short and long-term side effects from chemotherapy. The studies that showed that body composition was predictive of toxicities used body composition scans or CT scans at the L3 region to determine the participants LBM. However, these methods of assessing LBM are not used in clinical practice. The goal of our study was to demonstrate that we can use a clinical relevant cardiac assessments to determine LBM.
6. Our study demonstrates that there is a moderate relationship between LV mass and LBM. When univariate analysis was completed for each parameter the results showed that LV mass is most predictive of LBM with an AIC of 857.8, while combination of all parameter in multivariate fashion show improvement in prediction with AIC 851. The subset selection analysis was also completed to select the parameters that were most predictive of LBM. Mallow's C Selection showed that LV mass, CO, and total bilirubin was most predictive of LBM with the smallest AIC 848.71 ($p<0.001$).

Implications for Nursing Practice

Within nursing practice there is a wide range of implications for the use of LBM in drug administration. Firstly, Registered Nurses (RN) administer medications to all patients. By understanding how the drug will be distributed allows the RN to provide holistic care to patients across a life span. The body composition of patients differs at different stages of their life. Therefore, the RN needs to understand that as a patient grow older it is normal for the patient to have less LBM and this will affect the drug distribution, clearance, and side effects. Older adults and patients with low LBM may experience increasing amount of toxicities or side effects from their medications. By having this knowledge will allow the RN to be adequately prepared to monitor for these events.

The second implication to nursing practice is to the Nurse Practitioner (NP) area. One element of a NP practice is to prescribe medications and monitor the effects the medications has on the patients. The NP needs to understand the volume of distribution of each medication and how body composition affects the medications distribution. Our study demonstrates that there is a relationship between LV mass, CO, total bilirubin and LBM and provides a direction for a future study to validate this relationship using a clinically available and inexpensive cardiac testing such as the echocardiogram. By being able to assess the patient's LBM with a clinically relevant test will provide the NP with insight to patients who may have decrease volume of distribution due to decrease LBM and allows for personalized medicine through customized prescribing of medications.

Strengths

The data for this thesis was collected from a current research study being completed at the Cross Cancer Institute and therefore providing information from current clinical practice. The

data was also collected at baseline and used early stage breast cancer patients prior to the patients being exposed to anticancer therapy. This is significant as the cancer process can affect the patient's body composition due to cancer cachexia and anticancer treatment also has an effect on patient's body composition. Also, we used the cardiac MRI to assess cardiac function and LV mass and DEXA scans to assess body composition, both of these tests are the gold standard for each modality. The first author was not involved in the clinical setting or data collection therefore providing an unbiased perspective to data analysis. The results and advanced statistical analysis was supported by an expert in the field.

Limitations

One of the limitations of the study was that the cardiac assessment was completed using cardiac MRI. Although this is the gold standard for the evaluation of the cardiac muscle this is not a test that is routinely used in cancer therapy. Being that the relationship demonstrated in the study was shown using the detailed cardiac MRI the results need to be validated using clinically relevant cardiac assessment. The next steps for the study is to validate the relationship found using 2D echocardiograms.

Conclusion

Our study is the first to our knowledge that looked for a relationship between LV mass and LBM. Our data analyses showed that there was a moderate relationship between LV mass and LBM and the relationship improved with subset selection using the Mallow's C Selection which indicated that together LV mass, CO, and total bilirubin was the most predictive of LBM.

This is the first step towards being able to challenge the current practice of using BSA to dose chemotherapy.

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Appendix A

Personalized care in the prevention of treatment related cardiac dysfunction in female cancer survivors*

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Abstract

The American Cancer Society projects the number of US cancer survivors to exceed 20 million individuals by 2026. However, approximately 1 in 4 cancer survivors report decreased quality of life due to physical dysfunction and disabling symptoms. Many effective anti-cancer treatments are now understood to be associated with cardiotoxicity, such that, for many survivors, the risk of death from cardiovascular disease now exceeds that of recurrent cancer. This Clinical Review of cancer treatment-related cardiac dysfunction (CTRCD) will discuss risks associated with standard treatment regimens, particular risks experienced by female cancer patients, and strategies for the community health care provider to provide personalized detection and CTCRD risk reduction in female survivors.

Keywords: risk reduction, rehabilitation, chemotherapy, survivorship, personalized health

Personalized care in the prevention of treatment related cardiac dysfunction in female cancer survivors

Introduction

One in two North Americans will be diagnosed with a malignancy at some point in their life (*Canadian Cancer Statistics* 2015; Miller et al., 2016). Given improvements in the understanding of cancer biology, improved detection and the use of novel adjuvant therapies, the number of cancer survivors is increasing at twice the rate of new cancer diagnoses (de Moor et al., 2013). The American Cancer Society projects the number of US cancer survivors to exceed 20 million individuals by 2026.(Miller et al., 2016) These successes, however, have introduced a unique and rapidly expanding chronic disease population, one presenting distinct challenges to the health system. Approximately 1 in 4 cancer survivors report decreased quality of life due to physical dysfunction and disabling symptoms as a result of the necessary treatments (Miller et al., 2016). Many effective anti-cancer treatments are now understood to be associated with cardiotoxicity, a broad spectrum of cardiac injury that encompasses heart failure, myocardial ischemia, hypertension and thrombogenesis (Truong, Yan, Cramarossa, & Chan). In fact, for many survivors, the risk of death from cardiovascular disease now exceeds that of recurrent cancer(Hanrahan et al., 2007). This growing population will contribute to the exponentially increasing costs of heart failure, estimated to increase from $31 billion in 2012 to $70 billion in 2030 (Heidenreich et al., 2013) Importantly, these estimates do not account for the individual costs to the patient and family associated with managing disabling symptoms, loss of work and independence and loss of life. This **Clinical Review** of cancer treatment-related cardiac dysfunction (CTRCD) will discuss risks associated with standard treatment regimens, particular risks experienced by female cancer patients, and strategies for the community health care provider to provide personalized detection and CTCRD risk reduction in female survivors.

