The Experience of Adult Lymphoma Patients Referred for Cardiac Rehabilitation Following Autologous Hematopoietic Stem Cell Transplantation

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In

Aging

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Abstract

Background: Current therapy for relapsed lymphoma includes high-dose chemotherapy (HDCT) as part of autologous hematopoietic stem cell transplantation (HSCT). This life saving treatment has a 50%-70% cure rate at 10 years; however, patients who undergo HSCT are at an increased risk for both direct (i.e. cardio-toxicity) and indirect (i.e. decreased functional status) negative effects. Due to the known detrimental cardiovascular (CV) effects of treatment, lymphoma patients from a tertiary cancer centre are referred to an eight-week multidisciplinary cardiac rehabilitation (CR) program following HSCT. This innovative approach to HSCT patients has not been documented in the literature. **Aim:** The aim of this qualitative study is to gain understanding of lymphoma patients' experiences of being referred to a multidisciplinary CR program following HSCT. **Research Question:** What is the experience of adult lymphoma patients who are referred to a cardiac rehabilitation program after treatment with HDCT and HSCT? **Methods:** A qualitative research approach (interpretive description) was used to guide data collection and analysis. A total of 10 semi-structured interviews were collected. **Findings:** Four major themes highlighting HSCT recipients' prioritization of CR in recovery; impact of HSCT on the CR experience; coping and resiliency during recovery; and information uptake were found. The experiences of HSCT patients in CR shares similarities to other CR literature, however the added burden of HSCT presents unique experiences that influence patient perceptions regarding CV health and risks. **Outcomes:** The results of this research will inform and improve the delivery of CR, a necessary and urgent need in this complex patient population. This study allows researchers, program developers, and multidisciplinary care teams to better understand the experiences of lymphoma patients referred to a CR program and adjust program delivery.

Keywords: Autologous Hematopoietic Stem Cell Transplantation, Cardiac Rehabilitation, Lymphoma, Interpretive Description, Cancer Survivorship

Preface

This thesis is the original work of Derek Rothe completed as part of a research project that received ethical approval from the Health Research Ethics Board of Alberta (ID# CC-16-0503). Study design, data collection, analysis and thesis composition was led by Derek Rothe and supervised by Dr. Edith Pituskin. Chapter 3 is a manuscript of the qualitative research findings and main focus of the thesis prepared for submission to *Journal of Cancer Survivorship* co-authored by Derek Rothe, Dr. Kara Schick-Makaroff, Dr. Alex Clark, Dr. Tammy O'Rourke, Nanette Cox-Kennett, and Dr. Edith Pituskin. The manuscript that appears in Appendix A is a review paper regarding prevention of cardiovascular disease (CVD) in cancer survivors treated with cardio-toxic cancer therapies and the role of pre-existing CV risk factors submitted and accepted with minimal revisions to *Current Epidemiology Reports* as co-authored by Derek Rothe, Dr. Ian Patterson, Nanette Cox-Kennett, Dr. Gabor Gyenes, and Dr. Edith Pituskin. Appendix B is a quantitative analysis of exercise testing results in HSCT patients who took part in the Northern Alberta Cardiac Rehabilitation Program (NACRP) and will be submitted for publication to *Journal of Oncology Practice* as co-authored by Derek Rothe, Nanette Cox-Kennett, Dr. Chris Venner, Dr. Gabor Gyenes, Dr. Ian Patterson, and Dr. Edith Pituskin.

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Chapter One: Introduction to the Thesis

The aim of this thesis is to explore the experiences and perspectives of individuals diagnosed with relapsed lymphoma who are referred to cardiac rehabilitation (CR) following treatment with high dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplant (HSCT). With the number of cancer survivors surpassing those who are being diagnosed, new approaches to survivorship are necessary given the long-term sequelae of cancer treatment. To the best of the author's knowledge, the referral of HSCT recipients to CR has not been documented, however, it has been implemented by oncology practitioners at an urban cancer centre to mitigate the deleterious CV-related effects of transplant. It is important to determine how patients perceive and experience CR services as a new approach to care. Understanding how HSCT patients experience CR following HSCT can help to guide delivery of innovative program initiatives for optimal, intended outcomes of improved CV health in those treated with cardio-toxic cancer therapies.

Organization of Chapters and Thesis

This thesis is a publication based thesis. Chapter one includes the background information to the thesis. Chapter two contains the literature review. Chapter three will be a publishable manuscript which reports the main findings of the qualitative study. Chapter four is the discussion and conclusion section of the thesis. Appendix A is a clinical review manuscript that was accepted May 10, 2017 for publication in *Current Epidemiology Reports*. The review focused on prevention of cardiovascular disease in the context of pre-existing cardiovascular risk factors and the effects of cancer therapy. Appendix B is a manuscript including a quantitative analysis of the exercise testing results of lymphoma, HSCT patients referred to CR following transplant.

Background

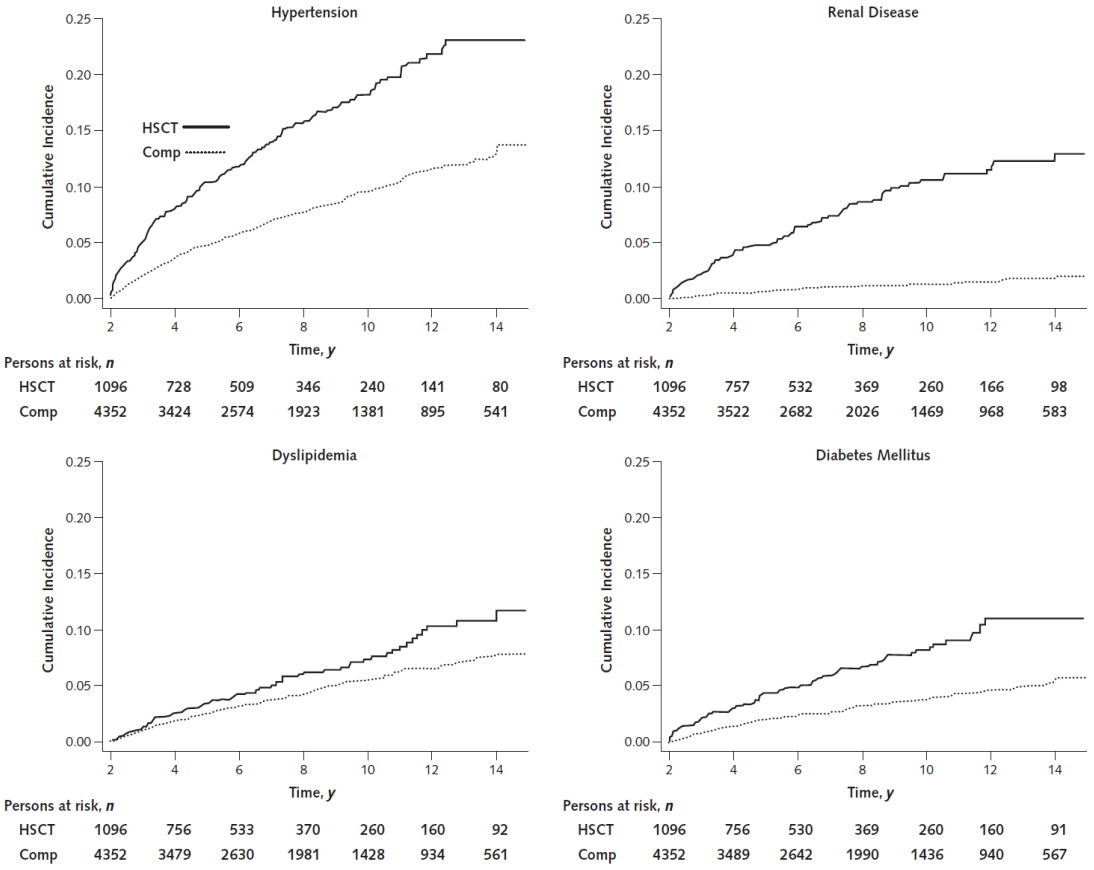
In Canada, lymphoma is the sixth most common cancer with approximately 9,000 individuals diagnosed each year (Canadian Cancer Society [CCS], 2016). While treatments for lymphoma have improved significantly over the past 50 years, patients with this life changing diagnosis face a long trajectory of treatment, recovery, and are at risk for long-term effects from the treatments they receive. Dependent on the subtype of lymphoma, up to 50% of lymphoma patients will experience a return of their disease after initial treatment (Adams, Nievelstein, & Kwee, 2016; Sehn et al., 2008). For those who relapse, an intense regimen of high dose chemotherapy (HDCT) and HSCT, also known as a bone marrow transplant, is often used with the hope of curing the disease (Sasse & Engert, 2014). After receiving lethal doses of chemotherapy, the previously collected hematopoietic stem cells are infused back into the patient as a means of rescue from the toxic effects of treatment (Keller, 2007; Sasse & Engert, 2014). Without reinfusion of stem cells and re-establishment of blood cell production, the patient would die (Keller, 2007). HSCT is recommended nationally and internationally for the treatment of relapsed lymphoma (Horowitz, 2015; Sasse & Engert, 2014), and the refinement of this treatment over the past 50 years has led to survival rates reaching beyond 80% at 10 years (Bhatia et al., 2005; Wingard et al, 2011).

Cardiovascular Effects of HDCT and HSCT

While a life-saving treatment, multiple longitudinal observations have found patients who receive HSCT have a significantly increased risk for cardiovascular disease (CVD) related morbidity and mortality in later life (figure 1.1 & 1.2) (Bhatia et al., 2005; Chow et al., 2011; Chow et al., 2014; Morandi, Ruffini, Benvenuto, Raimondi, & Fosser, 2005). The degree of CVD risk associated with HDCT, varies depending on the cumulative cardio-toxic chemotherapy dosing; however, irreversible damage to cardiomyocytes can occur even at low doses (Bleeker et al., 2012; Chow et al., 2014). Additionally, patients who receive radiation therapy to the chest, another common treatment modality, are at even higher risk for developing CVD (Myrehaug et al., 2008). Apart from the direct effects of treatments to organ

systems (i.e., heart and kidneys), patients who undergo HSCT also deal with the considerable indirect and long-term negative effects, including long-lasting fatigue and functional disability (Morandi et al., 2005; Morishita et al., 2012). The risk for CVD in HSCT patients is further compounded if they have pre-existing cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, renal disease, and tobacco use (Armenian et al., 2016; Bhatia et al., 2005; Chow et al., 2014; Majhail et al., 2012; Virani et al., 2016). In a case-cohort study by Chow et al., (2011), the incidence of late term CVD risk factors in HDCT survivors were noted to be up to three times greater than in control populations (see figure 1.1 and 1.2).

Figure 1.1 Cumulative Incidence of Cardiovascular Outcomes (Chow et al., 2011, p. 24)

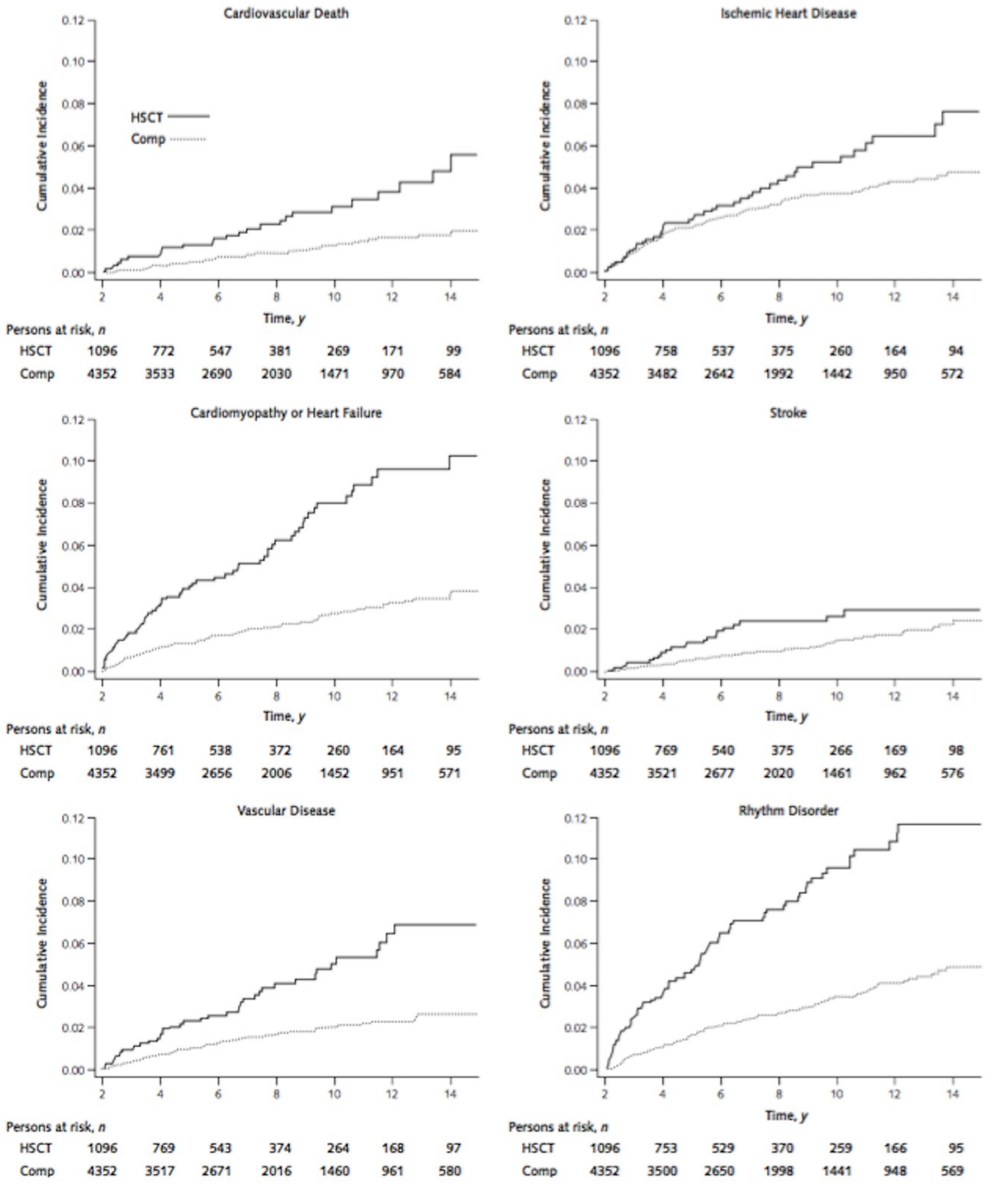


Data are shown for 1096 HSCT recipients who were matched to 4352 persons in the general population. The log-rank *P* value was <0.01 for all outcomes. Comp = comparison group; HSCT = hematopoietic stem cell transplant.

More recently, a review by Scott et al., (2016) found that there is a 2.3-4.0 risk for direct CV-related mortality (heart failure, myocardial infarction, and stroke), a 0.6-5.6-fold risk of

developing CVD, and a 7.0-15.9 risk for developing CVD risk factors such as hypertension, diabetes, and dyslipidemia.

Figure 1.2 Cumulative Incidence of Cardiovascular Outcomes (Chow et al., 2011, p. 25)



Data are shown for 1096 HSCT recipients who were matched to 4352 persons in the general population. The log-rank *P* value was <0.01 for all outcomes. Comp = comparison group; HSCT = hematopoietic stem cell transplant.

In addition to the risks for CVD associated with HSCT, eligibility for transplant has become increasingly liberal as transplant technologies and supportive care improve. This means that patients who are older and/or patients with comorbidities are more likely to proceed with bone marrow transplant than ever before (Popplewell & Forman, 2002). With cancer treatments becoming increasingly effective, survivors are now living long enough to experience the long-term consequences. Accordingly, efforts to prevent and manage CVD in HSCT recipients is necessary (Armenian et al., 2016; Virani et al., 2016). Focus on multidisciplinary CR and prevention of CVD in lymphoma patients treated with HSCT is an opportunity to mitigate the CV associated risks of HSCT and support survivors during and beyond recovery.

CVD Risk Reduction and Rehabilitation

The American Heart Association (AHA) (2016) describes CR as a multidisciplinary, medically supervised program with three main approaches, including: exercise counselling and training, education on heart healthy living, and counselling to reduce stress. The effectiveness of multidisciplinary CR programs has been investigated extensively in CV populations and plays an important role in the prevention of cardiovascular morbidity and mortality (Lavie & Milani, 2011; Silberman et al., 2010). Also, multidisciplinary team based CR programs have been shown to improve muscular strength, endurance, and quality of life of participants (Redfern & Briffa, 2011; Silberman et al., 2010).

CR programs are effective in positively impacting behavioural and traditional CV risk factors such as physical inactivity, smoking and tobacco consumption, dyslipidemia, hypertension, diet, excessive alcohol intake, obesity, and stress, all of which increase the risk for CVD (Stone et al., 2009). Furthermore, CR has psychological benefits as patients share stories, develop confidence, and feel empowered to pursue healthier lifestyles (Clark, Whelan, Barbour, & MacIntyre, 2005; Dolansky, Moore, & Visovsky, 2006; Sutton, Rolfe, Landry, Sternberg, & Price, 2012; Wong et al., 2016).

Pilot Project

Recognizing the need for cardiovascular risk reduction and rehabilitation, an innovative pilot project was initiated by the Cross Cancer Institute's (CCI) Bone Marrow Transplant team and the Edmonton Cardio-Oncology Research (ENCORE) program at the University of Alberta. Effective January 1, 2015, all lymphoma patients proceeding to HSCT were referred to the Northern Alberta Cardiac Rehabilitation Program (NACRP). The NACRP is a multidisciplinary CR program delivered through the Jim Pattison Centre for Heart Health (JPCHH) in Edmonton, AB. Normally reserved for patients with cardiovascular diagnoses, this is the first time a lymphoma HSCT population has been included in such a program (appendix C).

Northern Alberta Cardiac Rehabilitation Program: Metrics

The activity tolerance protocol (ATP) is used in the NACRP as a tool to assess the functional and physical status of participants. A baseline ATP was conducted prior to hospital admission for HSCT. Roughly six weeks following HSCT, participants completed another ATP before enrolling in the NACRP. Once the 8-week NACRP was completed, another ATP was conducted to assess how participants performed following CR. In addition to the functional and physical testing, participants are to complete questionnaires to capture their *perceived* QoL and functional abilities.

The ATP includes documenting resting and peak (following sub-maximal exertion) heart rate (HR) and blood pressure (BP). Left and right-handed grip strength, measured in kilograms (Kg) is included in the ATP to measure overall hand and upper body function and to assess overall functional strength (DeBeliso et al., 2015). Gait speed, measured in metres per second (m/s) is another measurement in the ATP. A recent review of 46 articles, found gait speed (< 1m/s over 4m) to be predictive of sarcopenia, disability, falls, early death, and hospitalization (Pamoukdjian et al., 2015). Timed up and go (TUG) is included in the ATP as a measurement of overall functional mobility and risk for falls (Podsialdo & Richardson,

1991). The TUG is a test whereby participants stand up from a chair walk forward 3 metres, turn around, and sit back down into the chair. A systematic review and meta-analysis of 53 studies, spanning 12, 832 participants, revealed that while TUG may not predict falls in high functioning individuals, TUG may be used to assess falls risk in lower functioning, older adults in institutional settings (Schoene et al., 2013).