Risks of standard anti-cancer therapies

The aims of oncology and cardiology care are completely opposed. Oncologic therapies disrupt vascular supply, interrupt mitosis and induce apoptosis, whereas cardiology care aims to re-establish angiogenesis, reperfusion and cell growth. Accordingly, for cancer survivors undergoing recommended treatments, the entire cardiovascular system (heart, blood vessels, lungs, skeletal muscle) is vulnerable to acute and chronic cardiovascular toxicity, morbidity and mortality(A. L. Jones et al., 2009; L. W. Jones, Haykowsky, Swartz, Douglas, & Mackey, 2007; Khakoo et al.; Lipshultz et al., 2013; Tichelli, Bhatia, & Socie, 2008; Tichelli, Rovo, & Gratwohl, 2008; Wang et al., 2014). Contemporary cancer care involves treatment modalities often combined for improved anti-cancer efficacy, but each increasingly recognized to cause CTRCD. As one example, breast cancer, the most common malignancy diagnosed in women (26% of all cases) is commonly treated with multiple modalities, administered concurrently or serially (for weeks to years) including anthracycline-based chemotherapies, monoclonal antibody-based therapies such as trastuzumab, radiation therapy involving the chest and/or mediastinum and anti-estrogen agents. Lymphoma, gynecologic and colorectal cancers(Miller et al., 2016), representing the majority of other female survivors, are also increasingly treated with these multimodality approaches.

Chemotherapy-induced cardiotoxicity is thought to be most commonly associated with anthracyclines (doxorubicin, epirubicin), however, all chemotherapy agents are potentially cardiotoxic, even at standard doses. An acceptable ceiling of doxorubicin dose is considered in the 400 – 450mg/m^2 range, allowing for an estimated 5% risk of developing overt heart failure. In 141 lymphoma patients assessed 5 years after completion of treatment, echocardiography demonstrated a decline in left ventricular (LV) function among 39 (27.6%) of patients.[24]

Importantly, only 8 of these 39 patients had received a doxorubicin dose > 300mg/m^2. Other chemotherapy agents associated with CTRCD include cyclophosphamide, cisplatin, ifosfamide and taxanes (docetaxel and paclitaxel), common agents in gynecologic, breast and lymphoma treatment regimens. Additionally, fluoropyrimidines routinely prescribed in colorectal cancers are associated with coronary vasospasm, which may occur acutely during 5-fluorouracil infusion or when therapeutic blood levels are achieved during a two-week treatment of oral capecitabine. Coronary vasospasm symptoms manifest in a spectrum, as subtle as indigestion or as major myocardial infarction, with resulting ischemia leading to CTRCD.

The timing of chemotherapy-associated cardiotoxicity is poorly understood, reported to occur acutely (during infusion), early (within the first year of therapy) and late (> 1 year) post-therapy.[3] Recent population-based data showed that within only 3 years of treatment completion, emergency room or hospital admission rates for heart failure in breast cancer survivors were 3 times that of age-matched controls(Thavendiranathan et al., 2016), showing that CTRCD is significant even in the short-term. In heterogeneous patients within and beyond 10 years of anthracycline exposure, abnormal cardiac function was observed among 18% of the former and 38% of the latter cohort,[26] indicating potential of very late development of LV dysfunction. Such findings imply an impending health issue for the >60 000 patients per year exposed to anthracyclines in the United States alone[27] and highlight the challenges in establishing personalized and effective surveillance guidelines and care pathways from treatment to survivorship.

Radiation directed to the thorax is a key therapy for many female cancer patients, including breast and lymphoma. Cardiotoxicity associated with radiotherapy exposure has been shown to increase over time, with 10 to 30% of patients having symptomatic heart disease by 5 –

10 years post-treatment and up to 88% of patients having asymptomatic abnormalities of ventricular function, conduction abnormalities and vasculature.[29] These effects are primarily related to radiation-induced fibrotic changes, with microvascular damage to the coronary vasculature accelerating age-related atherosclerosis. Chronic radiation-related effects may also manifest as pericardial disease (effusive, constrictive or both), dilated cardiomyopathy and valvular disease.[30] Lymphoma patients who present with bulky lymph node masses in the mediastinum or have evidence of isolated residual mediastinal disease, commonly receive radiation therapy after completing induction chemotherapy.[31,32] Adjuvant radiotherapy to the breast/chest wall in patients with left-sided breast cancers also results in exposure to the left ventricle. A retrospective analysis examined rates of myocardial infarction, coronary revascularization or cardiac death in 2168 women treated with radiation therapy between1958-2001.[33] Patients with left-sided breast cancers were noted to have a higher rate of major coronary events than right-sided patients, with events increasing linearly with the mean dose to the heart by 7.4% per Gray, with no apparent threshold. While approaches aiming to limit dose to heart and coronary vessels are now being employed (3-D planning, breath hold techniques, and patient positioning) data evaluating cardiovascular risk using these contemporary approaches are lacking.[34-36]

Targeted Cancer Therapies

Improved understanding of cellular activities and cancer pathways has led to the development of molecularly 'targeted' therapies contributing to improved cancer-specific outcomes in multiple patient populations. These agents are most effective when combined with chemotherapy drug regimens, as in lymphoma (rituxumab, doxorubicin, vincristine, and cyclophosphamide) and breast cancer (trastuzumab, carboplatin, doxorubicin, docetaxel,

epirubicin, and cyclophosphamide). However, the same pathways targeted in anticancer therapy are often the same cellular pathways essential for normal cardiovascular function. Epidermal growth factor receptors (ErbB) inhibitors such as trastuzumab, a HER2/neu directed antibody, indicated in approximately 20% of breast cancers, cause myocyte apoptosis, ventricular enlargement, and cardiac dysfunction in 15-20% of patients(Telli, Hunt, Carlson, & Guardino, 2007). A Cochrane review of trastuzumab randomized controlled trials in the adjuvant setting (11, 991 patients in 8 trials) showed a fivefold increase in the relative risk of heart failure and near doubling risk of LVEF decline.(Moja et al., 2012) Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, inhibits kinases and blocks PI3K/Akt activation and is a first-line therapy against hematological malignancies but with a 10-fold increased risk of atrial fibrillation, as well as fatal cardiac failure, stroke and severe bleeding events(Thompson et al., 2016). As these new agents are increasingly integrated into routine clinical care, potential 'off-target' effects leading to CTRCD must be considered, as the negative sequelae of chronic dosing are frequently not observed until after several months of therapy.

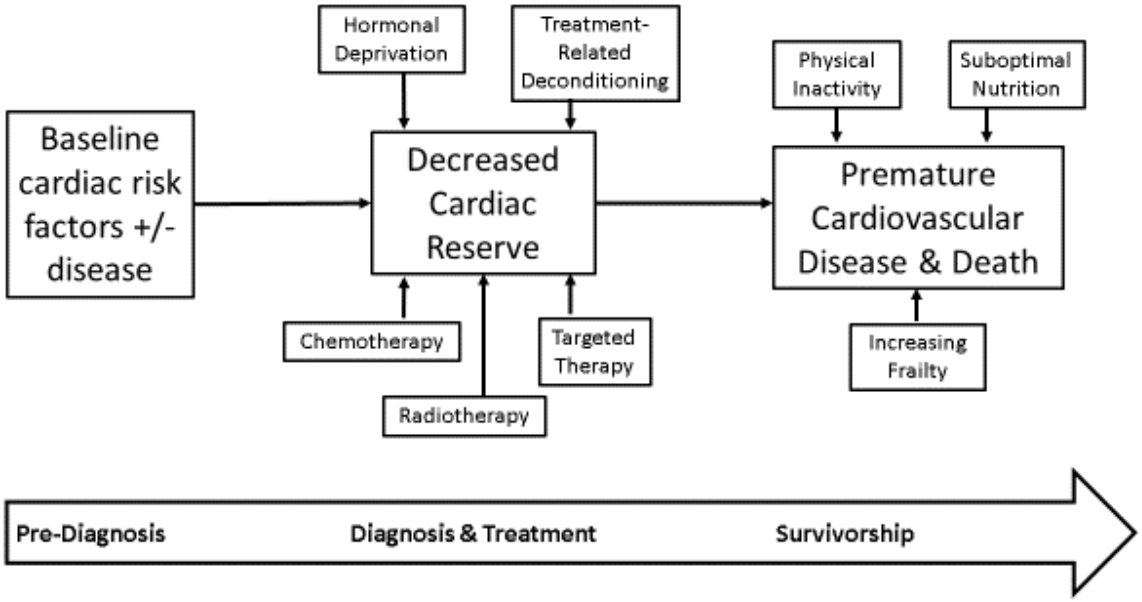
Female cancer survivors and increased risk of CTCRD

Women are more vulnerable to CTRCD due to multiple factors (Figure 1). Intravenous and oral chemotherapy drugs are hydrophilic, distributed in lean body compartment (muscles and organs). Chemotherapy dose is calculated by body surface area formula (BSA) using height and weight(Felici, Verweij, & Sparreboom, 2002), which does not account for the greater proportion of fat in female body composition, resulting in higher drug concentrations. Additionally, age-associated skeletal muscle atrophy is not accounted for in the BSA formula, again, increasing the risk of higher drug doses, greater toxicity and direct insults to organ function in older women(Prado et al., 2009; Prado et al., 2011).

The effects of anti-cancer treatment on the protective effects of estrogen on the cardiovascular system presents a unique risk of CTRCD. Younger women who undergo bilateral salpingo-oophorectomy as surgical treatment for gynecologic malignancy are accordingly at higher risk of coronary artery disease(Parker et al., 2009). Chemotherapy interferes with ovarian function, temporarily or permanently affecting menses, concerning for young females as early menopause conveys risk of premature coronary heart disease(Colditz et al., 1987). Patient age influences post-treatment menstrual status: among women receiving anthracycline-based regimens, menses resume in 50% of women younger than 40 years, but permanent amenorrhea occurs in the majority of women older than 40 (Walshe, Denduluri, & Swain, 2006). While estrogen therapy may be potentially useful to attenuate risk in gynecologic populations, such treatment is contraindicated in breast cancer survivors.

The cardiovascular system of female cancer patients is potentially more vulnerable to CTRCD, with low function commonly observed even before cancer therapy is administered. Cardiopulmonary function, measured as peak pulmonary oxygen uptake (VO_{2peak}) of cancer patients has been consistently demonstrated as 30% below age-matched healthy sedentary individuals (L. W. Jones, N. D. Eves, et al., 2007; L. W. Jones et al., 2008; Lee W. Jones et al., 2007) with a significant proportion of adult female cancer patients unable to meet the minimum threshold for independent living (VO_{2peak} of 15mL/kg/min)(Paterson, Cunningham, Koval, & St Croix, 1999). Consequently, female cancer patients commonly report fatigue and breathlessness, due to poor cardiopulmonary reserve and accordingly greater vulnerability to CTRCD and cardiac events (Thavendiranathan et al., 2016).

Figure 1: Model of female cancer patient at risk of CTRCD (Adapted from Jones(L. W. Jones, M. J. Haykowsky, et al., 2007 & Clegg Young, Iliffe, Rikkert, & Rockwood, 2013)



In patients able to participate in interventional studies, exercise can be effective and feasible during cancer treatment or survivorship to improve cardiopulmonary function(Scott et al., 2013). McNeely *et al* undertook a meta-analysis of randomized, controlled trials of exercise interventions in breast cancer patients(M. L. McNeely et al., 2006). In spite of significant heterogeneity in the timing of interventions, type of exercise interventions and reported outcomes in the individual studies, pooled results showed a moderate to large effect size of the effect of exercise on fatigue symptoms. Three of the included studies reviewed showed statistically significant improvements in quality of life measures; further, VO_{2peak} showed an improvement of 3.39mL/kg/min, or nearly 1 metabolic equivalent. In 122 lymphoma patients randomized to a 12-week supervised exercise intervention or usual care, exercise improved patient reported outcomes (physical functioning, overall QOL, fatigue, happiness, depression and

general health), cardiovascular fitness and lean muscle mass(Courneya et al., 2009). VO_{2peak} improved from 24.7 ± 7.2 mL/kg/min at baseline to 29.4 ± 8.6 mL/kg/min, a mean improvement of 4.6 mL/kg/min; the usual care group declined by 0.6 mL/kg/min. While the prognostic relevance of these improvements in adult cancer patients is not yet known, mortality risk has been shown to decrease by 12% for each 1-metabolic equivalent (**MET**) improvement in aerobic capacity in women(Gulati et al., 2003). Therefore, the importance of personalized exercise rehabilitation following cancer diagnosis and during treatment cannot be underestimated.

Pharmacotherapy is an attractive approach in prevention of CTRCD, for many patients are not capable or nor have access to facilities to perform routine exercise during treatment. We were the first to show that standard dose bisoprolol or perindopril can preserve cardiac function in breast cancer patients receiving trastuzumab-based chemotherapy regimens(Pituskin et al., 2016). No study-drug related adverse events occurred. Furthermore, delays in treatment were prevented, which in the long term may positively impact cancer outcomes. Based on these findings, international guidelines now recommend prophylactic therapy during cancer treatment in high risk patients(Virani et al., 2016; Zamorano et al., 2017).