The final measurement used in the ATP is the six-minute walk test (6MWT). The 6MWT is used to assess overall functional capacity in those with congestive heart failure (Pollentier et al., 2010). While these tools have not been validated exclusively in HSCT patients, they can be used to assess differences in pre-transplant, post-transplant, and following CR to gauge the impact of treatment and rehabilitation at respective time points.

Quality of Life and Perceived Functional Status

In addition to biometric data collected as part of the ATP, psychometric indicators are assessed by CR staff. At clinic visits, participants are to complete several tests to assess their psychological status, quality of life, and perceived functional status. The Screening Tool for Psychosocial Distress (STOP-D) questionnaire is a tool used to assess psychosocial distress and depression (Wong, 2016). The Euro-Qual 5 Dimension (EQ5D) is one of the most simple and common health Related quality of life (QoL) tools to assess social, physical, and psychological well-being in community-dwelling older adults. The components of the EQ5D address mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Rabin, Oemar, Oppe, Janssen, & Herdman, 2015). The EQ5D generally includes the EuroQol Visual Analouge Scale (EQVAS) giving participants the opportunity to rate their current perceived health status from 0-100; 100 being best perceived health (Rabin et al., 2015).

The third functional questionnaire is the Late Life Functional Disability Instrument (LLFDI) which consists of a 16-item disability focused questionnaire, and a 32-item function oriented component (Jette, Haley, & Kooyoomjian, 2002). While these tools have not been exclusively validated for HSCT recipients, they are commonly used in CR and provide a

thorough understanding of the participants' perception of their QoL. Unfortunately, the lack of consistency with patients completing the aforementioned questionnaires, meant it was not possible to conduct statistical analyses on this portion of the ATP results.

As expected, patients who participated in the NACRP experienced improvements in functional indicators such as 6MWT, left and right handed grip strength, and gait speed following HSCT. Quantitative analysis of the data shows benefits to participants; however, it is important to understand the ways CR programs may affect the survivorship experience of lymphoma patients during HSCT recovery (Rothe et al, 2016). The aim of this research is to gain understanding of the experience of lymphoma patients referred to a cardiac rehabilitation program following HSCT.

Research Question

What is the experience of adult lymphoma patients referred to a cardiac rehabilitation program after receiving autologous hematopoietic stem cell transplant? The interview protocol used by the researcher can be found in appendix D

Methods

Creswell (2014) identifies the importance of understanding the researcher's worldview and the research problem as a means to guide selection of a research methodology. The aim of this research project was to create meaning from the experiences of patients, thus constructivist and interpretive approaches guided the design and methods (Creswell, 2014). Interpretive description (ID) is an appropriate means to address the complexities of clinically focused health research (Thorne, 2016). ID is a qualitative research approach that draws aspects of inquiry from various established qualitative research methods (i.e. ethnography, grounded theory, and phenomenology) to explore complex applied practice health questions (Thorne et al., 2010; Thorne, 2016)

Thorne (2016) posits that an inductive approach to describing a phenomenon coupled with an interpretive goal seeking patterns and relationships within the phenomenon is

essential in understanding health research concerns. She believes that through ID, health researchers can flexibly work within their own disciplinary field to defend and create new knowledge that has relevance toward their clinical context.

ID was used to guide the investigator in data collection, analysis, and translation of findings into context. Understanding the complexities of the lymphoma transplant patient experience with CR illuminated the unique perspectives faced by this specific population. Creating meaning in this way assisted the researcher to understand the phenomena, and informed appropriate and desired clinical outcomes within HSCT survivorship (Thorne, 2016; Thorne, Kirkham, & MacDonald-Emes, 1997). For a complete timeline of the project refer to Appendix E.

Recruitment and Sample

Inclusion criteria. Following Health Research Ethics Board Approval (HREBA) (Study ID # CC-16-0503), all lymphoma patients from the CCI over the age of 18 who were eligible for, and successfully completed HSCT, and who were referred to the NACRP, were recruited to participate in the study. In ID, Thorne (2016) acknowledges purposive sampling as a legitimate method of recruiting a sample. In purposive sampling, the goal is to include a variety of experiences to provide well-rounded findings (Thorne, 2016). In an effort to gain a richer understanding of the patient experience, all patients who successfully completed HSCT were selected for recruitment. Additionally, those who were referred and who did not complete the NACRP (i.e. drop out) were recruited to ensure diversity in the sample (Thorne, 2016).

On July 28, 2016, eligible participants were mailed an recruitment letter, study description information, and a consent form from the Cross Cancer Institute's bone marrow transplant team office (see Appendices F and G). In the letter, participants were invited to contact the researcher directly if they were interested in taking part in the study, or required additional information. If the potential participant agreed to be involved in the study, the

researcher ensured all inclusion criteria had been met, discussed the study purpose, anticipated timeframe, and arranged a meeting at the earliest convenience of the participant. At this meeting, the researcher confirmed the purpose and procedures of the study, clarified any questions the participant may have had, and obtained signed consent. Following confirmation of the participants' consent, the researcher proceeded with conducting the interview. No follow up interviews were deemed necessary to complete data analysis.

Sample size. Thorne (2016) identifies the need to accept ambiguity when determining sample size in qualitative research. She cautions relying on the term *saturation* to delineate when to halt data collection as she believes it impossible to truly learn *all* potential information within complex phenomena (Thorne, 2016). Instead, she believes that an appropriate sample size is one that best leads the researcher to the desired knowledge required to answer the clinical question. As such, sample size was determined sufficient when concurrent data collection and analysis demonstrated adequate data to answer the research question. At the time of recruitment there were approximately 40 patients who had been referred to the NACRP and 20 of those who had completed the NACRP. A total of 10 participants were interviewed.

Data Collection

After written consent was obtained, the participant and researcher collaborated to determine an appropriate time and place to complete the interview. Interview location varied and was determined based on participant preference. In qualitative research, participants may be more likely to provide uninfluenced and honest information when interviewed in their natural setting (Creswell, 2014; Thorne, 2016). Thus, the researcher always initially offered to interview the participants in their homes. For participants who did not wish to complete the interview in their home, the researcher arranged a quiet and private conference room in the Edmonton Clinic Health Academy (ECHA), on the University of Alberta north campus. One participant was interviewed, by his choice, at his place of work.

An audio-taped, face-to-face, semi-structured interview was used with guiding questions to facilitate the interview process (refer to Appendix D). Interview length varied with a range of 34 to 82 minutes. A second interview to clarify any questions was to be considered, however was not necessary in this study. As part of the collection methods, the researcher wrote observational notes during the interview (see appendix H) to document participant non-verbal communication. On this document, researcher reflections were also made immediately following the interview. This assisted the researcher with creating meaning in the phenomena and the context of the interview during data analysis (Thorne, 2016).

Data Analysis

Collected data was transcribed through a confidential transcription service in a timely manner (within 72 hours of the interview). All potential identifiable information was removed so as to maintain anonymity. After each interview the researcher began to consider potential themes emerging in the data (Thorne, 2016). As data collection continued, the process of identifying patterns and themes emerged to develop concepts at a broader level, deepening the researcher's understanding of the phenomena (Thorne, 2016). Similar to constant comparative analysis in grounded theory, Thorne (2016) recommends that the researcher compare each piece of data with all other data as a means to identify the emerging relationships. To assist with analysis, the researcher maintained a notebook reserved for note making to capture the emerging thought and inquiry (Thorne, 2016). Coding was performed first in a line-by-line fashion, then with axial coding, broad categories and patterns were discovered. Finally, with selective coding, the main themes and sub-themes were made to capture the essence of the patterns and relationships deduced from data analysis (Thorne, 2016).

Credibility and Rigour

Carcary (2009) insists developing an audit trail of all research activities is an

important step to prove “trustworthiness” in qualitative research. An audit trail is a means to track all research activities and encounters with participants to ensure transparency to the audience (Carcary, 2009). The audit trail allows readers to trace how the researcher reached their conclusions, and if desired, to make the results accessible to readers (Carcary, 2009; Thorne, 2016).

To ensure the credibility of the findings in qualitative research, Thorne (2016) suggests a number of methods. While she does not believe that “member checking” should be the only method of assessing credibility of findings, she supports presenting the researcher’s observations and tentative interpretive findings to the participants for their reflection. All participants were contacted by phone and/or email by the researcher to share the findings. One participant was not available through provided contact information. All participants who were available for discussion, had no suggestions that would impact the findings.

Another way qualitative researchers can ensure the findings are credible is via critical reflection or reflexivity of the analytic process (Thorne, 2016). By returning to the initial data and examining the analytical notes on the data as a whole, the researcher was able to seriously question findings and compare themes with other findings. This process, allowed the researcher to assess if the findings informed the research question (Thorne, 2016).

Relevance and Future Directions

This study helped to facilitate understanding of lymphoma patients' experiences in a multidisciplinary CR program after receiving HSCT. As the risks for CV morbidity and mortality after treatment have been well documented, steps to better understand how to provide first-class cancer survivorship care is pertinent. The findings of this study may inform program developers and decision-makers considering how to appropriately deliver a multidisciplinary CR program for HSCT patients.

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Chapter Two: Literature Review

On December 3, 2015, a literature search was conducted using the databases CINAHL Plus with Full Text, MEDLINE, Academic Search Complete, and SPORTDiscus with Full Text with the search terms "hematopoietic stem cell transplantation" and "cardiac rehabilitation." One article was retrieved (Dimeo et al., 1997) related to an exercise alone intervention in an HSCT population. A librarian designated to the Faculty of Nursing also reviewed the search strategy and confirmed that there is no documented literature regarding the impact of multidisciplinary CR in HSCT patient population. Single modality interventions (i.e., the effects of exercise alone) in various stem cell transplant patient populations, such as in leukemia and myeloma, have been shown effective to improve physical functioning prior to and/or post autologous or allogeneic transplant (Hacker et al., 2011; Schmitz et al., 2010; Wiskemann & Huber, 2008). More recently, there are studies investigating combined modality interventions (i.e., exercise and relaxation or stress reduction) to improve physical and psychological functioning following HSCT (Jacobsen et al., 2014; Jarden, Nelausen, Hovgaard, Boesen, & Adamsen, 2009).

Many studies have shown the benefits of exercise programs in stem cell transplant populations; however, the findings of most studies acknowledge that further investigation is needed to assess how effective these interventions are in allowing patients to return to every day functioning after stem cell transplant (Dimeo et al., 1997; Hacker et al., 2011; Jarden, Baadsgaard et al., 2009; Jarden, Nelausen et al., 2009; Knols et al., 2011; Wiskemann & Huber, 2008; Wiskemann et al., 2011; Wood et al., 2013). Furthermore, several systematic reviews and meta analyses have been conducted to assess the optimal exercise intervention to produce the most effective improvements in patient functioning (Haren et al., 2013; Persoon et al., 2013; Wiskemann, 2013). Not surprisingly, these studies also highlight the need for more investigation into how exercise programs can further improve physical, psychological and every day functioning and quality of life (Haren et al., 2013; Persoon et al., 2013). One

deficit of exercise studies in HSCT populations is that there is little discussion of CV risk factors when developing single or multiple modality exercise interventions.

The role of CR programs in individuals at risk for, or with current cardiovascular disease (CVD) has been identified as an important tool to limit the extent of CVD related morbidity and mortality (American Heart Association, 2016; Lewanczuk, Suskin, & Arthur, 2009; Menezes et al., 2014; Redfern & Briffa, 2011; Silberman et al., 2010; Stone et al., 2009). Traditional patient populations who partake in CR include those who have experienced a major adverse cardiac event (i.e., myocardial infarction or cerebral vascular accident), cardiovascular surgery, heart failure, or CVD with a high risk for morbidity (Haennel et al., 2009). The multidisciplinary aspects of CR are an important part of how such programs go beyond exercise alone to influence individual modifiable risk factors (Lavie & Milani, 2011).

In most cases, CR employs the expertise of exercise physiologists, pharmacists, dieticians, psychologists, social workers, occupational therapy, physiotherapy, registered nurses, and cardiologists to promote healthy lifestyles in relation to CVD and education to prevent and manage modifiable risk factors (Lavie & Milani, 2011; Silberman et al., 2010). Traditionally, CR programs have been in tertiary care facilities; however, it has been found that CR principles can be effectively employed in the home setting allowing for flexible secondary prevention in high risk populations who may have difficulties attending facility led CR programs (Scalvini et al., 2013; Taylor, Dalal, Jolly, Moxham, & Zawada, 2010).

Cardiac Rehabilitation: Experiences of Traditional Cardiac Rehabilitation Populations

A basic understanding of the existing qualitative literature regarding the experiences of CV patients was necessary to place the findings of this research into context. Within the literature there are several common factors which influence traditional cardiac populations' experiences taking part in CRPs. Additionally, there are common system level barriers which

prevent uptake and adherence to CRPs and patient specific barriers that contribute to poor uptake.

Gender Differences

The literature identifies several common findings related to gender differences and experience with CR. One finding is the gendered nature of CR which, in general, do not take into consideration female-specific needs resulting in low uptake or poor adherence by women (Clark et al., 2013; Sutton et al., 2012). This has been found to be a complex phenomenon but likely related to health care providers being less likely to refer women to CR, an environment perceived to be unsafe (i.e. anxiety exercising in public), and many other impacting factors related to age, socioeconomic status, marital status, and perceived social and familial responsibilities (Clark et al., 2013; Rolfe, Sutton, Landry, Sternberg, & Price, 2010; Sutton, Rolfe, Landry, Sternberg, & Price, 2012). Recognizing the impact gender has on the uptake of CR, there have been attempts to mitigate gendered barriers with staff education to promote supportive environments and female-only CRPs (Rolfe et al., 2010).

In their qualitative systematic review and meta-analysis of 62 articles capturing 1646 patients, Clark et al. (2013) found men who participated in CR generally believed that they were different than other participants who took part. For example, they believed that the program was meant for others who were more ill, of older age, or lived riskier lifestyles than they perceived themselves (Clark et al., 2013). To support participation in CR, staff must recognize the gendered differences perceived by individuals, and tailor their approaches of education regarding heart healthy lifestyle accordingly.

Program Enablers

There are several documented factors that increase the uptake and participation of CR. Enabling factors include the perceived benefits of participating in CR (i.e. exercise, lifestyle education), the social connection made with other participants, and the patients' perceptions of safety associated with being monitored by CR staff (Clark, Whelan, Barbour, &

MacIntyre, 2005; Sutton et al., 2012; Wong et al., 2016). Perceived accessibility to programs was also a factor which influenced uptake with easier perceived access increasing participation (Clark et al., 2013).

System and Patient Level Barriers

Various system related barriers are cited in the literature and are related to staff and services provided, financial burden, getting to and from programs, and health care provider attitudes towards CR. These burdens highlight the heterogeneity of individuals attending such programs and re-inforce the notion that CR services should be tailored to individuals based on their specific needs. Barriers perceived by participants were noted to impact uptake and adherence of CR. Experiences that were viewed as negative and impacted adherence included services and staff that were not perceived as meeting the needs of individuals (i.e. timing, insensitivity, too narrow of an education focus, overly standardized delivery of services) (Clark et al., 2013). Not surprisingly, the approach of CR staff do impact patients' willingness to take part in CR.

A commonly identified barrier to patients participating in CR is related to financial burden. The costs associated with transportation, parking, medications, and lifestyle changes (i.e. diet and exercise) all contribute to poor uptake of programs (Dhaliwal et al., 2017; Neubeck et al., 2012)**.** The degree of perceived financial burden varies across individuals but can even contribute to social isolation as patients attempt to save money so as to meet the needs of attending and participating in CR (Dhaliwal et al., 2017).

Apart from associated costs to attend CR, ease of transportation plays a role in the adherence (Dolansky, Moore, & Vivovskyet al., 2006). In one study, those who were able to use public transport and this allowed them to complete the program. However, having to arrange transit schedules and fluctuating weather impacted participants' decisions to take transit. (Rolfe et al., 2010). Spousal support with getting to and from the program was found to be beneficial and participants who were able to drive themselves found the flexibility to

adopt their own schedule appealing despite having to pay for parking services (Dolansky et al., 2006; Rolfe et al., 2010).

Health care provider (i.e. physicians) buy-in and support of CR plays a role in how patients perceive CR and associated services. A lack of information regarding the role of CR and, at times, beliefs that referral is not important, understandably impact patients' perceptions of such programs (Rolfe et al., 2010). More information regarding the benefits of CR and patient education about the purpose of CR may influence the adherence to CR (Dolansky et al., 2006; Madden, Furze, & Lewin, 2010; Moja et al., 2012; Shahsavari, Shahriari, & Alimohammadi, 2012)

In addition to system and program associated barriers, patient-related barriers also decrease adherence and uptake of CR. One of the main barriers is a lack of understanding of the role of CR in secondary prevention of CVD. Individuals who do not fully understand the importance of adopting health behaviours to prevent future adverse CV events are less likely to prioritize CR, and consequently adherence will be compromised (Dullaghan et al., 2014). Other patient-related barriers are related to maintaining healthy behaviours. For individuals who have experienced an adverse CV event, they may be required to make considerable changes to their previous lifestyle involving diet modification, exercise, stress reduction, smoking cessation and, as such, long-term health maintenance can be challenging (Pryor, Page, Patsamanis, & Jolly, 2013). Some suggestions would be to incorporate longer term follow-up and staff support following program completion to encourage long term, sustainable health changes (Pryor et al., 2013).

While this is not an exhaustive search of the literature, these sources highlight the common findings regarding patient experiences with CR. It could be anticipated that the HSCT recipients may also share experiences similar to traditional CV patients. However, due to the differences in illness trajectories, it is hypothesized that there will also be differences in how HSCT recipients experience CR. Regardless, the CV-related benefits of CR are well

documented, and cancer populations who have received treatments that increase the risks for CVD morbidity and mortality should be considered for multidisciplinary CR interventions. Just as an increased understanding of how CR is experienced by traditional CV populations can be used to improve program delivery, a better understanding CR the HSCT context will help to guide implementation of a similar program aimed at cancer survivors at an increased risk for CVD.

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Chapter Three: Cardiac Rehabilitation Following Autologous Hematopoietic Stem Cell Transplantation: Patient Perceptions

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Abstract

Purpose: The risk for cardiovascular disease (CVD) in those treated with hematopoietic stem cell transplant (HSCT) is high, as such cardiac rehabilitation (CR) has been purposed as a means to mitigate the associated CV risks. The aim of this paper is to share the experiences of lymphoma patients who are referred to CR following autologous HSCT.

Methods: Guided by the qualitative approach of interpretive description, the researcher used semi-structured interviews to capture how participants perceived their experiences with CR following HSCT. Themes were derived using a constant comparative analysis and coding of verbatim transcripts of the interviews.

Results: Ten participants were interviewed (9 male; 1 female). Major themes included participants' priorities in taking part in CR, the impact of their HSCT experience upon attitudes toward CR, ways participants coped during recovery, and the uptake of heart healthy education and associated barriers.