Prevention of CTRCD during survivorship

Following completion of anti-cancer therapy, survivors are commonly referred back to the care of the primary care provider, who is challenged to maintain competency in the rapidly changing oncology treatment environment. Survivorship care plans, summarizing the treatment modalities, doses administered, diagnostic imaging and laboratory results, ongoing (and potential) side effects and recommendations for surveillance are extremely helpful tools for both the survivor and primary care provider(LaGrandeur, Armin, Howe, & Ali-Akbarian, 2018).

Clinical surveillance.

The American Society of Clinical Oncology Clinical Practise Guidelines recommend careful history and physical examination in cancer survivors treated with potentially cardiotoxic regimens(Armenian et al., 2017). Serial screening for clinical signs of CTRCD should be routinely performed, such as crepitations on lung auscultation, elevated jugular venous pressure, edema and weight gain. Serial review of symptoms is also recommended, to detect early changes such as increasing fatigue or exercise intolerance, which may indicate underlying, sub-clinical cardiac dysfunction (Schunemann, Anker, & Rauchhaus, 2008). Cardiac diagnostic imaging may be considered as a baseline assessment to assist with evaluation and potential referrals, however, there are no known benefits of continued surveillance in asymptomatic survivors.

Cardiovascular Risk Reduction and Healthy Living.

Modifiable risk factors which precipitate CV disease are also established factors that exacerbate CTRCD. Hypertension, smoking, diabetes and dyslipidemia are significantly associated with increased risk(Advani, Ballman, Dockter, Colon-Otero, & Perez, 2016; Goldhar et al., 2016; Hooning et al., 2007; Pinder, Duan, Goodwin, Hortobagyi, & Giordano, 2007; Romond et al., 2012) . Regular evaluation and personalized management of cardiovascular risk factors including smoking, hypertension, diabetes, dyslipidemia and obesity is recommended (Armenian et al., 2017). The ongoing relationship between the survivor and primary care provider is key for successful management and CVD treatment adherence(Feehan et al., 2017). Systematic reviews have shown that poor psychosocial well-being in women with heart failure is associated with negative views of self-management(Thomas & Clark, 2011) . Distress is highly prevalent in breast cancer patients in the early survivorship phase, with up to 56% of patients reporting persistent fatigue, worry and anxiety at one year(Lester et al., 2015) . Furthermore, few women perceive cardiovascular disease as a major threat to their lives, in spite of heart disease

and stroke the primary killer of American females(Kochanek, Murphy, Xu, & Tejada-Vera, 2016). In a survey of 1654 women, less than ¼ could identify hypertension or dyslipidemia as risk factors of cardiovascular disease, and less than half could identify major cardiac symptoms such as pain or shortness of breath(McDonnell et al., 2014). Female cancer survivors would potentially benefit from cardiac rehabilitation educational programming, aiming to better understand their risk for CTRCD, and the need for clinical surveillance and adherence to therapy.

A heart-healthy lifestyle including diet and exercise is also recommended for cancer survivors in prevention of CTRCD. The American Cancer Society Guidelines on Nutrition and Physical Activity advise three general categories of intervention, including weight management, physical activity and diet quality (Table 1) (Rock et al., 2012).

Table 1. The American Cancer Society Guidelines on Nutrition and Physical Activity

Achieve and maintain a healthy weight
• If overweight or obese, limit consumption of high-calorie foods and beverages and increase physical activity to promote weight loss
Engage in regular physical activity
• Avoid inactivity and return to normal daily activities as soon as possible after diagnosis
• Aim to exercise at least 150 minutes per week
• Include strength training exercises at least 2 days per week
Achieve a dietary pattern that is high in vegetables, fruits, and whole grains

Female cancer survivors face multiple challenges adopting regular exercise, not only due to family and financial concerns, but additional physical treatment-related dysfunctions. Chemotherapy-induced peripheral neuropathy (**CIPN**) is a debilitating effect thought to result from damage to peripheral nerves, including motor, sensory and autonomic. Neurotoxic chemotherapy agents include taxanes, platinum analogues, vinca alkaloids, and fluoropyrimidines, routinely prescribed in breast, gynecologic, lymphoma and colorectal cancers. The incidence of CIPN varies with each individual agent, however, chemotherapy regimens are

routinely prescribed as 2 – 3 drug combinations, as in breast (docetaxel, carboplatin) and gynecologic cancers (paclitaxel, cisplatin) affecting nearly 100% of patients during and after treatment. Symptoms most commonly experienced are sensory neuropathies, including paresthesias and pain(Pachman, Barton, Watson, & Loprinzi). However, CIPN may also manifest as persistent polyneuropathies affecting strength, balance and function(Visovsky & Daly, 2004) which may be permanent and present challenges in planning safe exercise activities. Involving physiotherapy expertise in the multidisciplinary team can assist in assessing for assistive devices and developing an exercise program, especially important considering that aerobic and/or resistance exercise may reduce pain and improve physical functioning(Stubblefield, McNeely, Alfano, & Mayer, 2012).

Lymphedema is a common and disabling sequelae of breast cancer treatment, associated with recurrent infections in the affected limb, functional impairment and pain. Reported incidence rates vary significantly, ranging from 2 – 65%, influenced by multiple variables including surgical techniques, axillary sampling, radiotherapy fields and chemotherapy regimen(Shah & Vicini). When treated conservatively in the earliest stages, complications of lymphedema may be diminished or reversed(Stout Gergich et al., 2008). Compressive garments and bandaging offer a low-cost and symptomatically effective approach. Manual lymphatic drainage, consisting of intensive massage therapy provided by experienced physiotherapists, may be beneficial in some patient groups(M. McNeely et al., 2004), or in those where compressive garments are not sufficiently effective(Margaret L. McNeely, Peddle, Yurick, Dayes, & Mackey). Recent systematic reviews have shown that exercise does not exacerbate existing lymphedema in breast cancer survivors, rather, structured exercise interventions reduce severity of symptoms and improve shoulder range-of-motion(M. L. McNeely et al.). These findings are

additionally relevant, as weight loss (which may be induced with exercise) has been shown to reduce upper extremity lymphedema volume by 44%(Margaret L. McNeely et al.; Shaw, Mortimer, & Judd, 2007). Taken together, personalized regular exercise should be considered the cornerstone of care for female cancer survivors.

Future directions

With the exponentially increasing numbers of cancer survivors in the context of health systems with limited resources, evidence-based personalized care for survivors is urgently required. Prediction tools have been developed in various specialties with the intent of providing some degree of personalized health care. However, no such tool exists for personalized risk prediction of CTRCD, and to develop such models, large prospective registries are necessary to identify and quantify baseline and treatment-related risk factors for CTRCD(Chen, Colan, & Diller, 2011; Parent, Pituskin, & Paterson, 2016). We anticipate that such an algorithm could serve both as a personalized care plan for patients and providers, available on handheld devices to provide guidance regardless of urban or community setting.

Conclusions

With the increasing numbers of cancer survivors in North America(*Canadian Cancer Statistics* 2015; Miller et al., 2016), increasing awareness of the short and long term effects of the necessary treatments is required. Survivors with CTRCD represents an entirely new population at risk of morbidity and mortality. With better understanding of the unique risks, with holistic primary care CTRCD in female cancer survivors may be attenuated.

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Appendix B

The Role of Cardio-Oncology in the Interprofessional Care of Adult Patients Receiving Cancer Therapy*

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Abstract

Objective: To discuss the toxic effects of therapy to the structure and function of the cardiovascular system and the role of the cardio-oncology team in the interprofessional care of adult patients, including current approaches, research findings, and future endeavors

Data source: Published articles, and international cardiology and oncology association guidance documents.

Conclusion: Although a new field of study, cardio-oncology is a rapidly expanding area of great clinical need. Evidence is only now accumulating, with most guidelines based on opinion or extrapolated from cardiovascular literature. Oncology care providers face complex decisions on a daily basis, whether before, during or following definitive cancer treatments.

Implications for Nursing Practice: In the era of both traditional and targeted cancer therapies, the long term side effects to the cardiovascular system and consequently the needs of cancer survivors are increasingly complex. Accordingly, oncology nurses must not only be aware of such potential effects, but conduct careful serial symptom review and consider risk reduction and cancer rehabilitation strategies across the disease trajectory.

*Keywords***:** cardiotoxicity, heart failure, chemotherapy, prevention, rehabilitation, symptom screening, interprofessional collaboration

The Role of Cardio-Oncology in the Interprofessional Care of Adult Patients Receiving Cancer Therapy

Introduction

With improved understanding of cancer biology, early detection and multimodal adjuvant therapies, an increasing number of North Americans are surviving cancer diagnosis and treatment. The American Cancer Society projects the number of US cancer survivors to exceed 20 million individuals by 2026.(Miller et al., 2016) Currently, the number of survivors is increasing at twice the rate of new cases.(de Moor et al., 2013) Cancer therefore represents a new 'chronic' disease that many patients will experience and survive, however, one that often requires complex interprofessional medical management and resource utilization over many years.

Toxicities associated with many effective and commonly prescribed adjuvant therapies may persist for many years. In particular, toxic effects to the structure and/or function of the cardiovascular system, or 'cardiotoxicity' may lead to arrhythmias, heart failure and, in some patients, death.(Wells & Lenihan, 2010) In fact, for many survivors, the risk of death from cardiac disease now exceeds that of recurrent cancer.(Hanrahan et al., 2007) Aiming to manage these potentially devastating effects, a new sub-specialty in cancer care has emerged, a combination of cardiology and oncology called 'cardio-oncology' or 'onco-cardiology'. The aim of this review is to discuss the role of the cardio-oncology team in the interprofessional care of adult patients, including current approaches, research findings, and future endeavors. While specific tumor types are referenced here, the observations may be applicable to different tumor types (for example, patients with esophageal cancer) who face new risks as treatment recommendations evolve.

Definition and Detection

Left ventricular (LV) dysfunction and heart failure represent the most concerning and potentially life-threatening cardiovascular toxicities, characterized by poor pump function and potentially associated with clinical symptoms such as fatigue, shortness of breath, poor exercise tolerance and peripheral edema. There are several challenges in the clinical detection of cardiotoxicity. Symptoms such as dyspnea, fatigue and edema (the cardinal symptoms of heart failure) are common among cancer patients and are difficult for the practitioner to distinguish from true cardiac causes.'(Chu et al., 2007; Force & Kerkela, 2008) Further, the routine assessment of cardiac symptoms, vital signs(Fromme, Eilers, Mori, Hsieh, & Beer, 2004; Janjan & Cleeland, 2008), and the screening of cardiac risk factors are infrequently performed in the oncology outpatient setting(Lenihan & Esteva, 2008; Wilson et al., 1998), and symptoms of fatigue and dyspnea are typically not pursued (38% and 77% of the time, respectively). (Fromme et al., 2004)Current guidelines arbitrarily define cardiotoxicity as a drop in LV ejection fraction (EF) by >10 points to a value of <53%.(Plana et al., 2014). However, in oncology patients receiving anti-neoplastic treatments, LVEF of at least 50% has been considered adequate functioning. Identification of cardiotoxicity relies on the routine ordering of baseline and surveillance imaging tests aimed at identifying changes in LVEF. Many patients will have up to five serial imaging tests performed (some modalities involving radiation exposure) over a routine course of chemotherapy.

The predominant therapies associated with cardiotoxicity are anthracycline-based chemotherapies, monoclonal antibody-based therapies (anti-HER2 agents) such as trastuzumab, and radiation therapy involving the chest and/or mediastinum. Other classes of anti-neoplastic therapies, such as alkylating agents, anti-microtubule agents, anti-estrogen agents, and several

others are also recognized for cardiac complications, however associated declines in heart function are less common.(Truong, Yan, Cramarossa, & Chan, 2014) Indeed, with the common use of multi-modality treatments, cardiotoxicity represents a wide spectrum of additional cardiac injuries that include tissue inflammation, electrophysiologic instability, changes in blood pressure control, myocardial ischemia, and thrombogenesis.(Truong et al., 2014)

Cardiotoxicity has been previously shown to be related to cumulative dose exposure to anthracyclines**.** An "acceptable ceiling" dose of doxorubicin dose is thought to be in the 400 – 450mg/m^2 range, allowing for an estimated 5% risk of developing overt heart failure. One study of 135 consecutive lymphoma patients treated with standard dose of anthracyclines showed that early onset cardiac toxicity was identified clinically in 27 (20%) at 1 year.(Limat et al., 2003) Among these, 14 patients had clinical signs of heart failure attributable to their treatment, and 3 patients died from cardiac causes. Another study by Hequet, et al.(Hequet et al., 2004) in 141 lymphoma patients assessed outcomes at 5 years post-chemotherapy, demonstrating a drop in LV function among 39 (27.6%) of patients by echocardiography. Importantly, only 8 of the 39 patients had received a doxorubicin dose > 300mg/m^2, indicating that even conservative doxorubicin dosing conveys long-term cardiac sequelae.