Conclusions: Including CR into HSCT recipient recovery was viewed by participants as a positive intervention and beneficial to recovery. HSCT survivors are a heterogeneous group and should have their individual needs assessed during CR exercise planning and education. For HSCT recipients, CR education sessions may not be viewed as applicable, but nonetheless attendance should be emphasized given the high CVD risk in this population.

Implications for Cancer Survivors: As the efficacy of cancer treatments like HSCT improve, survivors live longer to see the effects of treatment related sequelae, such as CVD. Rehabilitation programs like CR can assist in recovery and promote heart healthy lifestyles for those with heightened risk for CVD following cancer treatment.

Keywords: lymphoma, cardiac rehabilitation, hematopoietic stem cell transplantation, recovery, survivorship

Cardiac Rehabilitation Following Autologous Hematopoietic Stem Cell Transplantation: Patient Perceptions

Introduction

The treatment for relapsed lymphoma after first line therapies is autologous hematopoietic stem cell transplantation (HSCT). HSCT involves administration of high dose chemotherapy followed by a rescue infusion of the patients previously collected hematopoietic stem cells. Worldwide, over an estimated 50, 000 hematopoietic stem cell transplants (autologous and allogeneic) are conducted each year (World Health Organization [WHO], n.d.). With survival rates exceeding 80% at ten years following transplant (Wingard et al., 2011). Despite the evolution and improvement in HSCT practices, survivors of this treatment have up to a 5.6-fold increased risk for cardiovascular disease (CVD) and adverse cardiovascular (CV) events such as myocardial infarction (MI), heart failure (HF), and stroke (Armenian et al., 2012; Chow, Wong, et al., 2014; Scott et al., 2016).

Additionally, those who receive HSCT develop CVD risk factors at an alarming rate of 7.0-15.9 times greater than age-sex matched control groups (Eric J Chow, Wong, et al., 2014; Scott et al., 2016). These increased risks lead to HSCT recipients being up to four times as likely to die from a CV related incident versus those who have not been treated with HSCT (Chow et al., 2011; Scott et al., 2016). To mitigate the cardio-toxic effects, lymphoma patients receiving HSCT at an urban, tertiary cancer centre are referred to cardiac rehabilitation (CR) following HSCT. This paper explores the perspectives and experiences of HSCT patients who have taken part in this novel approach to cancer survivorship care.

Background

HSCT Associated Cardio-Toxicity

The direct cardio-toxic effects of HSCT are related to the chemotherapy (both from HSCT and previous treatment) and potentially radiation therapy to the mediastinum, if part of the treatment plan (Eric J. Chow, Baker, et al., 2014; Scott et al., 2016). The effects of

treatment on the CV system can lead to left ventricular dysfunction (LVD) (usually defined as an ejection Fraction <50%), heart failure (HF), arrhythmias, and coronary artery disease (Marmagkiolis et al., 2016; Schultz-Hector & Trott, 2007; Tonorezos et al., 2015; Zhao, Diz, & Robbins, 2007). Indirectly, HSCT is associated with physical deconditioning, decreased exercise capacity, and decreased endurance, leading to reduced cardiac output and strain (Blaes, Konety, & Hurley, 2016; Saltin, B., Blomqvist, G., Mitchell, J.H., Johnson Jr., R.L., Wildenthal, K., Chapman, 1968; Scott et al., 2016). Pre-existing CVD risk factors such as hypertension, dyslipidemia, obesity, smoking, and diabetes also compound the risk for CV related complications and are found in up to 25% of individuals prior to HSCT (Armenian et al., 2010; Bleeker et al., 2012). The complexity of interacting factors that contribute to CVD in HSCT recipients highlights the need to address ways to mitigate the risks.

The Role of CR

CR programs are designed as secondary prevention interventions to limit morbidity and improve quality of life in individuals who have experienced an adverse cardiac event such as MI, have HF, or who have undergone CV procedures such as revascularization (Anderson & Taylor, 2014). CR programs generally consist of two major components – guided exercise plans and education on reducing modifiable CVD risk factors (Stone et al., 2009). A multidisciplinary team consisting of exercise specialists, nurses, dieticians, social workers, pharmacists, nurse practitioners, and cardiologists work together with patients to establish heart healthy lifestyles for those at risk (Mampuya, 2012). CR is delivered in tertiary settings as well in community settings, with studies finding equally efficacious results in either mode of delivery (Redfern & Briffa, 2011; Taylor, Dalal, Jolly, Moxham, & Zawada, 2010).

A recent Cochrane review examining the efficacy of exercise-based cardiac rehabilitation in patients with coronary heart disease found while all-cause mortality is not decreased from participation in CR, hospitalizations and CV-related mortality were decreased, and quality of life (QoL) was improved (Anderson et al., 2016). For patients

suffering morbidity from CVD, the opportunity to improve their functional status and overall QoL is extremely important to both individuals and health systems. In HSCT populations, CR provides an opportunity to support initial recovery following treatment and emphasize the importance of modifiable CV risk reduction.

Exercise in Stem Cell Transplant Populations

Exercise has long been known to decrease heart disease and is the cornerstone of CR programs (Anderson et al., 2016). Interestingly, there has been a considerable amount of research with regards to the benefits of exercise for the HSCT populations prior to, during, and following transplant (Buffart et al., 2017; Persoon et al., 2013; Wiskemann, 2013). Exercise has been identified as an effective tool to improve treatment response, expedite recovery, and improve overall QoL (Haren et al., 2013; Persoon et al., 2013). The benefits of exercise in HSCT patients have been demonstrated by numerous studies, and patients receiving HSCT are at an increased risk for CVD. Therefore, referral to CR is an opportunity to support HSCT recipients during recovery and to promote heart-healthy lifestyles to prevent CVD in the future.

Methods

To the best of the authors' knowledge, the referral of HSCT patients to CR has not been documented in the literature and is currently not a standard of care. Biometric data from CR exercise testing outcomes demonstrates favorable clinical outcomes in these patients (Rothe et al., 2016). However, HSCT recipients likely experience a different illness trajectory than cardiovascular patients, and there is much unknown about how HSCT recipients experience CR. Using qualitative methods to better understand phenomena in health care is an established method to gather evidence to improve care delivery to patients (Portela, Pronovost, Woodcock, Carter, & Dixon-Woods, 2015). This research was guided by the qualitative approach of interpretive description (ID) (Thorne, 2016).

Prior to recruitment, the study was approved through a cancer research ethics board

(Health Research Ethics Board of Alberta ID#: CC-16-0503). Through purposive sampling, a recruitment letter and consent form expressing the researcher's interest were mailed with pre-paid return envelopes for potential participants to express interest. In-depth interviews were conducted by the primary researcher either in participants' homes, at their place of work, or in a reserved, quiet space on a university campus. Interview recordings were submitted to a confidential transcription service, then cleaned by the researcher to ensure all non-identifying information was removed. During and after the interview, the researcher compiled field notes to better capture the participants' actions or reactions during the interview as well as researcher reflections.

Table 3.1 Participant Demographics

	N=10
Age (yrs)	
Mean (range)	58 (46-67)
Gender	
Male	9
Female	1
Distance From Tertiary Centre (Km)	
Median (range)	23.5 (6-389)
CR Setting	
Tertiary Centre	4
Community/home-based	6
Drop-out	1
Self-Identified as Physically Active Pre-HSCT	
Yes	9
No	1
Days Admitted to Hospital For HSCT	
Mean (range)	28 (22-36)
Previous CV History	
Yes (n=4)*	
CAD	1
Hypertension	2
Peripheral vascular disease	1
Atrial Fibrillation	1
No (n=6)	
Lymphoma Diagnosis	
Diffuse Large B-Cell	4
Mantle Cell	4
Hodgkin's	2

*One participant had 2 documented CV illnesses

The researcher identified common themes from the transcripts. To determine themes, a sequential analysis method was used via reading and re-reading hardcopy transcriptions while listening to the interview recordings. From there, a line-by-line approach was used to examine each transcript. Emerging trends were categorized and prioritized. The data was then selectively coded to develop the themes and subthemes. All transcripts were read by the researcher and supervisor and discussion of the themes was agreed upon.

Results

Twenty-seven eligible participants who were treated with HSCT and referred to CR

were sent a recruitment package in the mail. A total of ten participants expressed interest either through returning their consent form via mail or by contacting the researcher directly. The participants were a mixture of those who attended tertiary CR (n=4) or community/home-based CR (n=6). Interview lengths ranged from 34 minutes to 82 minutes. Of the ten participants, nine were male, one was female. Their lymphoma diagnoses included diffuse large B-cell (n=4), mantle cell (n=4), and Hodgkin's (n=2) (Table 1). One participant was identified as not completing the program in full, as exercise testing was not performed following completion of CR. However, the participant believes there was a miscommunication and intended to complete the program, but was not contacted to return for final exercise testing.

Findings

Four major themes were identified as shared experiences or perspectives among the participants and involved an interplay of experiences that contributed to taking part in CR after HSCT. The themes identified were, HSCT recipients' prioritization of CR; impact of HSCT on the CR experience; coping and resiliency during recovery; and uptake of CR education and associated barriers. While the focus of this work is on the experience with CR, the participants positioned themselves within the context of their HSCT and the interviews would circle back heavily onto their transplant experience (Figure 3.1)

Prioritizing CR in the HSCT Experience

Not surprisingly, participant priorities impacted attitudes towards CR. Most often, participants felt that their priority in their care was focused on receiving treatment for their lymphoma, and not the increased risk for CVD. Some acknowledged their increased CVD risk

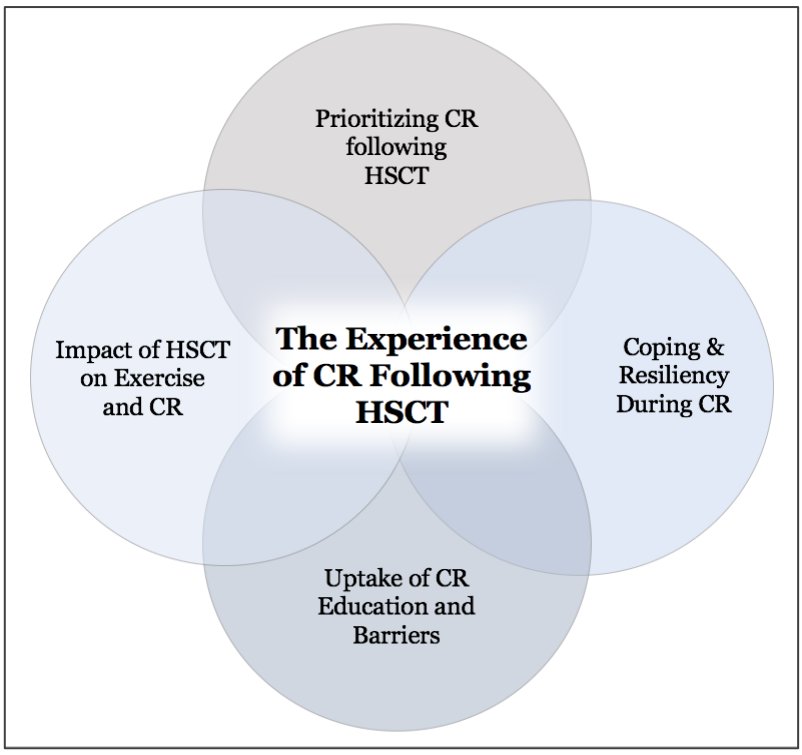

Figure 3.1 CR= Cardiac rehabilitation; HSCT = Autologous hematopoietic stem cell transplantation. The experience of CR following HSCT consists of the four major themes: prioritizing CR following HSCT; impact of HSCT on exercise and CR; uptake of CR education and barriers; and coping and resiliency during CR

as a motivating factor to complete CR. Other individuals made CR a priority as a means to demonstrate their trust and appreciation for the oncology team efforts in saving their lives. Additionally, some identified the desire to return to their previous level of functioning as their priority to attend CR.

Participants' perceptions of CV health and CR following HSCT allude that managing their risk for CVD was not their priority when they are first presented the information, usually at the pre-transplant evaluation. As Travis pointed out, "you're a little pre-occupied before…Because you're, you know, 'well, what's this shit I'm getting? Ah, are my affairs in order?' Um… you're a bit pre-occupied." For James, it was a different scenario. He said, "I was fairly healthy going into this…. I wasn't really too worried so much. The notion that oh, this might affect my heart and stuff, I don't really know that I really thought that that as a big

deal."

The belief that CR was important, was also influenced by the participant's view of identity as either a CV patient or a cancer patient. For example, Travis had been seen by a cardio-oncology team for low ventricular ejection fraction prior to HSCT. He was one of the few that made attending education sessions a priority, and said the following:

> they had some courses after, which was just basic heart health and um…diet. Which is not specific to lymphoma. But it is specific if you've got a heart problem. You know, so –which is really –I was there as a heart patient but not as a cancer patient. (Travis)

Conversely, James said,

> I guess I kind of thought this was maybe… um, geared more to heart patients or something, or um, a bit more…um, like a… ah, I wasn't really sure –well, why am I doing some of this stuff? But I guess…you know, I understand that it's for your heart. (James)

James understood that the purpose was to support heart health, but there was still a disconnect, and he felt that the material was not aimed at him or HSCT patients.

One factor that influenced participants' buy-in and perceptions of CR was their pre-existing relationship with their oncology health care providers and the health care providers' opinion of CR. As Cody identified when he first heard about the CR program,

> the [HSCT team] helped me out so much, that when they said, 'No, we think you should do this and um, I think you are going to benefit from it'… and stuff. And I felt so committed to them, that was part of the reinforcement, part of the motivation for me doing it [CR]. I know it probably sounds weird. But it was a – it was um, quid pro quo… [the nurse practitioner] especially was really committed to me. She made the calls…and really went to bat for me. And if she said, "no, I need you to do this, and stuff." I would stand on my head for her. Ah, and that team. Because they, - well, they saved me. There's no doubt about it. (Cody)

Cody's trust and appreciation for the HSCT team's facilitation with his transplant led him to take part in CR because he felt it was a way to demonstrate his gratitude for the health services he received.

For James, he identified that heart concerns were not a priority in the face of his cancer diagnosis, but he attended CR as his oncology team identified it as an important step in his recovery. He stated the following:

> I mean, I never really thought at all, going through the whole cancer process, about how it might affect my heart. Um, and so I didn't really think, 'oh, um, I really need to do this.'...But um, they just made me aware that, yeah, this was something that they ah, they think would benefit me and so, sure. I'd go ahead and I'd do it. (James)

As with other CR literature, health care provider beliefs of the efficacy and importance of CR have an impact on patient participation (Ghisi, Polyzotis, Oh, Pakosh, & Grace, 2013).

Another factor that impacted participants' priorities and perception of CR was the degree to which they were debilitated by their HSCT. For example, Travis said,

> The way I look at it is you've got two choices. One to play it safe and do nothing, and have no quality of life. Or the other is to give it –try and get your quality of life.... Because if you don't have any quality of life, you're already dead. Because if you don't have the stamina, you can't do anything.... I'm gonna go on a road trip to San Diego. Well, if I can't get out of the car, it's not much of a trip. (Travis)

He believed that CR was a means to combat the debilitating effects of transplant and to regain a quality of life. He saw CR as a means to regain his life back. Alternatively, James pointed out, "Why wasn't I going to the gym and stuff? Um... I guess again, just not so much interested, because um... I just felt pretty good already." For James, while he did decondition mildly as a result of transplant, he did not perceive the impacts of HSCT to be so great that it impacted his overall quality of life. As such, he did not feel the need to consistently put in effort above and beyond the once weekly sessions at the CR centre.

The degree to which participants incorporated exercise into their life prior to HSCT also impacted perceptions of CR. For Eckhart, he was first treated for his lymphoma 12 years prior, and had been encouraged to exercise at that time. He stated, "So, I started running. Um, I didn't ah, run to the extent that I was training for a marathon. But it became a part of my weekly…just to stay in shape." Likewise, Cody found his level of activity prior to his transplant positively impacted his tolerance of HSCT and recovery, motivating him to stay active following treatment. He said,

> the reason why I'm committed to the –this program, and stuff, is that I believe my pre…um, stem cell conditioning [exercise] and the conditioning [exercise] program that I did afterwards, myself, was absolutely critical to the way I turned around, honestly…. And –and surviving the actual transplant itself. (Cody)

Similar to Cody, Greg believed physical activity helped his recovery:

> I guess in my mind, I was ah –I wanted to get back somewhat into shape again and… get some muscle back in my body and get more energy and… I felt good about it, because it's not like you're taking someone from scratch and putting them on an exercise program. I can see where, if you're not used to doing any exercises, I can see where the person could be reluctant to do it. (Greg)

Those who were already physically active prior to HSCT, understood the benefits of active living and were happy to take part in the program and made exercise a priority in their recovery.

Impact of HSCT on Exercise and CR

Much of the participants' reflections dealt with the changes associated with HSCT both in the short and long-term in relation to their exercise capacity. As Travis put it, "One thing that shocked me with the transplant is how weak I got…. Once I had the transplant, and crashed, if you tried to tell me to exercise, I would have told you to piss off." Cody also found the transplant challenging stating,

> I think if [patients] are not that strong, mentally –because it's –it is as much a mental deal as it is a physical deal…. There was some days during the end of the transplant where I couldn't even turn on my phone I was so fucking sick. (Cody)

While most of the patients discussed the physical and mental changes they experienced and how it impacted their functional ability to partake in exercise, one participant, James, found he was not greatly affected by HSCT. He stated, "I didn't have any issues with – with the transplant…. I um, wasn't sick afterwards. Um so, it went very well, actually– I didn't have a lot of ah, really bad side effects from my chemo even…." This range of response demonstrates the variability between individuals and their experiences of HSCT. It also highlights the variances in the rehabilitative needs of participants following treatment.

Individuals assessed their physical changes through returning to exercise. For Andrew, he noticed his loss of strength after transplant when he returned to the gym saying, "I definitely knew my strength level and stamina and all kinds of things were way down…I knew that I used to be able to do let's say 30 pounds, and I was down to like 10-pound weights." Similarly, Greg recognized his most apparent change in his strength and endurance when he returned to the gym stating, "And you don't realize how bad you are until you start [exercising] on some machine. You go 'that's all I can do with that?'"

Many noted their strength and endurance increased as the CR program progressed. Much of the experience of regaining their physical abilities was an internal process whereby they subjectively felt their gains. Andrew framed that internal experience as follows:

> Cause even myself, just seeing the progress has made me… like feel better. I can see that there's progress, which makes me just… you know, I don't know what's all going inside there…but at least I feel better that I – I'm feeling better. 'Cause I couldn't do this before. (Andrew)

The ability to identify their progress through exercise was found to be a motivating factor for participants to continue with CR and something tangible to indicate gains. Greg

noticed abrupt changes during recovery, saying, “I was on some machines and I was maybe doing 10 pound weights. And all of a sudden, I’m up to 30-40 pounds. And with repetitions…so you start with ten, and you’re up to 40 or 50.” Andrew agreed that physical progress was quickly tangible, stating, “…coming out of the stem cell, and you know… like I said, doing bench presses with the bar and that’s all I can do is 10 reps with that. And now to the point where you got 25 pounds.”