A high prevalence and negative influence of cardiovascular risk factors in breast cancer patients has been observed.(Jones, Haykowsky, Peddle, et al., 2007; Jones, Haykowsky, Pituskin, et al., 2007) Patient characteristics predicting the development of anthracycline-related cardiomyopathy include concurrent cardiac irradiation, hypertension, coronary artery disease, and age > 65 years and those with ≥3 or more risk factors are known to have a fivefold increased risk compared to low risk patients.(Wells & Lenihan, 2010)·(Lotrionte et al., 2013) Additionally, the timing of chemotherapy-associated cardiotoxicity is poorly understood, reported to occur

acutely (during infusion), early (within the first year of therapy) as well as late (> 1 year) post-therapy.(Wells & Lenihan, 2010) This poses a significant challenge in establishing appropriate surveillance guidelines and care pathways. While studies evaluating serial standardized measures of LV function have been performed, most of these have been small (n<100 patients) and of insufficient size to adequately identify subgroups likely to experience early versus later onset disease. A cross-sectional study explored the prevalence of LV dysfunction among patients with prior anthracycline therapy, and compared those within and beyond 10 years from their index exposure. While confounders likely exist, abnormal cardiac function was observed among 18% of the former and 38% of the latter cohort suggesting a potential for (very) late development of LV dysfunction – potentially beyond 10 years.(Steinherz, Steinherz, Tan, Heller, & Murphy, 1991) Such findings would imply a looming health issue for the >60 000 patients per year exposed to anthracyclines in the United States alone.

Radiation is a key therapy for many cancer patients, directed to the thorax among many common patient groups including breast, lymphoma, and testicular cancer. Cardiotoxicity associated with radiotherapy is a well-established phenomenon and has been shown to increase in prevalence with time from exposure, with 10% - 30% of patients having symptomatic heart disease by 5 – 10 years post-treatment and up to 88% of patients having asymptomatic abnormalities of the heart muscle, valves, conduction abnormalities or vasculature.("Effects of Radiotherapy and Surgery in Early Breast Cancer — An Overview of the Randomized Trials," 1995) These effects are primarily related to radiation-induced fibrosis and scarring of the heart tissues, with microvascular damage thought to incrementally occur to the coronary vasculature. The latter may accelerate age-related atherosclerosis and the development of obstructive coronary artery disease. Radiation therapy to inner-quadrant tumors of the chest (including

internal mammary chain) has also been shown to increase cardiovascular events, with 2.3-fold increased risk of cardiovascular death.(Bouchardy et al., 2010) Chronic radiation-related effects may also be manifested as pericardial disease (effusive, constrictive or both), dilated cardiomyopathy, conduction abnormalities, and valvular disease.(McGale et al., 2011) This may be of particular concern for lymphoma patients who present with bulky lymph node masses in the mediastinum, or have evidence of residual disease after completing induction chemotherapy.(Pugh et al., 2010; Xu et al., 2013) Adjuvant radiotherapy to the breast/chest wall in patients with left-sided breast cancers also results in a non-negligible exposure to the heart from ionizing radiation. A retrospective analysis examined rates of myocardial infarction, coronary revascularization, or cardiac death in 2168 women treated with radiation therapy between 1958-2001.(Darby, Ewertz, & Hall, 2013) Patients with left-sided breast cancers were noted to have a higher rate of major coronary events than right-sided patients, with events increasing linearly with the mean dose to the heart by 7.4% per Gray, with no apparent threshold. While approaches aiming to limit dose to heart and coronary vessels are now being employed (3-D planning, breath holding techniques, and patient positioning) data evaluating contemporary cardiovascular risk using these approaches are lacking.(Cutter et al., 2015; Darby et al., 2010; Darby, Ewertz, McGale, et al., 2013)

Cardiotoxicity in the Era of Targeted Cancer Therapy

The development of molecularly 'targeted' therapies (kinase inhibition, or KI) has contributed substantially to improved outcomes in multiple patient populations. Among the success stories are imatinib, which has dramatically improved survival for patients with chronic myeloid leukemia; sunitinib, an inhibitor of vascular endothelial growth factor (VEGF), which has improved the outcomes of renal cell cancer patients; and trastuzumab, which has

significantly improved survival in breast cancer patients with overexpression of the receptor tyrosine kinase HER2.(Slamon et al., 2011; Vogel et al., 2002)

The classic toxicities associated with chemotherapy, such as alopecia, myelosuppression, mucositis, nausea, and vomiting, may now be replaced by a different (and potentially equally debilitating) toxicity profile, including vascular, endocrine, coagulation, pulmonary and cardiac toxicities.(Dy & Adjei, 2013) For example, VEGF inhibitors are associated with dose-limiting hypertension, thrombosis, and cardiomyopathy.(Bair, Choueiri, & Moslehi, 2013) Ibrutinib, while an effective bruton tyrosine kinase inhibitor, has presented unexpected toxicities. In 56 chronic lymphocytic leukemia patients treated with ibrutinib, atrial fibrillation occurred in 5%-9% of patients and was persistent in 35/56 (62%) cases despite treatment. Other events included 3 episodes of severe cardiac failure (one fatal), one stroke and in 8 (14%) non-thrombocytopenic patients, severe bleeding adverse events occurred. Ibrutinib was permanently discontinued in 26 of 56 cases (46%) with the authors concluding that cardio-oncology expertise is essential for patient safety.(Thompson et al., 2016) Trastuzumab is a HER 2/neu directed antibody, indicated in approximately 20% of breast cancer cases. A Cochrane review of trastuzumab randomized controlled trials in the adjuvant setting (11, 991 patients in 8 trials) showed a fivefold increase in the relative risk of heart failure and near doubling risk of LVEF decline.(Moja et al., 2012) It is important to consider that the risk of developing cardiotoxicity may be considerably higher in the community among patients whom may not have met stricter clinical trial criteria. Bowles et al(Bowles et al., 2012) performed a population-based study of 12,500 breast cancer patients and found that the incidence of heart failure and/or cardiomyopathy was more than four times higher (hazard ratio (HR) =4.12) for trastuzumab therapy alone, and more than seven times greater (HR=7.19) for anthracycline plus trastuzumab five years following treatment initiation. Of note,

some authors have suggested that trastuzumab-related cardiotoxicity may be 'reversible, however this has not been reliably observed.(Ewer et al., 2005) For example, Wadhwa, et al(Wadhwa et al., 2009) noted that of 36 of 152 (22%) patients that stopped trastuzumab due to LV systolic dysfunction, even with optimal cardiac treatment, 14/36 (40%) showed no improvement or worsening LVEF over time. Taken together, cardiomyopathy associated with targeted agents presents a major clinical issue in both short and long-term.