Cody found that seeing his progress reflected objectively as part of exercise testing results supported his perceived physical improvements. “The measurement aspect of where you are before the baseline, where you are during [CR], where you are afterwards…it was positive enforcement to me.” James too reflected on his gains: “So you know, the - the muscle toning sorts of things that I did, I think I thought, well that’s helping me out. I’m feeling a little bit – like I’m getting a little bit more muscle mass back.” The program provided the participants a chance to monitor their progress, contributing to a positive and motivating experience during recovery.

Coping and Resiliency During Recovery

The CR program took place during recovery. All patients were affected by HSCT in different ways and to varying degrees. As this was a challenging time for them, the theme of coping and resiliency during CR was very relevant. Coping during recovery was a multi-factorial process and related to goal setting, self-motivation, attitude, and the CR program itself.

The participants’ goal-setting was presented as either an internal process or was influenced by external factors in participants’ lives. Travis found the ability to set goals for himself paramount to his experience. He said,

> You know, you have a goal. And you’ve got unpleasantries along the way. But don’t focus on the unpleasantries. Focus on the goal. And I think that is what people need, is to see the – they have a goal and there’s hope. And the rehab program is how you

> get there. You know, I don't know what my heart output is now. But I am fairly focused on not letting it slip. (Travis)

Cody's motivation to improve his functional status was related to external life factors:

> I had a goal for admitting one of my students for an exam the first week of July of that year. And so, I did everything humanly possible to get myself in shape to do that…I had to be fit – mentally and physically fit. (Cody)

Another sign of resiliency in participants was their attitude. For John, he believed his attitude was important to help him get through the experience, saying,

> And as far as hope… [sighs] attitude going in, or during… the whole treatment and everything else, in my mind, makes a huge difference…. Just in terms of believing that you're gonna get out the other side. And… basically, just…you'll do what – what it takes, you'll plug away. (John)

Staying optimistic and remaining open to the plan was expressed by many as an important tool to achieve successful recovery.

The CR program itself was also identified as a coping mechanism following HSCT. John said, "I guess the biggest thing was, it's just nice to be…to feel looked after, after the treatment, right? Like, to try and get you back into normal life again. There was support." Andrew echoed that sentiment:

> you know, [CR nurse] went through all of the stuff… like cholesterol levels and doing that kind of stuff. So, it was fine. You know, to know somebody looked at those things, though. Right, to give you that little bit of peace of mind…. Like my other doctors, they're just looking for – you know, the cancer coming back… whereas here, they [CR staff] looked at… you know your cholesterol levels. (Andrew)

James believed that CR played a significant, and motivating role in his recovery, saying,

> I don't know that I would have been exercising for at least eight weeks, immediately following my stem cell transplant. Um, if I'd have just been… you know, laying on the

> couch… So I mean, it was a benefit to get me doing stuff. And get me exercising, and I did that, ah, at home. So that was good, ah, because I probably would have – wouldn't have been doing anything otherwise.

Paula agreed that CR was a motivating factor to remain active in her recovery. She said, "I don't think I did seven days a week, but I tried to do at least five. I think it helped to motivate, a little bit. Motivation is hard." John agreed that CR contributed to staying active following HSCT saying, "…it really was a great rehab program, period. Like it got you back into the swing of things and… there was a level of motivation there…"

The Uptake of CR Education

The individuals in this study gained information regarding a heart healthy lifestyle from several sources. They would discuss lifestyle changes face-to-face with CR staff, receive written information, or had the option to attend educational sessions. These education sessions were facilitated by CR staff and cover topics such as stress reduction, heart healthy diet, energy management, smoking cessation, and cardiac medications. In this study, only two of the ten participants attended at least one session. When asked about their experience with sessions, several factors had influenced attendance. Reasons for poor attendance included the following: a lack of advertising, the time it would take to attend, the inconvenience of physically attending the session, and that participants believed sessions were not applicable to them.

When asked if education sessions had been advertised to him, Greg said, "No, I don't think so." When asked if he would have attended if he had known about the sessions, he replied, "I don't think [I] would have benefitted by that, 'cause we kind of… try to follow a healthy lifestyle. But I sure think it would for a lot of people." Cody echoed Greg, saying he likely would have not attended. Travis said, "I think I missed the first one, 'cause I didn't know it was there." Similarly, Andrew found, "[I] don't remember those… I might not have remembered, or not given them any thought at that point in time."

When sessions were advertised, the degree to which attendance was encouraged by CR staff varied. Fred said, “yeah, I never went to those…. Well, they said you don’t have to go to those if you don’t want to.” Inconsistencies in advertising and attitudes towards sessions impacted the degree of uptake. Participants who believed the sessions would be beneficial were more likely to attend; those who perceived little benefit from participating in sessions were less inclined to attend.

The mere act of attending the session was a barrier for some. For Fred, the time it would take to attend the session presented a challenge. He said, “My wife was driving me then, so I mean, she was off work, so I didn’t wanna spend another hour there to…taking up the time and stuff.” Additionally, there were physical barriers impacting Fred’s ability to attend: “… after I was done there [exercising]… then I had to walk back to the vehicle. My back was sore. So I didn’t feel like sitting around anywhere. It was hard enough just, you know, sitting down. I wasn’t gonna spend another hour sitting there [in a session] in pain.” The other reasons highlighted by participants were that they lived out of the city and could not justify driving into the city for sessions, returning to a geographical area close to the cancer centre also was unappealing, and for two individuals, anticipatory nausea even occurred.

For some participants, they did not attend the education sessions as they did not think that they were applicable to their needs. Fred, in addition to other barriers, believed that the sessions would not benefit him as “it was more into the hearts…. Ah, about the people that had – you know, were issues there, with their hearts, it was…what was in the educational part of it.” Conversely, while sessions may not have been applicable, Travis still found them interesting. He said, “Ah, some were excellent. And some really didn’t apply that much to me…. Overall, um…they were interesting. But they weren’t aimed at me.” Education sessions are an important part of secondary prevention in CR. Without attending sessions, the degree to which participants understand and in turn have the ability to control or limit

modifiable CVD risk factors is unknown.

While attendance of educational sessions was poor overall, John identified an energy conservation class as beneficial, saying, "…that energy management thing was a really good thing for me. 'Cause I was pushing too hard…. It put things in perspective, and I slowed down a little bit…. It was way better." While many participants did not attend sessions, or felt they were not applicable to them as HSCT recipients, there is value in sessions that may address the overlap of symptoms experienced by both CV and cancer patients like managing fatigue.

Discussion

While HSCT patients are an unique population referred to CR, similar findings appear in existing CR literature, especially in how perceived CV risk impacts uptake, how barriers impact CR uptake of CR, and also how health care provider attitudes towards CR impact the degree of uptake and adherence.

When considering the uptake of health behaviours, buy-in from participants is necessary (Clark et al., 2013; Neubeck et al., 2011). When HSCT recipients initially became aware of CR, they met a health care provider (medical oncologist or nurse practitioner) who discussed the stem cell collection, transplant processes, risks, and this moment was undoubtedly a stressful time. Stress impacts the retention of medical information (Kessels, 2003; Trammell & Clore, 2014); at the initial meeting, the CV risks associated with HSCT may be forgotten, and consequently not a priority for patients. If the impact of HSCT on their CV status is deemed not important by patients, then they may be less likely to partake in CR. A rehabilitation program developed to address common needs of HSCT recipients, such as cognitive changes or fatigue management, may be more relevant.

Nine of the ten participants identified the exercise component of CR as beneficial; education sessions were poorly attended and generally perceived as not applicable. The one participant who did not find that CR added benefit to his recovery noted that he was already taking part in a self-directed exercise program prior to HSCT. Accordingly, he believed that

he would have been exercising independently. Overall, the participants agreed that completing CR assisted their recovery process from a functional standpoint, as well as offered different levels of support based in individual needs. Support came from CR staff, as well as from community members the participants met while partaking in community based exercise programs.

As studies evaluating CV patient experiences in CR indicate, benefit of social support from peers and family members has been identified as an important contributor to increased participation in CR (Dalal, Doherty, & Taylor, 2015). Some studies have even found social support mediates uptake of physical activity in addition to behavioural goal setting (Stacey, James, Chapman, & Lubans, 2016). Within most CR programs, health related goals in addition to guided exercise, are established by patients with assistance from staff so as to create goals that are applicable to the individual's life context (Heron et al., 2016). For those recovering from HSCT, there is a decrease in functional ability and exercise capacity, and thereby CR provides an avenue to help individuals expedite physical recovery through social support and behavioural goal setting (Fernandez, Rajaratnam, Evans, & Speizer, 2012).

The perceived applicability of heart healthy lifestyle teaching varied from individual to individual. The majority of the participants already perceived their current lifestyle to be in alignment with heart healthy living. This phenomenon has been seen in traditional CR, whereby participants view CR as necessary in others, not themselves (Clark et al., 2013). Additionally, the perception that educational sessions were generally not relevant impacted the participants' desire to participate. The intent behind sending a HSCT patient to CR was to address modifiable CV risk factors through education and exercise. However, if participants do not perceive themselves at risk, then understandably, they were less likely to take part in formal education opportunities. This finding represents a disconnect in participants' knowledge regarding their risks for future CVD, and how they fail to perceive that those risks may impact them in later life.

A potential method to increase the uptake of CR educational content would be to offer alternative strategies of information dissemination outside of the tertiary centre, for example, online links to credible information regarding topics found in CR. Additionally, the use of audiovisual materials containing health promotion information would increase the accessibility to individuals taking part in the program. For those unable or unwilling to attend sessions at the tertiary centre, alternate methods of education delivery may be more effective. Increasing accessibility of information to those unable to attend the tertiary education sessions may improve uptake, however, individuals must first believe their CV risks pose a threat, or else they are unlikely to find the information applicable.

This research was intended to generate a better understanding of the experience of those who were referred to CR following HSCT. Their experiences in CR were linked directly to their time being treated for their lymphoma and were an important influencing factor to their overall experience with CR. This qualitative exploration of the experience of patients who are referred to CR after HSCT exposes a glimpse into the difficult nature of recovery following this life changing treatment. The participants were a heterogeneous group of individuals with varying experiences related to transplant experience, ranging from very little in the way of side effects, to others experiencing a debilitating life change. It would appear that the severity of their side effects from HSCT impacted perceived benefit and attitudes towards CR.

Study Limitations

One of the limitations of this study was the timing of the interview and potentially the cognitive effects of chemotherapy. In all participants, the length of time from treatment and CR, to the participant's interview was greater than one year. Therefore, perspectives on their experiences likely would have changed over time and/or participants may not have remembered their experience in as much detail than if the interview was conducted closer to their participation in CR. In addition to temporal aspects, potential cognitive deficits related

to chemotherapy could have had an impact on the ability of participants to recall their experiences (McDougall, Oliver, & Scogin, 2014).

Another potential limitation is a selection bias. All but one participant identified as being physically active prior to HSCT. Accordingly, most were happy to take part in a program that would assist them in returning to an active lifestyle. It has been identified in exercise studies that volunteers are often more fit than those who do not volunteer (De Souto, Ferrandez, & Saliba-Serre, 2013). It would have been an asset to understand the experiences of more HSCT recipients who were previously not active, and how CR impacted their beliefs regarding exercise and their recovery.

Implications for Cancer Survivors

As cancer therapies continue to improve, cancer survivors are living longer to experience the cardio-toxic effects of certain treatments. Rehabilitative programs such as CR are feasible and safe options for supporting HSCT recipients in the initial recovery following transplant, simultaneously promoting long-term CVD prevention. The benefits experienced by HSCT recipients taking part in CR supports the use of similar cancer rehabilitation programs in other tumor groups (Kirkham, Bland, Sayyari, Campbell, & Davis, 2016; Rajotte et al., 2012; Tomasone et al., 2017). Those treated with HSCT often learn about the long-term risks during stressful conversations (i.e., prognosis, transplant procedures) and may not retain information regarding CV risks following transplant. Efforts should be made to educate recipients about CV risk and prevention prior to HSCT, during treatment *and* throughout recovery.

Conclusion

Including CR into the care for those treated with HSCT has been viewed overall as a positive intervention for recovery post HSCT. The experiences of the participants reflect the heterogeneity of status post HSCT and highlight the need for a CR team to address specific concerns that are apparent in this population. A thorough assessment of the patient

throughout the CR experience is essential to better understand the specific needs of the individual. HSCT recipients found much benefit in subjectively and objectively acknowledging their gains during recovery. Providing individuals with exercise testing reports and verbal acknowledgment of progress may be motivational and have positive effects on patients. Team members should encourage attendance of the education sessions despite individuals taking part in CR as HSCT recipients. Further, CR staff members should be given learning opportunities to better their understanding of the HSCT and common concerns that individuals treated with HSCT may encounter. A resource of common side effects associated with recovery following HSCT and how CR could mitigate those effects should be made available to patients. Of particular significance would be to include a resource explaining (in lay terms) the role of multidisciplinary team members, and how those disciplines can help HSCT patients. Without the direct link to understand how certain team members can address HSCT concerns, patients may not discuss the questions or concerns they experience.

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Chapter Four: Discussion and Conclusions

Significance

This thesis contributes to the literature in several different ways. Within the realm of oncology, it contributes to better understanding the experience of HSCT recipients taking part in rehabilitative programs. While this research focused on *cardiac* rehabilitation (CR) specifically, it could be expected that participants would have similar experiences and perceptions taking part in other, similar exercise based rehabilitative programs. In addition to a rehabilitative lens, this research lends to the growing body of research within the sub-specialty of cardio-oncology.

With health care providers (HCP) recognizing the associated CV risks in cancer survivors, guidelines from the American Society of Clinical Oncology (ASCO) and the Canadian Cardiovascular Society (CCS) are targeting health promotion and disease prevention as a means to limit adverse CV-related outcomes (Armenian et al., 2016; Virani et al., 2016). Consequently, future directions in cancer survivorship care will focus on prevention strategies in cancer survivors treated with cardio-toxic therapies (Faithfull et al., 2017). This research has identified that including CR into the care trajectory of the HSCT is a feasible, and beneficial experience. A strength of the study is my proximity to HSCT processes and patient care. Being certified in stem cell transplant and regularly working as a registered nurse with HSCT recipients allows me to appreciate how debilitating the HSCT process can be. My professional experience in this clinical area was beneficial in better understanding the participant description of their experiences. In ID, it is expected that clinician researchers do have prior knowledge in the area of interest (Thorne, 2016).

Limitations

In addition to the limitations identified in chapter 3, there are other areas that have been identified as limitations. It would have been beneficial to the results of the study to have had more variability in the sample. Specifically, gaining the perspectives of the HSCT

participants who dropped out of the CR program, or who chose not to attend, could have enriched the findings. Perhaps there are other reasons specific to HSCT recipients that would have contributed to those who chose not to attend above and beyond the usual reasons for not attending CR (i.e. geographical, financial barriers, cancer related, perception of the benefits or applicability of CR).

Beyond sample limitations, I found conducting qualitative research using interpretive description (ID) was challenging. Despite regularly consulting a book dedicated to ID, as a novice researcher it is difficult to place qualitative theory into context, particularly when it comes to data analysis. Compared to other traditional qualitative research methods (e.g. phenomenology, grounded theory, ethnography), there are less restrictions in ID. This difference in approach actually contributed to considerable ambiguity in the research process. As Thorne, Reimer-Kirkham, & O'Flynn-Magee (2004) note, the process of data analysis in ID can illuminate seemingly endless possibilities, relationships, and interpretations within the data. Not surprisingly, ID has been identified as posing challenges to novice researchers (Hunt, 2009). Despite the challenges, I believe the degree of uncertainty I was feeling with data analysis could have occurred regardless of the chosen approach. Through practicing critical skepticism when working through my findings, and guidance from experienced qualitative researchers, I learnt to acknowledge the interpretations that I continued to circle back to through repeatedly revisiting the data (Thorne, 2016).

Implications and Recommendations

Cancer patients are living longer as treatments improve, therefore, managing the temporary and long-term effects of cancer therapies must be a priority. While there is no one approach to survivorship care that has been found to be most effective, incorporating innovative approaches to meet the complex needs of cancer patients is the goal (Hebdon, Abrahamson, McComb, & Sands, 2014; Hewitt & Ganz, 2006). Given the known HSCT-

associated CV risks, the referral of transplant recipients by HCPs to CR was an ideal opportunity to use existing resources to expedite short-term recovery, and to teach HSCT recipients about heart healthy life styles. This study found that overall, participants believe that CR is beneficial to recovery, and it provides insight into the experience of HSCT who partake in CR. The following are recommendations based on the findings:

1. CR or cancer rehabilitation programs should be incorporated into HSCT survivorship as a standard of care. Programs that enhance recovery through physical activity and educate patients about limiting modifiable CV risk factors is important. Those treated with known cardio-toxic cancer therapies may especially benefit from a cardiac-focused rehabilitative program.

2. CR educational information should be tailored to include information specifically for HSCT recipients. There were discrepancies in how HSCT recipients viewed their risks for CVD. Reminders for patients about the CV-related impact of HSCT and how CR educational sessions can help them limit their CVD risk may improve participation in educational sessions. In addition to education regarding CV risks, oncology team members may need to provide patients with several reminders (not only prior to HSCT) of their CV risks to emphasize the importance of maintaining positive health behaviour changes.

3. Apart from CV information specific to HSCT recipients, the CR staff should provide information on the role of the multidisciplinary team and how those team members can support individuals during their recovery. During the interviews, participants identified that they were unaware of the number of disciplines that they had access to during CR. As health care providers, we often take for granted our knowledge of the roles of the team members; patients may not understand those roles and consequently not know that there is available support for their specific concern. As HSCT recipients have specific concerns different from traditional CV patients who take part in CR, CR staff may need support from oncology staff with regards to resources and teaching. Providing resources to patients is

important, however participants must also be encouraged to *ask* questions if they have concerns during recovery.

4. Increasing formal social support for HSCT patients. While the findings of chapter 3 do not focus on social support during HSCT and into recovery, participants would often acknowledge that social support played a role in their recovery. Social support from family as well as other patients was identified as motivating to maintain exercise and health lifestyles. In addition to the perceived beneficial impact of social support on exercise, participants also identified that they could have found social support from other transplant recipients beneficial. Further, some believed they could have benefitted from mentorship from other survivors who have been treated with HSCT.

Participants highlighted the benefits of sharing stories with others and how hearing about others experiences carried more weight than hearing about HSCT from HCPs. While this does not necessarily focus on CR in particular, finding community and social support with other HSCT recipients may improve the recovery experience in various domains (Amin, Neuner, Duthie, Finn, & Kong, 2014; Pistrang, Jay, Gessler, & Barker, 2013; Rini et al., 2007) . Developing a social support group for HSCT patients who enroll in CR or using programs such as the "Peer Support Program" developed by Lymphoma Canada should be advertised to patients for added support from someone who has been through HSCT (Lymphoma Canada, n.d.).

The benefits of exercise in cancer patients is widely acknowledged as beneficial (Saxton & Delay, 2010). As CR is a well-established exercise-based program in Alberta, existing resources, methods of delivery, and principles of health behaviour change can easily be incorporated into cancer survivorship care. Newer cancer specific rehabilitation programs are still in infancy stages, and accessibility is lacking when compared to CR, which has proven delivery methods such as community-based and telehealth approaches for remote communities. Currently, cancer rehabilitation programs are limited to urban centres in

Alberta therefore, CR is a way to support HSCT recipients who may have limited access to other rehabilitative programs during recovery.