Referral Recommendations

Expert opinion has defined cancer therapeutic related cardiac dysfunction as a decrease in LVEF by > 10% to a value < 53%, with significant changes from baseline requiring prompt referral to cardio-oncology expertise.(Plana et al., 2014) Unfortunately, when LV dysfunction is detected, cardio-oncology services are consulted late, if at all, and improvement in clinical cardiac outcomes is not always possible. Cardinale and colleagues(Cardinale et al.) showed a four-fold decrease in the chance of complete recovery from cardiac dysfunction for each doubling in time-to-heart failure treatment (measured in weeks), emphasizing the urgency for early cardio-oncology referral and intervention. Furthermore, given the wide spectrum of potential cardio-oncology concerns, LVEF is not the only consideration. Accordingly, we have proposed common scenarios and recommend timely referral to cardio-oncology expertise depending on patient status and treatment plan (Table 1).(Parent, Pituskin, & Paterson, 2016) For patients currently undergoing or under consideration for active cancer therapy, symptomatic heart failure or angina, or uncontrolled arrhythmia or hypertension, we recommend urgent cardio-oncology consultation within a 2 week timeframe. A semi-urgent referral should be considered for stable patients with a new or existing heart failure diagnosis. In patients or

survivors with stable cardiovascular disease, we advise a routine cardio-oncology referral within 6 weeks.

Table 1. Suggested referral times for common cardio-oncology scenarios

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Suggested referral time	Clinical scenario
Urgent (<2 weeks)	New referral, active cancer therapy pending or ongoing Progressive heart failure New or worsening angina Uncontrolled arrhythmia Uncontrolled hypertension Post-hospitalization heart failure
Semi-urgent (<4 weeks)	New diagnosis of heart failure, compensated Heart failure with mild to moderate symptoms (New York Heart Association class II – III)
Scheduled or routine (< 6 weeks)	New referral with stable cardiovascular disease, no active cancer therapy

Parent S, Pituskin E, Paterson DI. The Cardio-oncology program: a multidisciplinary approach to the care of cancer patients with cardiovascular disease. *Can J Cardiol.* 2016;32(7):847-851.

Prevention of Cardiotoxicity

While evidence is slowly accumulating, current cardio-oncology recommendations are largely based on opinion, or extrapolated from cardiology literature. In terms of preventive strategies, the American Society of Clinical Oncology (ASCO) clinical practice guideline refers

to screening and active management of modifiable cardiovascular risk factors.(Armenian et al., 2016) The major modifiable risk factors for cardiovascular disease are well-established, and include tobacco use, high blood pressure, high cholesterol, alcohol use, obesity and physical inactivity. The Canadian Cardiovascular Society has modified the American College of Cardiology/American Heart Association guideline, with approaches suggested for each stage (Table 2).(Abdel-Qadir, Amir, & Thavendiranathan, 2016)

Table 2. Stages of heart failure modified from Canadian Cardiovascular Society/American College of Cardiology/American Heart Association guidelines.

Stage	A	B-1	B-2	C	D
Definition	At high risk for HF	Occult LV dysfunction	Overt LV dysfunction	Symptomatic HF, responsive to conventional therapy	Symptomatic HF, unresponsive to conventional therapy
LVEF	No detectable cardiac dysfunction	LVEF > 53%, abnormal strain and/or biomarkers	LVEF < 53%	LVEF < 53%	LVEF < 53% (usually much lower)
Symptoms	Asymptomatic	Asymptomatic	Asymptomatic	Symptomatic	NYHA Class IV
Key management consideration	Aggressive treatment of CV risk factors	Aggressive treatment of CV risk factors	Add ACE-I/ARBs, β-blockers per guidelines	Add aldosterone antagonists, with consideration of diuretics, digoxin, device therapy	Establish goals of care. If appropriate, consider inotropes, mechanical support,

					transplant.
Area for further research	Prophylactic therapies such as dexrazoxane, ACE-I/ARBs, statins	Protective therapies such as dexrazoxane, ACE-I/ARBs, statins	Threshold for initiation of protective therapy (LVEF < 53% rather than 40%)	Therapy discontinuation in recovered patients	Criteria for consideration of advanced therapies
Role of further cardiotoxic chemotherapy *	Continue	Continue	Personalized decision making, with preference for continuation or temporary discontinuation	Personalized decision making, with preference for interruption	Discontinue

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular, HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

* Recommendations predominantly based on experience with breast cancer patients.

(Abdel-Qadir et al., 2016)

Here, multi-modality prevention of cardiotoxicity includes not only treatment of cardiovascular risk factors, but consideration of prophylactic heart failure pharmacotherapies. In

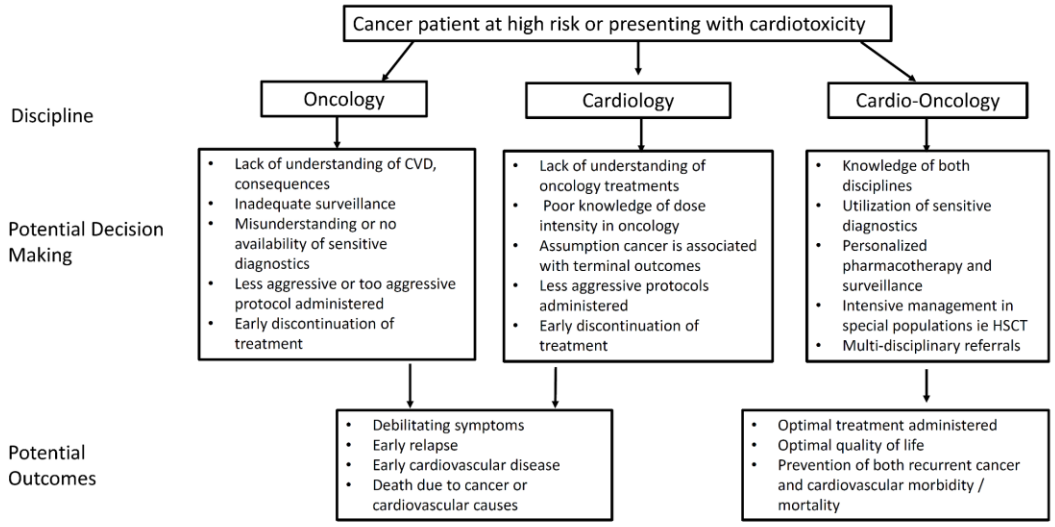
a placebo-controlled randomized clinical trial, we showed that bisoprolol or perindopril not only prevent trastuzumab-related LV dysfunction in HER2-overexpressing breast cancer patients, but also prevent delays in necessary treatment.(E. Pituskin, J. R. Mackey, et al., 2016) Importantly, these medications were well-tolerated with no treatment-related events, showing that community-based oncology providers can safely integrate these measures into usual care.

Certain patient populations may be at especially high risk of cardiotoxicity, for example, those requiring high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT). It is well established that HSCT survivors experience significantly increased cardiovascular death and heart failure compared to population-based controls.(Chow et al.) In this vulnerable population, diligent screening and risk factor management is indicated. Such assessments and referrals are ideally performed by a nurse practitioner, with experience in both oncology and cardiology. In serial patients (n = 231) referred for consideration of transplant, systematic screening by a nurse practitioner resulted in 20% (n = 46) requiring cardio-oncology interventions.(E. Pituskin, N. Cox-Kennett, et al., 2016) Common problems included decreased LV function, abnormal LV wall geometry and arrhythmia. Following cardio-oncology interventions, 100% of patients who remained eligible proceeded safely to HSCT. During the HSCT treatment, prevention of cardiotoxicity is also possible. In a randomized controlled trial in 90 patients undergoing HSCT, combined treatment of enalapril and carvedilol not only prevented cardiac dysfunction, but lowered the risk of death.(Bosch et al., 2013) Again, risk reduction maneuvers should universally be recommended, with additional consideration taken regarding multi-modal and/or high-intensity treatment approaches required in many malignancies. Ideally, cardio-oncology team assessments and preventive care should be seamlessly integrated throughout treatment and survivorship whenever possible.

Future Considerations

As a new field of study, 'cardio-oncology' has few experts, and those with experience are located within major urban and academic centers. As a result, not only is prompt referral (as recommended by guidelines) to cardio-oncology clinics frequently difficult, but patients may subsequently receive sub-optimal care based on the limited experience and training background of available providers. (Plana et al., 2014) Figure 1 outlines potential decision making and associated clinical outcomes of cancer patients at risk or presenting with cardiotoxicity. This is supported by the findings of an international cardio-oncology survey (n = 393) that included a clinical scenario of trastuzumab-related cardiotoxicity(Sulpher et al., 2015). Twenty percent of cardiologists recommended discontinuing treatment permanently compared to 7% of oncologists. Optimizing cardiac pharmacotherapy was chosen by 52% of cardiologists but only 22% of oncologists. These findings highlight potential discrepancies between the approaches of cardiology and oncology providers and the need for effective and evidence-based cardio-oncology guidelines.

Figure 1. Potential decision making and outcomes of cancer patients at risk for cardiovascular disease depending on assessing discipline.



The natural history of cardiotoxicity among cancer survivors remains poorly understood. Specifically, the frequency of symptomatic LV dysfunction and potential impacts on morbidity and mortality are unknown. Large patient registries with informative and comparable data points need to be developed internationally. Ideally, these registries would also include diagnostic imaging and biomarker data to inform optimal scheduling and informative modalities.(Marwick, 2016) There is great interest in development of personalized risk algorithms to direct surveillance, treatment and rehabilitation. Such algorithms would evaluate prior or current cardiovascular risk while considering the degree of anticipated toxicity of each treatment modality, ultimately informing optimal supportive and survivorship care plans.(Abdel-Qadir et al., 2016) Again, large registry datasets are required in the development of such algorithms. 'Real-world' testing of these algorithms will assess effectiveness and value, not only to the system but to the cancer survivor.

To assess the impact of cardiotoxicity on quality of life in cancer survivors, systematic screening over the disease trajectory is necessary. Patient-reported outcomes should be serially evaluated and linked to cancer therapies and diagnostic tests, again in large-scale registries. As

one example, the 'Screening for Distress' tool is routinely used across the cancer continuum (tertiary to palliative home care) and has been adopted in a pan Canadian effort.(Bultz et al., 2011; Waller, Garland, & Bultz, 2012; Watson et al., 2016) Similarly, the National Comprehensive Cancer Network (NCCN) Survivorship Guideline advises routine assessment for common consequences of cancer and cancer treatment.(Denlinger et al., 2016) Serial assessments with such validated tools allows not only comparison of patient-reported symptoms over time, but may provide early identification of symptomatic cardiotoxicity to the oncology nurse.

ASCO guidelines advise management of modifiable cardiovascular risk factors, with recommendations based on established multidisciplinary cardiac rehabilitation programs. Smoking and tobacco consumption, dyslipidemia, hypertension, poor diet, excessive alcohol intake, obesity and stress are all effectively addressed with such programs.(Balady et al., 2011) However, level 1 evidence for such an approach in the oncology population is lacking. To address this problem, the TITAN study (multidisciplinary Team IntervenTion in cArdio-oNcology) was designed as a randomized study comparing intensive multidisciplinary team intervention to usual care in the prevention of LV remodeling in patients receiving anthracycline or trastuzumab-based chemotherapy.(E. Pituskin, M. Haykowsky, et al., 2016) Another question that will be addressed by the TITAN study is the optimal cardio-oncology team complement and effect on quality of life over the treatment and recovery trajectory. Cardiac rehabilitation has had a long history of multidisciplinary care provision, with involvement of nursing, dieticians, psychologists, pharmacists and exercise therapists, but the effectiveness of this approach in oncology populations has not been formally tested. We are also evaluating a pilot project of integrated multidisciplinary cardiac rehabilitation in HSCT patients, assessing not only physical

capacity but the contributions of other rehabilitation specialists as well.(Edith Pituskin et al., 2016) Such projects will not only inform the effectiveness of such supportive care, but take into consideration preferences and abilities of the individual patient.

Conclusion

Although a new field of study, cardio-oncology is a rapidly expanding area of great clinical need. Evidence is only now accumulating, with most guidelines based on opinion or extrapolated from cardiovascular literature. .In the era of both traditional and targeted cancer therapies oncology care providers face complex decisions on a daily basis, whether before, during or following definitive cancer treatments. Oncology nurses must not only be aware of potential effects side effects to the cardiovascular system, but conduct careful serial symptom review and consider risk reduction and cancer rehabilitation strategies. Multicenter interprofessional collaborations and large-scale research projects are necessary to inform best cardio-oncology practices.

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