Knowledge Dissemination

The findings within this thesis have already been shared in multiple venues, and there are several opportunities for dissemination in the future. The manuscript attached as Appendix A has been submitted to *Current Epidemiology Reports*. The findings of Chapter 3 will be presented at the annual Cardio-Oncology Summit 2017 in London, UK. I have submitted an abstract for both to present in poster format, and have applied for the young investigators award which will provide the opportunity for an oral presentation if successful. For future dissemination, it is my plan to submit Chapter 3 findings to other venues, specifically, the 2018 Canadian conference on lymphoproliferative disorders (CCOLD), and the 2018 annual Canadian Association of Nurses in Oncology (CANO) conference.

The findings in Appendix B have already been presented at several venues. Poster presentations at Cancer Research Institute of Northern Alberta (CRINA), CCOLD 2016 (Author nominated for young investigator's research award), CANO 2016. In addition to poster presentations, I was an invited speaker to Mazankowski Alberta Heart Institute's cardiology rounds (November 2, 2016) and Oncology Nurses Interest Group of Alberta (ONIGA) south chapter learning day (February 17, 2017). I have worked hard to share the results of this novel approach to cancer survivorship and have had the opportunity to develop presentation skills and connections with other health care providers interested in cardio-oncology provincially, and nationwide. The manuscript attached as Appendix B will be submitted for publication to the *Journal of Oncology Practice*.

Future Questions and Theory Development

The outcomes of this thesis, naturally have me left considering future research opportunities and even considering a theory to help explain the uptake of CR in HSCT populations. More importantly, how HSCT recipients are influenced to maintain healthy

behaviours.

Future Areas of Research

There are several potential avenues to focus research efforts. In the qualitative realm, I believe that there is a good opportunity to gain the perspectives of CR staff who provided care to HSCT recipients. It would be beneficial for further program development to understand the experiences of the staff who were challenged to provide a familiar service, to an unfamiliar patient population. How did the change in patient population impact their practices? What approaches worked, or didn't work? How comfortable were they providing lifestyle advice to a different population? How did they perceive the uptake of services by HSCT recipients? What where the differences they found between the typical CV patients and HSCT recipients? How did their lack of familiarity with oncology as a whole impact their confidence with working with HSCT patients? It may be of benefit to understand the challenges or differences, perceived by CR staff, in program delivery so as to inform future initiatives to rehabilitate cancer survivors in programs generally reserved for other specific populations, or for educative purposes for fitness instructors in community fitness facilities.

Within the quantitative realm, a randomised controlled trial (RCT) examining current standard of care vs including CR and its impact on ATP results is necessary. Presumably, those who take part in a guided exercise program (CR) would be found to have an expedited recovery compared to those left to navigate their recovery independently as with current standard of care practices. A RCT would provide the necessary evidence to support the inclusion of HSCT patients into CR programs and potentially support including this program for other populations treated with cardio-toxic cancer treatment.

The benefits of a controlled environment would be that data would be collected and monitored by a designated coordinator to ensure minimal missing data. For example, it was found during the process of data collection for appendix B, various QoL and functional questionnaires were inadequately collected creating a large gap in the data. The ability to

consistently capture perceived QoL and functioning data would help illuminate what changes occur in HSCT recipients' perceived QoL and functional status with statistical analysis. Quantitative data could then be viewed in combination with qualitative data to better understand how HSCT recipients perceive CR *and* how they perform during exercise testing as a result of enrolling in CR.

Theory Development

Another area of future work would be to develop and test a theory to help explain the uptake of health behaviours in HSCT recipients. One criticism of CR is that the changes are not maintained in the long-term in most patients (Clark, Whelan, Barbour, & MacIntyre, 2005). The poor uptake of *long-term* healthy lifestyle behaviours has been investigated in a variety of chronic health conditions and is a challenging health phenomenon that continues to puzzle researchers. From the use of technology, to incentivizing health behaviour, to interventions as simple interventions as simple as learning how to plan activity into one's schedule; the secret to guaranteeing permanent health behaviour change eludes most (Desroches et al., 2013; Fappa et al., 2008; Mitchell, Goodman, Alter, Oh, & Faulkner, 2014; Van Vugt, De Wit, Cleijne, & Snoek, 2013). For HSCT patients, they are placed in a position where limiting modifiable CV risk factors is important given the deleterious CV effects of the treatment they receive (Abdel-Qadir, Amir, & Thavendiranathan, 2016; Baker, Armenian, & Bhatia, 2010; Chow et al., 2011; Chow et al., 2014; Truong, Yan, Cramarossa, & Chan, 2014; Virani et al., 2016).

In the context of CR, the goal is primary or more commonly secondary prevention of CVD and CV related adverse events (Astley et al., 2016; Dalal, Doherty, & Taylor, 2015). The rationale for the referral of HSCT recipients to CR was to 1) rehabilitate patients after deconditioning while admitted in hospital for HSCT and 2) provide heart healthy lifestyle education to prevent CVD in later life. Within the data analysis for this research (Chapter 3 findings) I couldn't help but begin to piece together the relationships that may predict the

uptake of healthy behaviours geared at limiting CV risk factors in HSCT recipients (Figure 4.1).

Analysis of the transcripts revealed that there are some potential factors in the HSCT-recipient context that may impact the degree of CR uptake and long-term health behaviour changes. The extent of pre-HSCT attitudes towards exercise and baseline exercise behaviours; the patient perceived degree of cancer treatment and/or HSCT-associated morbidity; the patient perceptions of CV risks associated with HSCT (influenced by personal views and HCP teaching); and the amount perceived social support may impact the degree of HSCT recipients' uptake and buy-in to CR, and even long-term health behaviour changes.

Pre-HSCT Health Behaviours.

Familiarity with exercise and health behaviours in general appear to have an influence on the desire to maintain physical activity as part of one's lifestyle. In the transcripts, participants identified exercise as an important part of successful recovery, however, they generally would reflect on past experiences. Their views on exercise were based on their past activity levels which they perceived as beneficial and having positive effects on their life. This understanding of exercise as beneficial was a motivating factor to return to previous levels of functioning, and an understanding that exercise could bring the goal of reaching previous levels of functioning a reality. For the one participant in the study who did not consider himself physically active prior to HSCT, he acknowledged that he continued to live an inactive lifestyle upon CR completion. Despite understanding the potential negative effects on his risk for CVD and overall health status, he continued to lead a minimally active lifestyle. The familiarity of exercise, and an understanding of the subjective benefits previously experienced by individuals, may impact the likelihood that HSCT recipients will be motivated to continue with exercise, or other healthy behaviours (i.e. diet) in the long-term.

Degree of HSCT-Associated Morbidity.

Another influencing factor impacting the uptake of CR and long term health behaviours is the severity of perceived morbidity experienced by patients. While it was never explicitly stated, it would appear that the degree to which participants were debilitated during HSCT hospital admission may play a role in the desire to return to baseline functioning. For one participant, he believed he experienced very little side effects compared to others. He did note muscle loss and a considerable decrease in exertional stamina, however, he did not believe that the transplant was a cumbersome experience. Consequently, he did not feel as though he had suffered an extreme loss to his level of functioning, and as such, the drive to pursue an aggressive exercise regimen to regain functioning was not apparent. For this individual, he was not previously physically active, and as such, living an active lifestyle was not a priority for him.

Interestingly, for those who perceived being treated with HSCT as a debilitating or life-changing experience were motivated to return to previous levels of functioning. As most of the participants in the study were previously active, perhaps attempting exercise that had been familiar to them prior to HSCT, and recognizing the difficulty and stark decrease of their strength and endurance immediately following treatment, created motivation to return

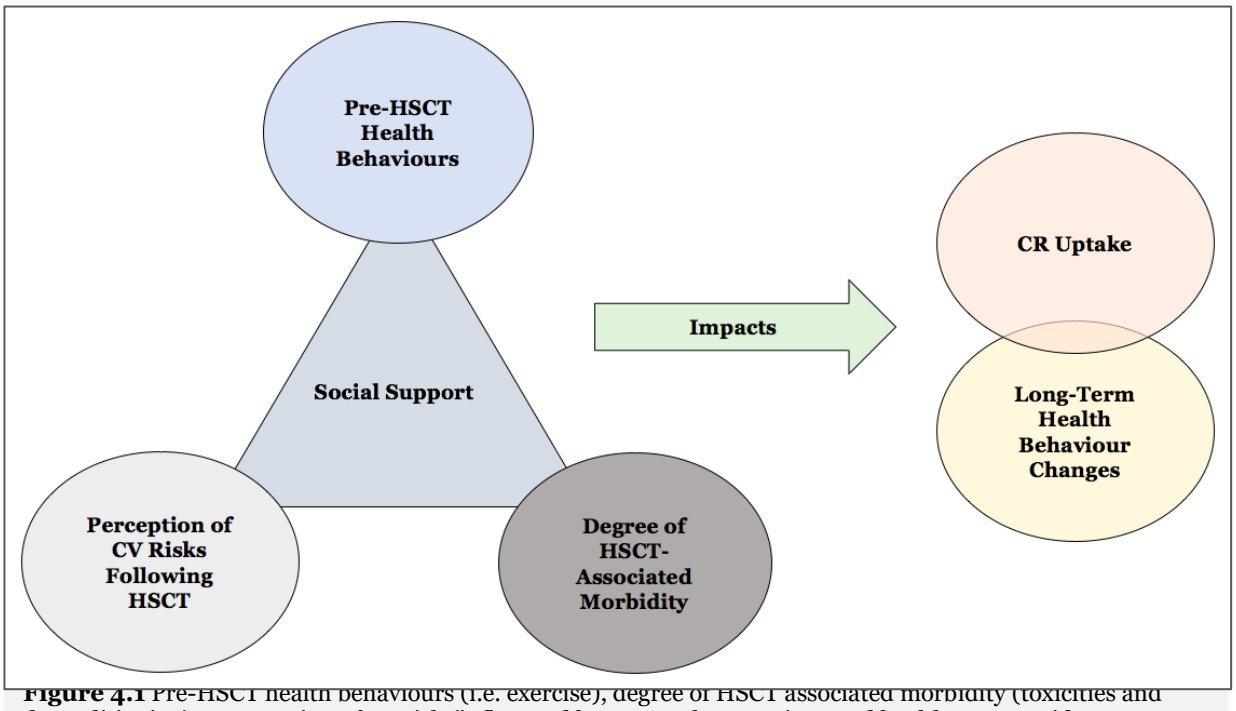

Figure 4.1 Pre-HSCT health behaviours (i.e. exercise), degree of HSCT associated morbidity (toxicities and deconditioning) & perception of CV risk (influenced by personal perceptions and health care provider emphasis) = Degree of CR uptake and long term health behaviour maintenance. Another impacting factor was the degree of perceived social support during CR from friends, family, and/or peers also enrolled in exercise programs.

to the previous level of functioning they had before treatment.

Perception of CV Risks Following HSCT.

The rationale for HCPs to refer HSCT recipients to CR was initiated due to the known risks for CVD following treatment. However, in the interviews it would appear that the risk for heart disease was not generally a priority for HSCT recipients. While there were several who acknowledge that they understood they had an increased risk for CVD, they tended to focus more on their cancer diagnosis and risk for recurrence. Understandably, when they first hear about CR, they are being taught about the whole HSCT process and plan, and their focus is not on CR at the time. I believe that another impacting factor on the degree of behaviour change and management is likely influenced by HSCT recipient's perceptions of their CVD risk, and the role it plays in relation to other priorities in their lives (i.e. risk for cancer recurrence).

The potential to develop and test this theory could result in providing a framework to guide appropriate and focused interventions that would allow for optimal uptake of health behaviours. HCPs could use this theory to facilitate supporting HSCT recipients in the short term following HSCT and in the maintenance of long-term health behaviour changes to mitigate the risk of CVD in later life. For example, increased exposure to information in the risk of CVD following HSCT may increase the degree to which patient perceive CR as a priority. For those who were greatly affected by the effects of HSCT, they may benefit from support that focuses on motivating them to achieve baseline levels of function and a mutual (between CR staff and patient), agreed-upon goals to reach for. Conversely, those who may not have experience debilitating side effects may need even more support (i.e. more reminders, longer follow-up) to make exercise a priority in their lives. In addition to extra support, their level of understanding of this CVD risk must be assessed and education provided in order to begin to prioritize healthy behaviours.

Social Support.

A potential contributor to the uptake of health related behaviours is the degree of social support available to individuals. Several participants in this study found internal motivation when taking part in CR, however, there were several who agreed that social support positively impacts motivation to exercise. Social support in the form of fellow participants, friends, family, and even CR staff all appeared to improve the uptake of health behaviours. Perhaps a screening tool to assess the degree of social support that the participant has available may help to guide the approach to adopting healthy behaviours. For example, if a HCP found the patient to have low social support, they could educate the patient on how important having social support can be to increase exercise and increase other healthy behaviours (i.e. smoking cessation, diet, stress). Also, the HCP could inform the CR program that the participant may benefit with social interaction with other participants.

Conclusion

This study was aimed at exploring the experiences and perceptions of HSCT recipients referred to CR following transplant. The findings suggest that there are similarities and differences between the experiences of HSCT recipients and traditional CV patients who partake in CR. The findings suggest that HSCT recipients focus their priorities differently during recovery. Some prioritized CR as a way to give back to the oncology team, others were more focused on a recurrence of their cancer and so CV health was not necessarily their priority. Additionally, participants' experiences and views on CR are directly linked to their experiences during HSCT.

Resiliency and coping throughout recovery and taking part in CR highlighted the role of goal-setting, self-motivation, patient attitudes, the CR itself for contributing to successful recovery. Finally, how participants experienced the uptake of CV related information was influenced by the perceived applicability of the information to them as cancer patients versus CV patients, the amount of advertising of educational sessions, and the CR staffs' attitudes towards patient participation. Despite the participants largely believing the educational

sessions were not applicable to their needs, there is still potential to highlight how certain sessions may benefit participants as HSCT recipients (i.e. fatigue management). As cancer treatments improve, patients live longer, cancer survivorship care practices are gaining more attention. This work contributes to the growing body of knowledge regarding the experience of those recovering from HSCT, and how they may view their health risks long-term. It is clear that rehabilitative programs for cancer patients provide benefit, how exactly those programs should be deliver remains to be seen.

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Appendix A

Prevention of Cardiovascular Disease Among Cancer Survivors: The Role of Cancer Treatments and Pre-Existing Risk Factors*

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Abstract

The two leading causes of death in North America are cardiovascular disease (CVD) and cancer. As a result of necessary cancer treatments, survivors are at an increased risk of CVD. The contribution of cardio-toxic chemotherapy, targeted therapy and radiation therapy to CVD are discussed. **Purpose of Review:** This paper addresses shared CVD and cancer risk factors (smoking tobacco, diet, obesity, sedentary lifestyle, hypertension, alcohol consumption, and hyperlipidemia) and the influence on cardiovascular outcomes in those treated with cardio-toxic cancer therapies. **Recent Findings:** Strategies for prevention of CVD in cancer survivors is gaining more attention through rigorous screening, long-term surveillance, and referral to multidisciplinary cardio-oncology teams. Additionally, interventions such as exercise prescription in the setting of cardiac rehabilitation, and pharmacologic approaches are suggested to lessen the burden of CV related toxicity in cancer survivors treated with cardio-toxic therapies. **Summary:** Those with modifiable CVD risk factors treated with cardio-toxic cancer therapies are at an increased risk for cardiac dysfunction. Strategies for prevention, surveillance, and management include the integration of cardio-oncology teams and rehabilitation programs into cancer survivorship care.

Keywords: Cardio-oncology, cardio-toxic treatment, cardiovascular disease, risk factors, prevention

Prevention of Cardiovascular Disease Among Cancer Survivors: The Role of Cancer Treatments and Pre-Existing Risk Factors

Introduction

Approximately half of all deaths in North America are a result of cardiovascular disease (CVD) or cancer (Statistics Canada, 2015; States, 2015). Despite the progress and improved efficacy of today's cancer therapies, the toxicities associated with cancer treatment can have detrimental effects on the cardiovascular (CV) system. Specifically, toxicities associated with many necessary cancer treatments may result CV morbidity such as hypertension (HTN), atherosclerosis, arrhythmias, and serious cardiac events such as myocardial infarction (MI), stroke, and heart failure (HF) (Arthur et al., 2010; Bloom et al., 2016; Truong, Yan, Cramarossa, & Chan, 2014). With both CVD and cancer sharing many of the same modifiable and non-modifiable risk factors (Koene, Prizment, Blaes, & Konety, 2016), it is especially relevant that pre-existing CVD risk factors are considered in cancer patients receiving cardio-toxic therapies (Figure i) (Johnson, Davis, Law, & Sulpher, 2016).

With the number of cancer survivors estimated to reach over 19 million by 2024 (Institute, n.d.), the need for early and intensive prevention and monitoring of modifiable CVD risk factors is necessary for optimal CV health following cancer treatment (Johnson et al., 2016). This growing health issue must be taken seriously, for as treatments improve, individuals are now surviving to experience the potentially debilitating effects of treatment-associated CVD (Truong et al., 2014). Furthermore, as the world of cancer therapy continues to evolve, the risk for treatment associated CVD may expand into tumor groups not currently affected. Accordingly, diligent assessment of risk, prevention, and observation of those who have received cardio-toxic cancer treatment is paramount.

The aim of this review is to briefly discuss modifiable risk factors of CVD in the context of cancer survivors following cardio-toxic therapies. Common cancer treatment modalities known to contribute to the development of CVD will be described. Modifiable CVD

risk factors and the need for their prevention will also be reviewed. Lastly, preventative approaches in this complex population will be addressed.

Figure i. Intersection of cardiovascular and cancer-related factors

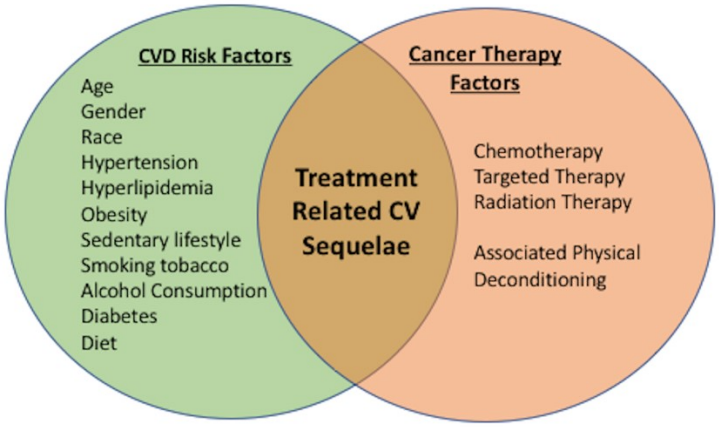

Figure i. CVD=Cardiovascular Disease; CV=Cardiovascular

Cancer Treatment Associated Cardio-Toxicity

Modifiable risk factors which precipitate CV disease are also established factors that lead to cancer, including obesity, smoking, unhealthy dietary habits, and sedentary lifestyle (Johnson et al., 2016). As such, it is not uncommon for cancer patients to also have sub-clinical or established heart disease among other comorbid conditions (Patnaik, Byers, Diguiseppi, Denberg, & Dabelea, 2011). With multiple modalities commonly used to treat cancer, there are several mechanisms where by CV health is impacted. Chemotherapy, targeted therapy, and radiation therapy are avenues in which cancer patients may have an increased risk for CVD. Previously, the known cardio-toxic side effects of treatment were largely ignored due to the guarded prognosis associated with cancer (Truong et al., 2014). Today, cancer–specific outcomes have substantially improved, with patients living long enough to experience cardiac dysfunction related to cardio-toxic therapies (Truong et al., 2014). As the cardio-toxic effects may be seen many years after completion of treatment, the need for early consideration of CVD prevention is important to preserve long term CV health for cancer survivors.

Chemotherapy

Despite known cardio-toxic effects, the anthracycline chemotherapies (e.g. doxorubicin and epirubicin) have been an effective mainstay of cancer treatment for both solid tumors as well as within malignant hematology (Groarke & Nohria, 2015). Effects of anthracyclines on the CV system are attributed to direct cellular damage to cardiomyocytes through multiple pathways affected by oxidative stress and DNA mutations (Geisberg & Sawyer, 2010; Kankeu, Clarke, Passante, & Huber, 2017). The resulting cumulative effects lead primarily to cardiac dysfunction demonstrated by a decrease in left ventricular ejection fraction (LVEF), however atrial fibrillation has also been reported (Kankeu et al., 2017; Truong et al., 2014). Cumulative doxorubicin doses of 350mg/m^2-450mg/m^2 are thought to be acceptable, however, 18% and 38% of patients experience left ventricular (LV) dysfunction, respectively (Swain, Whaley, & Ewer, 2003). The onset of detectable cardiac dysfunction varies, occurring early as during the administration of anthracycline-based regimens or many years thereafter (Volkova, Russell, & Russell Iii, 2011). Unfortunately, HF is associated with considerable morbidity and approximately 35%-50% will die within 5 years of diagnosis (Gaglianello, , Nunzio, Mahr, & Benjamin, 2016).

Immunotherapy

Another cardio-toxic and commonly prescribed systemic therapy in the treatment of HER2 expressing breast cancer is the monoclonal antibody trastuzumab (Hudis, 2007). Trastuzumab targets the erbB2 (HER2) receptor tyrosine kinase 2, promoting cell death in breast cancer cells overexpressing the HER2 receptor (Hudis, 2007). Unfortunately, the HER2 receptor plays a key role in the growth and preservation of cardiomyocytes (Crone et al., 2002). Consequently, trastuzumab's anticancer effects through HER2 dysregulation results in potentially significant cardiac dysfunction (Crone et al., 2002; Escalante et al., 2016). In a Cochrane review of 8 studies (n = 11, 991 patients), Moja et al. (2012) emphasized that the overall survival benefits of trastuzumab-based therapy (HR 0.66) must be balanced with the significantly increased risks of congestive heart failure and left ventricular ejection

fraction decline (RR 5.11 and RR 1.83 respectively). Other reviews showed that common CVD risk factors (HTN, diabetes, and age) and previous anthracycline exposure contribute to the incidence of cardiac dysfunction in patients treated with trastuzumab (Jawa et al., 2016).

Other common targeted agents utilized in multiple cancer populations, include the monoclonal antibody bevacizumab and tyrosine kinase inhibitors such as, sorafenib and sunitinib which can convey an increased risk for impaired LVEF, HF, and HTN (Z. Chen & Ai, 2016; Menezes et al., 2016; Ranpura, Pulipati, Chu, Zhu, & Wu, 2010). The mechanism by which cardio-toxicity occurs in vasoendothelial growth factor (VEGF) agents like bevacizumab is not fully understood, however, it is hypothesized that associated HTN with anti-VEGF therapy such as bevacizumab occurs via a decreased vasodilation from lack of nitric oxide, oxidative stress, vascular remodelling, and potentially even dysfunction of the autonomic nervous system (Escalante et al., 2016; Menezes et al., 2016). A meta-analysis by Escalante et al. (2016) found those treated with targeted agents are also at considerable risk for MI (RR of 11.0 in sorafenib) and decreased LVEF RR of 9.4 and 4.3 in sorafenib and sunitinib, respectively. The impact of sorafenib and sunitinib on HTN varies with RRs ranging from 3.6-10.3 in some studies (Escalante et al., 2016). Targeted therapies represent a new era for cancer treatment and as this class of therapy evolves, so too should the CV status of patients be considered

Within the specialty of malignant hematology, anthracyclines and targeted therapies are commonly prescribed sequentially and/or concurrently. A recent study examining CVD in lymphoma survivors found 42% of individuals express subclinical cardiac dysfunction and demonstrate overt signs of HF 2 to 10 years following treatment when compared to age-sex matched cohorts in the general population (Reilly, Esiashvili, Parashar, & Higgins, 2016). Hematology patients treated with myeloablative, conditioning chemotherapy as part of hematopoietic stem cell transplant (HSCT) are also greatly affected by cardio-toxic outcomes. Not only does the risk of MI, HF, and cerebrovascular disease increase by 4-fold, but the

incidence of HTN, hyperlipidemia, and diabetes increases an astounding 7.0-15.9 -fold in those treated with HSCT (Armenian et al., 2012; Armenian, Chow, & E.J., 2014; Scott, Armenian, et al., 2016). In their review, Scott et al. (2016) highlight the multi-factorial nature of cardio-toxicity in HSCT patients as a result of direct and indirect mechanisms contributing to CV dysfunction. The combination of direct CV effects of high-dose chemotherapy, mediastinal radiation therapy (if necessary), and the indirect effects of pre-existing CVD risk factors exacerbated by physical deconditioning while patients are admitted for transplant, all contribute to the high rates of CVD in HSCT survivors (Chow, Wong, et al., 2014; Scott, Armenian, et al., 2016).

Radiation Therapy

The systemic therapies described are not the only causes of cardiac dysfunction related to cancer therapy. Common cancers such as, breast, esophageal, testicular as well as lymphoma with mediastinal disease undergo thoracic radiation, significantly increasing their risk for cardiac dysfunction through exposure of cardiac tissue and coronary vasculature (Marmagkiolis et al., 2016).

The pro-inflammatory state induced by radiation leads to fibrosis of the vasculature and cardiac tissues leading to altered perfusion, kinesis, and filling (Nolan, Russell, & Marwick, 2016). Additionally, oxidative stress-responses within the vasculature leads to hastened atherosclerosis in vessels exposed to radiation. Consequently, cardiac irradiation leads to accelerated coronary artery disease (CAD) and potentially HF (Yeboa & Evans, 2016). Survivors who received chest irradiation with fields overlapping the heart conveyed a relative risk of 7.4 for coronary events (i.e. MI) per 5 Gy over 50 years (Cutter et al., 2015; Darby et al., 2013). A recent systematic review of 38 articles examining the effects of heart irradiation found, in spite of heterogeneous approaches hazard ratios for HF ranged from 1.5-2.4 within the breast cancer population (n=71,378) and 2.7-7.4 in those treated for Hodgkins disease (n=8,501) (Nolan et al., 2016). Just as the heart vasculature is affected by radiation so

are the vessels of the head and neck (Mahmood & Nohria, 2016). Those treated with cranial or neck radiotherapy have been found to be at an increased risk for carotid stenosis contributing to stroke (Mahmood & Nohria, 2016). The effects of radiation to the CV system adds to the need for prevention, surveillance, and management to prevent CV-related morbidity following cancer treatment.

Risk Factors for CVD and Cancer

As the two leading causes of death in North America, CVD and cancer share certain modifiable and non-modifiable risk factors (Johnson et al., 2016). For the purposes of this review, only modifiable risk factors related to lifestyle practices and the need for their prevention will be addressed. In cancer patients receiving cardio-toxic treatments, the number of modifiable CVD risk factors impacts the degree to which cardiac dysfunction is likely to occur. As such, prevention of CVD risk factors is likely beneficial for patients receiving known cardio-toxic cancer therapies (Johnson et al., 2016).

Smoking

The use of tobacco, predominantly smoking, is one of the largest documented contributors to CVD and cancer. Currently, an estimated 15% of individuals smoke tobacco in the United States (Benjamin et al., 2017). Recently, a meta-analysis examined the number of premature deaths that were prevented as a result of tobacco control. It was found approximately 8 million deaths were prevented by tobacco reduction initiatives (Holford et al., 2014). Since smoking was initially publicised as detrimental to health in the 1960s, the rates of smoking have declined considerably however, there is still work to be done (United States Department of Health and Human Services, 2014). The known benefits of smoking cessation and tobacco control mean efforts must be made to reduce or eliminate the use of tobacco in cancer patients not only to improve CV health but to improve prognosis, prevent secondary cancers, and potentially prevent recurrence (Eyre, Kahn, & Robertson, 2004; Liu et al., 2016; Schnoll et al., 2004; United States Department of Health and Human Services,

2014). Additionally, for cancer patients receiving targeted therapies, specifically TKIs, smoking may interfere with efficacy of treatment (Zhang et al., 2015).

Obesity

Obesity has been a known contributing risk factor to both CVD and cancer and a major area of health promotion to be emphasized with patients (Koene et al., 2016). The direct CV effects of obesity can be found through mediated effects within cardiac circulation, endothelial dysfunction, and increased atherosclerosis (Bays, 2011). Other resulting clinical manifestations of obesity are HTN, Type 2 diabetes, metabolic syndrome, hyperlipidemia, all contributing factors to CVD (Bays, 2011). Importantly, being overweight is linked to the development of both colon and breast cancers and is believed to contribute to recurrence of cancer after treatment (Arnold et al., 2015; Kolb, Sutterwala, & Zhang, 2016). The increased incidence of obesity in breast cancer patients is worrisome as this population is more likely to receive cardio-toxic treatments (Guenancia et al., 2016). Additionally, Individuals with elevated body mass index (BMI) are at an increased overall risk for HF meaning, breast cancer patients who are obese *and* receiving cardio-toxic therapies are at a substantial risk for CV dysfunction (Guenancia et al., 2016; Pandey et al., 2017). Obesity must be addressed in cancer survivors, not only to prevent CVD, but to prevent recurrence. Weight loss should be encouraged through the initiation of dietary and exercise interventions to lower elevated BMI and improve the health of cancer survivors (Patlak & Nass, 2012).

Diet

Diet plays a large part in the maintenance of CV health. Current guidelines from the United States Department of Agriculture (USDA) and the United States Department of Human and Health Services (HHS) highlight five core dietary recommendations to promote CV health. Recommendations include: lifelong healthy eating patterns, diet that includes variety, aiming for the consumption of nutrient dense foods; maintaining a low caloric intake (<10% of daily calories) of foods high in sugar and fats and limiting the consumption of

sodium (Agriculture, 2015). Recent evidence regarding limiting sodium intake to less than 3G per day in individuals without HTN, suggests the restriction may actually increase the risk for heart attacks, HR 1.26 (95% CI 1.10-1.45; p=0.0009), as such education on limiting sodium intake should be directed to those with HTN (Mente et al., 2016). Positive dietary modifications should be stressed to those who are being treated or have been treated with cardio-toxic cancer therapies as a means to limit risk factors for CVD. Strategies to encourage the adoption of these recommendations have been achieved through various supportive interventions such as feedback and planning, individualized goal-setting, and self-monitoring of progress (Artinian et al., 2010; Janssen, Gucht, Dusseldorp, & Maes, 2013).

Sedentary Lifestyle

Often associated with obesity, sedentary lifestyle is a major contributor to CVD and an epidemic in North America. Not only is inactivity linked to the development of both CVD and cancer, but it poses considerable risks for those following cancer treatment (Nelson et al., 2016; Proper, Singh, Van Mechelen, & Chinapaw, 2011; Van Blarigan & Meyerhardt, 2015). A prospective study found that breast cancer survivors had low levels of physical activity with individuals spending nearly 80% of their day sedentary (Sabiston, Brunet, Vallance, & Meterissian, 2014). This highlights the likelihood that survivors of breast cancer patients will have a drop in moderate to-vigorous physical activity within the first year of treatment (Sabiston et al., 2014). A meta-analysis examining the effects and modifying factors of exercise in patients with cancer emphasizes the need for supportive cancer rehabilitation programs for cancer survivors (Buffart et al., 2017). Such programs would ensure physical activity is made a priority during recovery post treatment to increase physical functioning, aid early return to work and enhance overall quality of life (Buffart et al., 2017), but also for the long term prevention and management of CVD (Pandey et al., 2017).

HTN

A well-known modifiable risk factor for CVD, chronically high blood pressure contributes to the development of atherosclerosis, coronary artery disease, HF, and stroke (American Heart Association (AHA), 2017). The deleterious effects of HTN evolve over time as a result of adaptations to increased arterial pressure and workload (Vongpatanasin & Victor, 2016). Elevated blood pressure can be prevented and treated through lifestyle modifications such as weight loss, regular physical activity, medical management, reduced alcohol consumption, stress management, and low dietary sodium (Leung et al., 2016). As discussed previously, certain monoclonal antibodies and VEGF therapies, increases the risk for HTN (Wasserstrum et al., 2015). As HTN contributes to overall cardiac morbidity and mortality, efforts to prevent, diagnose, and treat early are paramount (Ranpura et al., 2010). Implementing the above lifestyle modifications would be anticipated to positively affect blood pressure, however, the use of pharmacologic agents (beta-blockers [BBs] and angiotensin converting enzyme inhibitors [ACE-Is]) to reduce blood pressure and overall workload on the heart can also be cardio-protective for patients who receive specific cancer treatments such as trastuzumab-based chemotherapy (Anderson et al., 2016; Parent, Pituskin, & Paterson, 2016)

Alcohol Consumption

While low to moderate alcohol consumption has been associated with cardio-protective effects, individuals who consume higher amounts of alcohol are at risk for cardiac dysfunction (O'Keefe, Bhatti, Bajwa, DiNicolantonio, & Lavie, 2014). In addition to HTN, increase in both ischemic and hemorrhagic stroke, atrial fibrillation, and dilated cardiomyopathy can be associated with moderate to high amounts of daily alcohol consumption (Catena et al., 2016; O'Keefe et al., 2014). The safe daily recommended volume of alcohol has been determined to be </= 2 drinks in men, and </= 1 drink in women (Leung et al., 2016). The AHA (2015) defines 1 drink as 12 oz. of beer, 4 oz. of wine, 1.5 oz. of 80-proof spirits, or 1 oz. of 100-proof spirits. Simply reducing one's intake of alcohol can have

positive effects on blood pressure. Health care providers must emphasize the importance of moderation in alcohol consumption for cancer survivors (Leung et al., 2016).

Hyperlipidemia

Hyperlipidemia affects an estimated 30% of individuals in the United States (Benjamin et al., 2017). Those most at risk for adverse CV events include individuals with a Framingham risk score of 7.5% or greater (Stone et al., 2014). The main effect of hyperlipidemia on the CV system is its role in the development of atherosclerosis, increasing the risk for ischemic coronary events and stroke (Gopalakrishnan & Smith, 2016). Current guidelines recommend the use of lifestyle modification (diet, weight loss, and physical activity) and pharmacologic agents (statins) to maintain satisfactory lipid levels and prevent CVD (AHA, 2017a). Hyperlipidemia frequently occurs in combination with other modifiable CVD risk factors, as in the case of metabolic disorder (Kassi, Pervanidou, Kaltsas, & Chrousos, 2011). Due to the insidious nature of hyperlipidemia, appropriate screening must be undertaken in cancer survivors at a high risk for CVD (Parent et al., 2016).

Diabetes

In the United States, an estimated 23 million individuals have diabetes, and nearly 8 million others are likely undiagnosed, and a staggering 81 million are considered pre-diabetic (Benjamin et al., 2017). In addition to being a well-known contributor to CVD, particularly in those with type II diabetes, the risk for cancer is also increased (AHA, 2016; Giovannucci et al., 2010; Vigneri, Frasca, Sciacca, Pandini, & Vigneri, 2009). Cancer survivors have also been observed to have a higher rate of developing diabetes following treatment compared to matched control groups (Allen et al., 2016; Armenian et al., 2012; Chow, Baker, et al., 2014; Singh et al., 2016). Further, the added burden of diabetes in addition to a past cancer, can contribute to worse overall health outcomes and quality of life in those affected (Onitilo et al., 2013; Tang et al., 2016). Care providers must conduct regular screening and comprehensive

assessments of diabetic management and care to improve quality of life, thus decreasing the risk for CVD in later life (Armenian et al., 2016).

Prevention of Cardiac Dysfunction:

Recommendations for CVD prevention, management, and surveillance

Expert opinion of both oncologists and cardiologists agree that the risk of developing cardiac dysfunction following cancer treatment is impacted by the number and degree of pre-existing traditional CV risk factors (Armenian et al., 2016; Virani et al., 2016). When considering the prevention of CVD and cardio-toxicity risk factors, targeting modifiable risk factors is essential. Additionally, patients who are at a higher risk for cardio-toxicity must be rigorously screened and risk factors addressed by integrating cardiology colleagues if necessary.

With increased recognition of the large scope of this problem, there have been efforts to establish recommendations to guide oncologists in determining the degree of risk for cardio-toxic effects of cancer treatment. The American Society of Clinical Oncologists (ASCO) outline the risks for cardiac dysfunction patients who are considered for cardio toxic treatment regimens (Armenian et al., 2016). Generally, any treatment protocol that includes high dose anthracyclines, high dose radiotherapy to the mediastinum, or combinations of anthracyclines, trastuzumab, and radiotherapy increases the risk for CV dysfunction (Armenian et al., 2016). Apart from treatment related risks, ASCO states that even at low doses of cardio-toxic treatments whereby pre, during, or post treatment the patient has at least 2 CVD risk factors including: known heart disease (borderline LVEF, valvular disease, and history of MI), ≥ 60 years of age, HTN, smoking, hyperlipidemia, diabetes, obesity; are at risk for deleterious CV sequelae. Those patients with known CVD risks require assessment and deliberation regarding the risks and benefits of receiving cardio-toxic therapies, and should be considered for other approved therapies if necessary (Armenian et al., 2016).

Regular screening and referral of individuals treated with known cardio-toxic therapies to cardio-oncology teams is an additional measure to assist in CVD prevention (Armenian et al., 2016; Parent et al., 2016; Pituskin et al., n.d.; Virani et al., 2016). The benefit of screening and identifying high risk individuals is the ability to engage patients in adopting heart healthy lifestyles as soon as possible and the opportunity to refer to a cardio-oncology team for medical management (Parent et al., 2016; Pituskin et al., n.d.). This approach has been used by the EdmontoN Cardio-Oncology REsearch (ENCORE) team to improve CV outcomes by adopting prophylactic cardio protective therapies prior to starting cardio toxic treatment to preserve LVEF both during and after finishing treatment (Pituskin et al., 2016).

Through diligent screening and appropriate referral to cardio-oncology teams, those who are at a higher risk of cardiac dysfunction will proceed with cancer treatment in the safest manner possible with the goal of preserving cardiac function (Parent et al., 2016; Virani et al., 2016). Evidence is growing regarding the cardio-protective properties of current commonly used and well-tolerated HF pharmacologic agents such as angiotensin II receptor blockers, ACE-Is, BBs, and statin therapy (Abdel-Qadir et al., 2017; Pituskin et al., 2016; Virani et al., 2016; Zagar, Cardinale, & Marks, 2016). More study is required regarding which patients will benefit the most from pharmacological prophylaxis, as well as how clinicians should risk stratify individuals (Mukku et al., 2016; Parent et al., 2016).

An effective method of CVD risk reduction and prevention is through multidisciplinary cardiac rehabilitation (CR) programs (Lavie, Thomas, Squires, Allison, & Milani, 2009; Menezes et al., 2014). The role of CR programs in individuals at risk for, or with current CVD has been identified as an important tool to limit the extent of CVD related morbidity and mortality (Arthur et al., 2010; Lewanczuk, Suskin, & Arthur, 2009; Menezes et al., 2014; Redfern & Briffa, 2011; Silberman et al., 2010). Exercise is a cornerstone of CR programs and has also been found to be beneficial in improving CV reserve and preventing

the long term adverse cardiac effects (Astley et al., 2016; Daskapan, 2010; Menezes et al., 2014; Pituskin, Paterson, & Haykowsky, 2012). Further, exercise in cancer patients treated with cardio-toxic treatments has been found to improve quality of life and potentially mitigate the effects of therapy (Campia, 2016; J. J. Chen, Wu, Middlekauff, & Nguyen, 2016; Fanous & Dillon, 2016; Johnson et al., 2016; Mishra, Scherer, Snyder, Geigle, & Gotay, 2015; Scott, Adams, Koelwyn, & Jones, 2016)

Despite a proven method of prevention and control of CVD, current CR programs are largely underused (Pack et al., 2014). More recently, a pilot project examining HSCT recipients referred to CR has shown high acceptability, safety, and demonstrated improvements to clinical metrics (six-minute walk test, grip strength, gait speed, and timed up and go) following HSCT (Rothe et al., 2016). With an increased focus on heart health and wellness following cancer therapy, there is an opportunity for future collaboration including moderate to high-risk and symptomatic cancer patients under the CR umbrella.

As part of survivorship care for patients at risk for cancer therapy-induced cardiac dysfunction, optimal surveillance is necessary for early intervention (Armenian et al., 2016; Virani et al., 2016). Currently, the degree of cardiac dysfunction in cancer survivors is likely underestimated, and those who may be asymptomatic may have image based evidence of LV dysfunction (Mukku et al., 2016). Therefore, it suggested that those exposed to cardio-toxic cancer therapy, and who are at a moderate to high risk for cardiac dysfunction be followed pre, during, and post treatment with clinical exams and imaging (Armenian et al., 2016; Bottinor, Migliore, Lenneman, & Stoddard, 2016; Virani et al., 2016). Additionally, lifelong follow-up with clinical examination, symptom interview and diagnostic imaging surveillance with 3D and strain echocardiography is necessary (Bottinor et al., 2016)

Conclusions

To mitigate cardiac dysfunction related to cardio-toxic cancer therapies, both experts in cardiology and oncology have suggested that efforts should be made to prevent CVD in

cancer survivors, monitor cancer survivors at risk, and treat those with asymptomatic or overt cardiac dysfunction to preserve quality of life and prevent future adverse events (Armenian et al., 2016; Virani et al., 2016). The subspecialty of cardio-oncology provides an opportunity for experts in both fields to share their knowledge to determine the best plan to monitor and treat high CV risk patients. The health and well-being of cancer survivors with pre-existing or emerging CVD risk factors and who have been treated with cardio-toxic cancer therapies represent a growing complex patient population that requires increased attention.

The growing number of cancer survivors reflects today's cancer therapy armamentarium and its efficacy. Unfortunately, many of those cured from their cancer are left with a real possibility of debilitating CV morbidity in the short or long term. Many cancer patients are at risk for CVD given the high prevalence of North Americans who exhibit unhealthy lifestyles. Those patients with pre-existing traditional risk factors are at an even higher risk for adverse cardiac events following cancer treatment. With this in mind, health care providers must consider the unique status of individual patients and implement preventative measures to preserve the heart health of survivors. Cardio-oncology teams demonstrate innovative care approaches to managing this complex patient population through appropriate screening, initiation of prophylactic cardio-protective medications, and careful observation. Additionally, cardiac and cancer rehabilitation programs are likely beneficial and should be used to preserve quality of life and limit cardiac morbidity in cancer survivors previously treated with cardio-toxic therapies.

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Compliance with Ethics Guidelines

Disclosures

The views expressed in this commentary are the views of the authors.

Conflict of Interest

D. Rothe declares no conflict of interest. I. Paterson declares no conflicts of interest. N. Cox-Kennett declares no conflict of interest. G. Gyenes declares no conflicts of interest. E. Pituskin declares no conflict of interest

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Appendix B

Cardiac Rehabilitation in the Recovery of Lymphoma Patients Who Receive Autologous Hematopoietic Stem Cell Transplant: A Cardio-Oncology Pilot Project*

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Abstract

Introduction: Worldwide there are over 50,000 hematopoietic stem cell transplants (HSCT) conducted each year. HSCT patients receive cardio-toxic cancer therapies (chemotherapy and radiation therapy), and experience considerable physical deconditioning during hospital admission. To mitigate the deleterious CV-related effects of transplant, the HSCT team at a tertiary cancer centre referred all lymphoma patients who received autologous HSCT to a multidisciplinary cardiac rehabilitation (CR) program following treatment.

Methods: Designed as a pilot project to assess for impact, safety and feasibility of CR in the survivorship of HSCT patients; this study examined the results of sub-maximal exercise testing to assess patient progress. HSCT patients underwent testing before HSCT, 6 weeks following HSCT/prior to CR, and again following CR.

Results: Exercise tests results (n=30) were analysed, using repeated measures ANOVA, to assess resting and peak heart rate and blood pressure, left (LGS) and right grip strength (RGS), gait speed (GtS), timed up and go, six-minute walk test (6MWT). Statistically significant improvements were found in LGS ($p<.005$), RGS ($p<.005$), GS ($p=.02$), and 6MWT ($p=0.001$). The findings suggest that CR plays a role in assisting HSCT recipients to meet, or even surpass baseline exercise levels and overall functioning during recovery.

Limitations: This pilot project does not compare results with a control group, thus the degree of impact of CR on HSCT patient recovery in relation to standard of care cannot be measured.

Conclusion: Including CR into HSCT survivorship care is a safe and feasible intervention to assist in recovery and address cardiovascular risk factors in this population.

Keywords: cardiac rehabilitation, hematopoietic stem cell transplant, recovery, survivorship, cardiovascular disease prevention

Cardiac Rehabilitation in the Recovery of Lymphoma Patients Who Receive Autologous Hematopoietic Stem Cell Transplant:

A Cardio-Oncology Pilot Project

Introduction

Worldwide, more than 50,000 hematopoietic stem cell transplants are performed each year (World Health Organization, 2016). Approximately half of transplants are autologous for the treatment of relapsed lymphoma (HSCT) (Wingard et al., 2011). Approximately 84% of those treated with HSCT will live beyond ten years following treatment (Sasse & Engert, 2014; Wingard et al., 2011). While clinical procedures and supportive care have advanced over the years, interventions focusing on the long term cardiovascular (CV) sequelae have not, in spite of cardiac related illness being the leading cause of mortality in this group (Armenian et al.., 2014; Armenian et al., 2017; Baker, Chow, & Steinberger, 2012; Bhatia et al., 2005; Chow et al., 2011; Chow et al., 2014). A review by Scott et al. (2016) revealed that following HSCT, recipients have a 4-7.9 fold increased risk for adverse CV events (myocardial infarction [MI], heart failure [HF], and stroke), and an astounding 7.9-15.6 fold increased risk for developing CV risk factors.

The cause of cardiac dysfunction is directly linked to treatments including: first-line systemic therapy with anthracyclines, HDCT as part of HSCT, and mediastinal radiation therapy (if applicable) (Armenian et al., 2014; Armenian et al., 2010; Bhatia et al., 2005; Chow et al., 2014; Scott et al., 2016). CV-related effects of HDCT include, HF, arrhythmias, and coronary artery disease (CAD) (Chow et al., 2014; Schultz-Hector & Trott, 2007; Scott et al., 2016; Zhao, Diz, & Robbins, 2007). Radiation therapy to mediastinal disease can lead to fibrosis of cardiac tissues and vasculature altering perfusion, kinesis and filling. Further, the atherosclerotic process is hastened, contributing and increased risk for ischemic coronary events (Marmagkiolis et al., 2016; Myrehaug et al., 2008; Nolan, Russell, & Marwick, 2016).

In addition to the direct effects associated with treatments, indirect contributing

factors to cardiac dysfunction include pre-existing CVD risk factors and physical deconditioning during hospital admission. Individuals with pre-existing CVD risk factors are known to have a compounded risk for CV events when treated with cardio-toxic cancer therapies included in HSCT (Chow et al., 2014). Furthermore, HSCT recipients physically decondition during their three to four week-long hospital admission leading to a loss of lean muscle mass, fat gain and decreased exercise capacity. The CV risks associated with HSCT represent a complex interplay of various factors which have the potential for considerable CV associated morbidity, and death.

Methods

The increased risk for adverse CV-related outcomes of HSCT led to a collaboration between the transplant office in a tertiary cancer centre and a cardiac rehabilitation (CR) program. The collaboration of a transplant program and CR program has two major intended benefits – to expedite recovery following HSCT through an exercise program, and to provide heart healthy education to prevent CVD in later life. A pilot project was developed to assess the impact, safety and feasibility of incorporating CR into the HSCT care trajectory (figure 1).

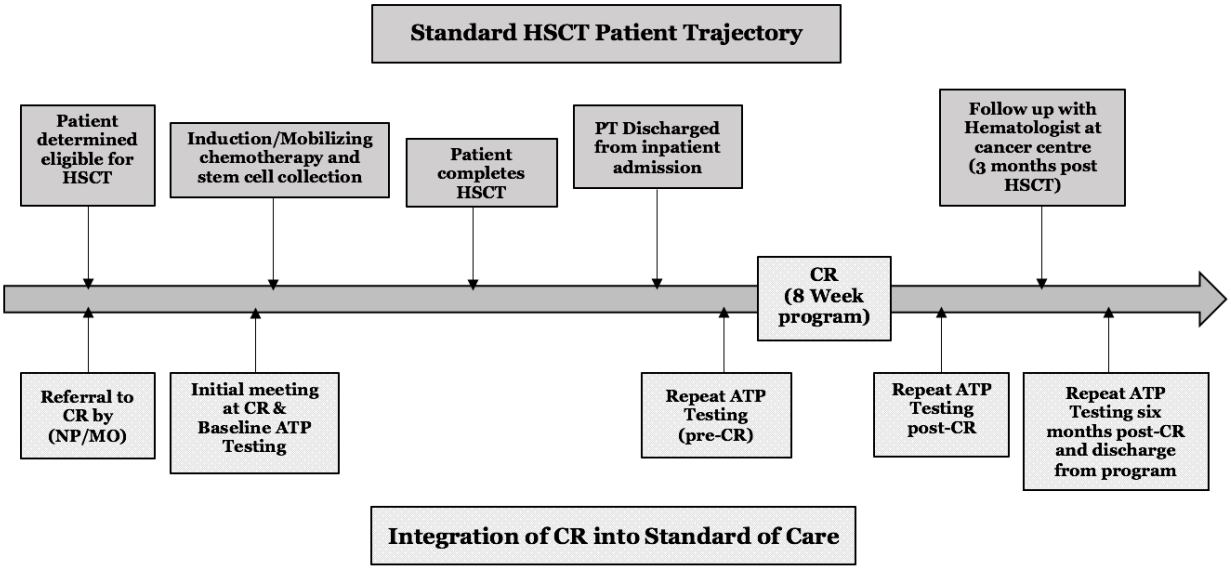

Figure 1. Flow diagram demonstrating standard HSCT care trajectory and integration of CR**. ATP** = Activity Tolerance Protocol (exercise testing), **CR** = Cardiac Rehabilitation, **HSCT** = Autologous Hematopoietic Stem Cell Transplant, **NP/MO** = Nurse Practitioner/Medical Oncologist

From December 2014 to December 2016, all lymphoma patients who were treated for

transplant were referred to CR. Participants underwent sub-maximal exercise testing at three time points: prior to HSCT (pre-HSCT), 6 weeks following HSCT (post-HSCT/pre-CR), and again after CR completion (post-CR). As part of the evaluation, participants underwent a variety of assessments used to monitor their progress. Assessment included multiple tests to assess biometric data, quality of life (QoL) and functional indicators.

Activity Tolerance Protocol

In the chosen CR program, the activity tolerance protocol (ATP) was used by staff as a tool to assess the physical and functional status of HSCT participants. The ATP includes documenting both resting and peak (following sub-maximal exertion) heart rate (HR) and blood pressure (BP). Left (LGS) and right-handed grip strength (RGS) is measured in kilograms (kg)to assess upper-body function and overall functional strength (DeBeliso et al., 2015; Wong, 2016). Gait Speed (GtS)(metres[m]/second[sec]) is used to measure the risk of falls, death, and hospitalizations in older individuals (Pamoukdjian et al., 2015). Timed up and go (TUG) is a measurement of mobility and may be predictive of falls (Podsialdo & Richardson, 1991; Schoene et al., 2013). The last test is the six-minute walk test (6MWT), which is particularly useful in assessing overall functional capacity and physical endurance.

In addition to exercise testing, participants completed questionnaires to capture their perceived functional status, psychological well-being, and quality of life. The tools used include: The Late Life Functional Disability Instrument, a tool to document perceived functional disability; The STOP-D questionnaire, used to (Jette, Haley, & Kooyoomjian, 2002) assess psychological distress; and the EQ5D, a simple and commonly used health-related QoL tool to assess social, physical, and psychological well-being (Jette et al., 2002; Rabin, Oemar, Oppe, Janssen, & Herdman, 2015; Young, Roth, Broadberry, Nguyen, & MacKay, 2012). Due to lack of consistency with completion of questionnaires, it was not possible to conduct statistical analyses on this portion of the ATP.

Results

The analysis of this pilot project was conducted to assess the impact of HSCT on ATP indicators, and to better understand how completing CR would impact ATP results following HSCT. Only those who completed all time points (pre HSCT, post –HSCT/pre-CR, and post-CR) were included in the data analysis (n=30) (table 1 for participant demographics). Using a repeated measures Analysis of variance (ANOVA) all ATP indicators were analyzed using the Statistical Package for the Social Sciences (SPSS) analytical software. The level of significance was determined by a two-tailed test with a probability of $p < 0.05$ (IBM Corp, 2015).

Table1. Participant Demographics of those who completed CR

	N=30
Age (yrs)	
Median (range)	56 (23-69)
Gender	
Male	24
Female	6
Cancer Diagnoses	
Hodgkins disease	9
Mantle Cell Lymphoma	4
T-Cell Lymphoma	2
Diffuse Large B-Cell Lymphoma	8
Follicular Lymphoma	5
Lymphoplasmacytic Disease	1
Plasma Cell Leukemia	1
Distance From Tertiary Centre (Km)	
Median (range)	13.5 (4-389)
Days Admitted to Hospital For HSCT	
Mean (range)	27 (22-36)
Documented CVD	
Yes (n=12)*	
CAD	3
Hypertension	6
Peripheral vascular disease	2
Atrial Fibrillation	1
Dyslipidemia	4
Cardiomyopathy	1
No (n=18)	
*6 participants had more than one documented CV illness	

A total of 60 patients were referred to CR, however, 12 did not proceed with HSCT and consequently did not take part in CR, due to disease progression or failure to mobilize stem cells. Of the 48 who were successfully transplanted, 32 participants completed the program in full (however, two of those participants did not complete all ATP testing points due to pre-syncope, and were therefore excluded from analysis) (table 2). 13 participants were considered to have dropped out of the program if scheduled ATP

appointments were missed and not rebooked. Geographic limitations and HSCT-specific patient concerns (i.e. peripheral neuropathies, fatigue) contributed to attrition. Of the 48 participants who were eligible to complete CR, three declined to attend altogether. There were no adverse events associated with completing CR. The findings demonstrate that including CR into HSCT survivorship care trajectory is a safe and feasible intervention to facilitate patient recovery following HSCT.

With regards to resting HR and resting systolic blood pressure (RSBP)/resting diastolic blood pressure (RDBP), only RSBP was found to have a statistically significant time effect, Wilks' Lambda = .792, $F(2, 28) = 3.67$, $p<.05$, $n^2=.21$. Pairwise comparisons revealed that RSBP was higher in the pre-HSCT time point with mean RSBP being 9 points greater than post HSCT time period ($p<.05$), and mean post-CR RSBP being 9 points greater than pre-CR ($p<0.05$). This suggests a drop in RSBP following HSCT, with a gain back to baseline levels after CR. There were no statistically significant differences in peak HR ($p=.18$), peak SBP ($p=.09$), or peak DBP ($p=.32$) across the testing time points.

Both left (LGS) and right handed grip strength (RGS) were found to have statistically significant differences with Wilks' Lambda = .56, $F(2, 28)=11.02$, $p<.001$, $n^2=.44$ and Wilks' Lambda =.46, $F(2, 28)=16.38$, $p<.001$, $n^2=.54$, respectively. There was a 4kg decrease in LGS following HSCT when compared to baseline measurement ($p<.001$). This suggests a decrease in upper body strength and overall functioning as a result of HSCT. In the case of RGS, there was a 5Kg decrease in strength following HSCT ($p<.001$), and a 3Kg increase in strength after completing CR ($p<.01$). These findings suggest a decrease in RGS following HSCT, and an increase in RGS following CR.

TUG results did not reveal statistically significant differences among testing time points ($p=.89$). GtS between the pre-CR and post-CR demonstrated an increase of .12m/sec ($p<.05$) following program completion [Wilks Lambda = .76, $F(2, 28) = 4.4$, $p<.05$, $n^2=.24$]. An improvement in GtS is to be expected as individuals following progressive exercise

Table 2. Mean (M) and Standard Deviations (SD) of ATP Indicators (N=30)

	Pre-HSCT		Post-HSCT/ Pre-CR		Post-CR		
Variable	**M**	**SD**	**M**	**SD**	**M**	**SD**	**p Value**
Resting HR (beats per minute)	86	15	90	18	85	16	p=.28
Resting Systolic BP (SBP) mmHg	112*	13	102*	20	112	15	**p=.04**
Resting Diastolic BP (DBP) (mmHg)	71	10	68	6	68	9	p=.31
Peak HR (beats per minute)	125	22	131	23	129	19	p=.18
Peak SBP (mmHg)	132	17	125	17	134	22	p=.09
Peak DBP (mmHg)	72	11	68	8	69	9	p=.32
LGS (Kg)	43*	13	38*	13	40	12	**p<.005**
RGS (Kg)	44	13	39	13	42	13	**p<.005**
Gait Speed (metres/ Second)	1.41	0.23	1.35*	0.22	1.47*	.22	**p=.02**
TUG (seconds)	6.6	2.1	6.6	2.2	6.5	2.2	p=.89
6MWT (metres)	497*	97	484*	95	532*	98	**p=.001**

*See text for a further explanation of where differences found in pairwise comparisons

regimens to increase physical endurance and functioning.

6MWT results demonstrated a statistically significant difference, Wilks' Lambda =.6, $F(2, 28)= 9.43$, p=0.001, $n^2=.4$. Pairwise comparisons indicated that differences in 6MWT outcomes are likely attributed to CR producing significant gains, not only improving scores 46m from pre-CR results (p<.001), but also a 34m improvement above pre-HSCT testing

($p<.01$). These findings indicate, CR may not only improve functioning after HSCT, but also surpass baseline functional levels.

Discussion

Summary of Results

The results of his pilot project demonstrate that there are certain areas where HSCT patients experienced statistically significant losses and gains following HSCT and CR respectively. LGS/RGS demonstrated significant losses following HSCT. 6MWT, GtS, and LGS/RGS results show improvements following CR.

Indirect Effects: Pre-Existing CV Risk Factors and Deconditioning

Individuals who receive cardio-toxic cancer treatments, and in particular, those receiving intensive regimens, are known to have a compounded effect to CV risks, influencing the likelihood of cardiac dysfunction. Current ASCO guidelines suggest that individuals be screened for pre-existing traditional CV risk factors such as age, CAD, dyslipidemia, hypertension, obesity, diabetes, smoking to stratify patient risk for cardio-toxicity. For those with ≥2 pre-existing traditional CV risk factors receiving cardio-toxic chemotherapy +/- mediastinal radiation therapy they are considered high risk and should be monitored more closely for cardiac dysfunction. Additionally, modifiable CV risk factors must be addressed and controlled where possible in the HSCT population (Armenian et al., 2016; Virani et al., 2016).

Exercise in HSCT Recipients

Exercise as a therapeutic intervention has been studied in HSCT populations and has been found to be an effective method to improve QoL and side effects such as fatigue pre, during, and post HSCT (Buffart et al., 2017; Hacker et al., 2011, 2017; Persoon et al., 2013; Wiskemann, 2013). In addition to the benefits associated with exercise attenuating side effects of HSCT, exercise can also be effective in preventing CVD (Lavie & Milani, 2011; Scott et al., 2016). Exercise interventions in both community and tertiary centre programs have

been found to increase overall functional ability and improve QOL in cancer survivors (Midtgaard et al., 2013; Mills et al., 2013). In some studies of cancer survivors who take part in rehabilitation programs there were both clinically and statistically significant improvements to a variety of physical and QoL indicatory. (Foley, Barnes, & Hasson, 2015; Rajotte et al., 2012).

Cardiac Rehabilitation

CR is a proven intervention to limit morbidity, hospitalizations, and improve quality of life for patients with a multitude of cardiovascular illnesses (American Heart Association [AHA], 2016; Dalal & Doherty, 2015). While HSCT survivors may not exhibit overt signs or symptoms of cardiac dysfunction, they may have subclinical heart disease. The physical and educational outcomes of CR present an opportune avenue to support HSCT recipients during their recovery. Expert opinion maintains that cancer patients receiving cardio-toxic therapies require preventing, monitoring, and managing adverse CV outcomes (Armenian et al., 2016; Virani et al., 2016). The results of this analysis indicate improvements to multiple functional metrics including GtS, grip strength, and 6MWT during recovery associated with CR following HSCT. While more research is needed to assess the effects of CR specifically in cancer survivors treated with cardio-toxic therapies, the benefits of rehabilitation programs has been well documented in cancer survivors and is gaining traction as a priority in survivorship care (Ibrahim & Al-Homaidh, 2011; Swenson et al., 2014; Tomasone et al., 2017).

Given the known benefits of exercise rehabilitation programs for cancer survivors, more must be done to support this model of cancer survivorship. Currently in Alberta, there are only cancer specific rehabilitation programs available in large urban centres. The availability of CR programs province-wide presents a convenient and potentially cost-effective opportunity to support HSCT recipients on their journey of recovery. The access to telehealth CR services allows for progress monitoring and patient teaching across the

province, increasing accessibility for rural patients. This project demonstrates that a monitored exercise program is safe and feasible to incorporate into the cancer survivor trajectory.

Limitations

This initiative was a pilot project and there were limited resources to co-ordinate an ideal research protocol. Therefore, the team was without a designated staff to ensure stringent data collection of QoL and functional indicators, and to liaison with participants. Unfortunately, due to poor completion of QoL and functional indicators, those results cannot be analysed to determine the impact of CR on perceived QoL and perceptions of functioning prior to and following HSCT, and again after CR completion. Another limitation is that there was no control group to compare recovery outcomes for those who do not participate in CR. Despite these limitations, including CR into HSCT care was found to be safe, with no adverse events occurring. Further, a qualitative study including 10 participants who were referred to CR following HSCT, found overall benefit with completing the program. Nine of the ten participants agreed that the CR directly contributed to a successful recovery following HSCT.

Conclusion

HSCT survivors are more likely to die from the CV-related effects of treatment compared to disease recurrence. Cardiac dysfunction in the form of HF, arrhythmias, and an overall propensity to develop CVD, increases the need for interventions that address the CV risks in this patient population. Despite its limitations, this pilot project demonstrated CR programs are safe and effective in restoring, and even surpassing baseline pre-HSCT physical functioning in certain functional indicators. Long-term CV benefits of CR in HCST cannot be commented on at this time. The collaborative efforts of both cardiology and oncology specialties has been recommended to deliver best care to cancer survivors treated with cardio-toxic therapies (Parent, Pituskin, & Paterson, 2016). Both oncology and cardiology experts emphasize the need for prevention of CVD in cancer survivors (Armenian et al., 2016;

Virani et al., 2016). Accordingly, practitioners should consider CR as one way to meet the complex care needs of HSCT recipients.

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Disclosure

The authors have no conflict of interest to disclosure

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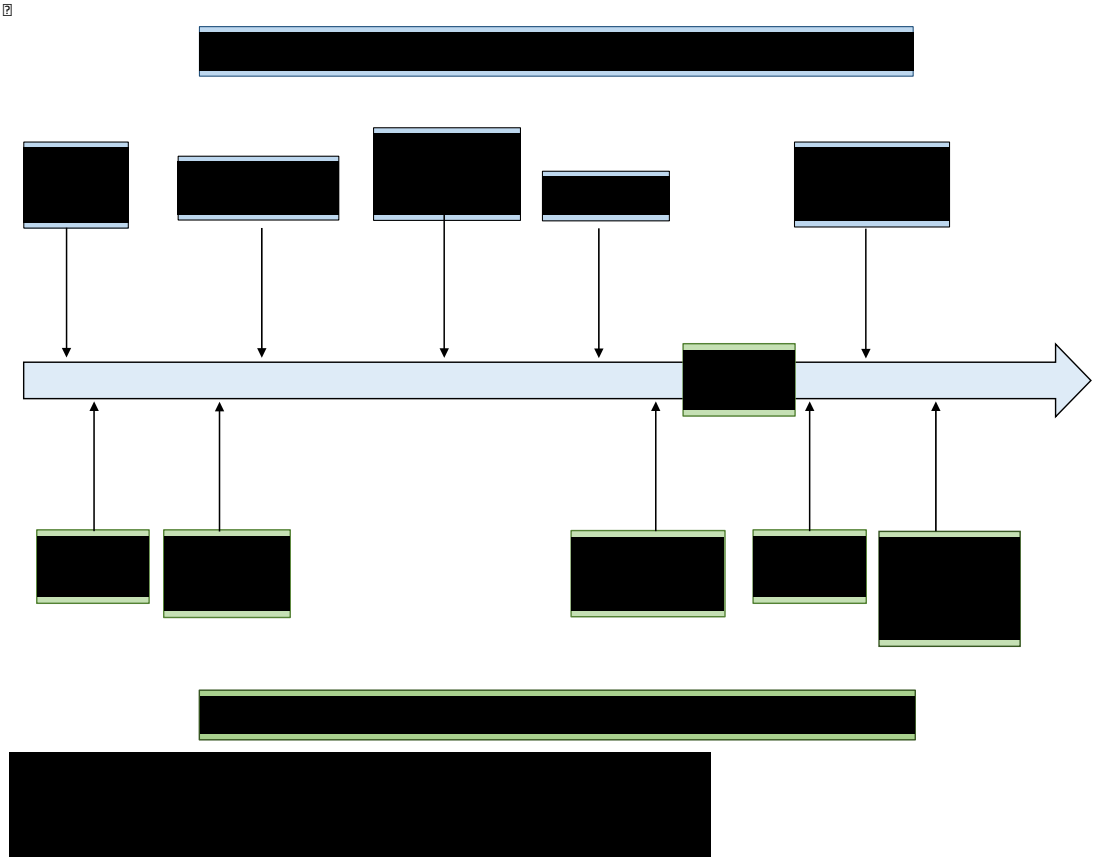
Appendix C

Integration of NACRP Into Standard HSCT Care



Appendix D

Guiding Interview Questions

Interview script for participants who did attend the NACRP

1. Can you tell me about when you found when you found out you were to receive a bone marrow transplant?
2. What went through your mind when you found out you would be referred to a heart rehabilitation program?
3. Do you remember who told you about the heart rehabilitation program and what did they say?
4. How did the completing the program make you feel?
5. Looking back is there anything that you would change about your experience?
6. What advice would you give to others who are referred to partake in the program?

Interview script for participants who did not attend the NACRP

1. Can you tell me about when you found when you found out you were to receive a bone marrow transplant?
2. What went through your mind when you found out you would be referred to a heart rehabilitation program?
3. Do you remember who told you about the heart rehabilitation program and what did they say?
4. What prevented you from completing the heart rehabilitation program?
5. Looking back is there anything that you would change about your experience?
6. What advice would you give to others who are referred to partake in the program?

Appendix E

Timeline

Anticipated Timeframe	Fall 2015	Winter 2016	Spring/ Summer 2016	Fall 2016	Winter 2017	Spring/ Summer 2017
Finalize Thesis Topic	X					
Complete Proposal		X				
Committee meeting		X				
Submit Ethics Proposal		X (Mid term)				
Mail recruitment letter		X (End of term)				
Participant Interviews/ Data Collection			X			
Interview Transcription			X	X		
Data Analysis			X	X	X	
Complete Thesis Rough Draft					X	
Complete Thesis and Final Oral Examinarion					X	X

Appendix F

Recruitment letter

Alberta Health Services

Edmonton – Cross Cancer Institute – Cancer Care
11560 University Avenue
Edmonton, AB, Canada
T6G 1Z2

albertahealthservices.ca

Total Albertan Satisfaction

July 28, 2016

You are being contacted about a study being conducted by a Master of Nursing student at the University of Alberta. You are being asked, as you were referred to the Northern Alberta Cardiac Rehabilitation Program (NACRP) after being treated with bone marrow transplant.

The purpose of this study is to better understand the experiences of the patients who received stem cell transplant and may have taken part in a heart rehabilitation program. We would like to know what the experience was like for you. The study will be used as part of the researcher's graduate degree thesis work.

If you are interested in learning more about this study, please **call the researcher (Derek Rothe) at [redacted]. If you wish to participate** please review the enclosed information, sign the consent form, and mail it back to us in the pre-paid envelope. You do not have to respond if you are not interested in this study.

It is important to know that this letter is not to tell you to join this study. It is your decision. Whether or not you participate in this study will have no effect on your relationship with The Cross Cancer Institute or the Jim Pattison Centre for Heart Health.

On behalf of the University of Alberta and the Cross Cancer Institute Bone Marrow Transplant group, thank you for your time and consideration we look forward to hearing from you.

Sincerely,

Nanette Cox-Kenrick on behalf of

The Bone Marrow Transplant Office
The Cross Cancer Institute

Alberta Health Services

Edmonton – Cross Cancer Institute – Cancer Care
11560 University Avenue
Edmonton, AB, Canada
T6G 1Z2

albertahealthservices.ca

Total Albertan Satisfaction

Study Title:

The experience of adult lymphoma patients referred for cardiac rehabilitation after high dose chemotherapy and autologous hematopoietic stem cell transplantation

If you would like to participate in the study please complete this form and return it using the pre-paid envelope provided

I am interested in learning more about this study. Please contact me using the following information:

Name: _____

Telephone(s): _____

Best time and day to call: _____

Email: _____

Appendix G

Information Letter and Consent Form

UNIVERSITY OF ALBERTA
FACULTY OF NURSING

3rd Floor, Edmonton Clinic Health Academy
Edmonton, Alberta, Canada T6G 1C9
Tel: xxx-xxx-xxxx
Fax: xxx-xxx-xxxx
www.nursing.ualberta.ca

THE EXPERIENCE OF ADULT LYMPHOMA PATIENTS REFERRED FOR CARDIAC REHABILITATION AFTER HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

A study to better understand the lymphoma patient experience with a heart rehabilitation program after bone marrow transplant

CONSENT FORM

This form is part of the process of informed consent. It is designed to explain this research study and what will happen to you if you choose to be in this study.

Read this consent form carefully to make sure you understand all the information it provides. You will get a copy of this consent form to keep. You do not have to take part in this study and your care does not depend on whether or not you take part. If you would like to know more about something mentioned in this consent form, or have any questions at anytime regarding this research study, please be sure to contact the researcher.

Your participation in this study is entirely voluntary. Please take your time to make your decision. It is recommended that you discuss with your friends and/or family about whether to participate in this study.

"WHY IS THIS STUDY BEING DONE?"

You are being asked to take part in this study because you were treated for your lymphoma with high doses of chemotherapy and autologous bone marrow transplant then were referred to a heart rehabilitation program. You were referred to the heart program as the treatment you received has been shown to increase the risk of heart disease. Heart rehabilitation programs have been shown to reduce the risk of heart disease. It is unknown how patient's like you experience a heart rehabilitation program as it has not been studied before. By better understanding your experience, hopefully a program can be developed to better meet the needs of lymphoma patients who take part in a heart rehabilitation program. In this way future patients will receive the best care possible.

"WHAT DO WE HOPE TO LEARN?"

We hope to learn about your experiences with the heart rehabilitation program. Whether or not you attended the program, we would like to hear about your experience and how you think the program could be improved.

"WHAT IS INVOLVED IN THIS STUDY?"

If you decide to take part in the study, the researcher will interview you and ask some questions about your experience to get a sense of how attending the heart rehabilitation program was for you. The interview process usually lasts about one hour and can be done in your home or another location like The Cross Cancer Institute or the University of Alberta campus (what ever is easiest for you).

"HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?"

About 10 people will take part in this study, however, more participants will be interviewed if the researcher requires more information.

"WHAT WILL MY PARTICIPATION INVOLVE?"

If you take part in this study, you will be interviewed by the researcher. The researcher will arrange with you a time and place to meet to have the interview. The researcher will come to your house if it is easiest for you, or if you would prefer, the researcher will arrange for a private space at the Cross Cancer Institute or at the University of Alberta. The interview will be recorded with a hand-held, digital audio-recorder and the interview will be typed for the researcher to analyze.

"HOW LONG WILL I BE INVOLVED IN THE STUDY?"

Usually the researcher will only require one interview. However, you may be contacted to discuss some of the initial findings to see if matches what you intended in your interview. If it is necessary, the researcher may ask to complete another interview with you to ask some further questions but this is unlikely.

It is very likely that the researcher will not require anymore of your time after one or two interviews. If you would like a final copy of the study when it is complete please feel free to ask the researcher.

"ARE THERE ANY BENEFITS TO PARTICIPATING IN THIS STUDY?"

Participation in this study may or may not be of personal benefit to you. However, based on the results of this study, it is hoped that, in the long-term, patient care can be improved.

"CAN I WITHDRAW FROM THIS STUDY?"

You may withdraw yourself from the study at any time. You do not have to answer any of the questions asked by the researcher if you not want to. You may end the interview at anytime if you wish. You may also request to have your interview removed from the study. However, once the study is complete, the information collected based on your interview may not be removed from the study. If you decide to stop participating in the study notify the researcher as soon as you can.

"WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?"

Identifiable health information will be collected from you (personal health number, date of birth and initials). This information may be used by the researchers who are carrying out this study. Any research proposal to use information that identifies you for a purpose other than this study must be approved in advance by the Health Research Ethics Board of Alberta – Cancer Committee.

Direct access to your identifiable health information collected for this study will be restricted to the researchers who are directly involved in this study. Any identifiable information will be removed when the study is in it's final written form. All confidential information will be kept in a secured environment in the Edmonton Clinic Health Academy, on the University of Alberta campus.

The researchers who are directly involved in your study may share information about you with other researchers, but you will not be identified in that shared information except by a number. The key that indicates what number you have been assigned will be kept secure by the researchers directly involved with your study and will not be released.

Although absolute confidentiality can never be guaranteed, the researcher will make every effort to keep your identifiable health information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information in accordance with the Alberta Health Information Act and other regulatory requirements.

The information collected during this study will be used in analyses and will be published and/or presented to the scholarly community at meetings, in journals, and as the

researcher's final thesis project, but your identity will remain confidential. It is expected that the study results will be published as soon as possible after completion.

"WHO DO I CALL IF I HAVE QUESTIONS"

If you have any questions about this study, you may contact the researcher (Derek Rothe, XXX-XXX-XXXX) or the researcher's supervisor (Edith Pituskin, XXX-XXX-XXXX).

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to speak to someone not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta – Cancer Committee at: XXX-XXX-XXXX or toll-free X-XXX-XXX-XXXX.

UNDERSTANDING OF PARTICIPANTS

I can refuse to take part or withdraw from this study at any time without jeopardizing my health care. If I continue to take part in the study, I will be kept informed of any important new developments and information learned after the time I gave my original consent.

I also give consent for the Principal Investigator and Alberta Health Services (the Custodian) to disclose identifiable health information, as per the Alberta Health Information Act, to the organizations mentioned on the previous pages.

I have read and understood all of the information in this consent form. I have asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review and discussion. My consent has not been forced or influenced in any way. I consent to participate in this research study. Upon signing this form I will receive a signed copy of the consent.

(PRINT NAMES CLEARLY)

_____	_____	_____
Name of Patient	Signature of Patient	Date
_____	_____	_____
Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

Patient Study Number: _____

Was the patient assisted during the consent process in one of the ways listed below?
□ Yes □ No

If yes, please check the relevant box and complete the signature space below:

□ The consent form was read to the patient, and the person signing below attests that the study was accurately explained to, and apparently understood by the patient.

□ The person signing below acted as a translator for the patient during the consent process.

_____	_____
Signature of person assisting In the consent discussion	Date

<u>Please note</u>: More information regarding the assistance provided during the consent process should be noted in the medical record for the patient if applicable.

Appendix H

Interview Notes Template

Interview Notes Page: ___ of ___

Date: _____ Time: _____

Participant: _____ Interviewer: _____

Setting: _____

OBSERVATIONS/DESCRIPTIVE NOTES	OBSERVER REFLECTIONS

Summary/Other:

Adapted from Creswell, J. W. (2014). *Research Design* (4th ed.). Thousand Oaks, CA: Sage