THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

REcovery of left ventricular dysfunction in CAncer Patients (RECAP trial) 2012-0379

Core Protocol Information

Short Title	RECAP Trial
Study Chair:	Anecita Fadol
Additional Contact:	Kimberly Willis Lisa A. Smith Valerie Shelton
Department:	Nursing
Phone:	713-792-8397
Unit:	458
Full Title:	REcovery of left ventricular dysfunction in CAncer Patients (RECAP trial)
Protocol Type:	Standard Protocol
Protocol Phase:	N/A
Version Status:	Terminated 09/14/2017
Version:	08
Submitted by:	Jenny L. Gay--8/17/2015 12:50:08 PM
OPR Action:	Accepted by: Yolanda Shorte -- 8/31/2015 10:41:20 AM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

The overall goal of this pilot study is to examine whether cancer survivors with a history of cancer-induced left ventricular dysfunction (CILVD) resulting in heart failure (HF) who achieve left ventricular ejection fraction (LVEF) recovery with recommended HF medications for at least 6 months will maintain their LVEF if HF medications are discontinued. The findings from this pilot study will provide baseline information for planning a larger confirmatory trial to support evidenced- based practice for the pharmacological management of cancer survivors with a history of CILVD.

Specific Aim 1: To determine the percentage of cancer survivors that can maintain their LVEF after discontinuing HF medications (beta blockers, angiotensin converting enzyme inhibitors (ACE-I), or angiotensin receptor blocker (ARB).

Specific Aim 2: To describe the characteristics of cancer survivors who successfully maintain their LVEF and those whose LVEF decrease as measured by an echocardiogram with contrast after they discontinue HF medications.

The **primary endpoint** for this pilot study is a decrease in the LVEF when HF medications are discontinued, and the **secondary endpoints** are the changes in the cardiac biomarkers, such as increased troponin I, B-type natriuretic peptide (BNP) or abnormal strain on echocardiogram that can predict the possibility of HF medication withdrawal failure. The cardiac biomarkers (troponin I, BNP) and abnormal strain on echocardiogram are early indicators of myocardial injury.

2.0 Background

Heart failure (HF) is a dreaded complication for cancer survivors that can result from the cardiotoxic effects of various antineoplastic agents especially anthracyclines (Carver et al., 2007; Ewer, Swain, Cardinale, Fadol, & Suter, 2011), high dose cyclophosphamide (Carver, et al., 2007), targeted therapeutic agents such as trastuzumab (Suter, Cook-Bruns, & Barton, 2004), and tyrosine kinase inhibitors (Khakoo et al., 2008). HF is a clinical problem of emerging importance because as advances in cancer detection and treatment have been made, the number of cancer survivors living years after their diagnosis has increased steadily, and hence the increased likelihood that cancer treatment induced left ventricular dysfunction (CILVD) will develop in these survivors. According to the National Cancer Institute's Surveillance, Epidemiology and End Results Program, an estimated 11.9 million cancer survivors live in the United States, and approximately 60% of those are currently 65 years of age or older (Howlader N et al., 2011). Likewise, the number of Americans over age 65 is predicted to double between the years 2000 and 2030 (Akechi et al., 2010), thus we can expect a corresponding increase in the prevalence of HF in cancer survivors, because both diseases are associated with aging.

In many cancer survivors, the risk of cardiovascular complications is higher than the risk

of tumor recurrence (Schultz, Beck, Stava, & Vassilopoulou-Sellin, 2003). More than 50 % of all cancer patients exposed to anthracyclines are expected to have some degree of cardiac dysfunction 10 to 20 years after treatment and 5% of those patients will develop overt HF (Steinherz, Steinherz, Tan, Heller, & Murphy, 1991). Until recently, anthracyclines-induced cardiotoxicity was thought to be irreversible. However, a recent retrospective analysis of breast cancer patients with doxorubicin-induced HF showed that 47% had improved heart function with cardiac medications (â-blockers, ACE I or ARB (Tallaj et al., 2005). Likewise, a retrospective analysis of patients treated with trastuzumab showed that cardiac function in those who subsequently had HF improved with standard HF medical therapy (ACE I and â-blockers (carvedilol or metoprolol succinate) (Suter, et al., 2004). In another study of 38 patients suspected of having trastuzumab related cardiotoxicity, who had previously received anthracycline-based chemotherapy, and were followed for 4 years showed that LVEF was improved in 37(97%) of 38 patients. The mean time to LVEF recovery was 1.5 months and was temporarily associated with medical treatment in 32 (84%) patients, but occurred without treatment in six (16%) of those patients(Ewer et al., 2005).

3.0 Rationale

Currently, no clinical guidelines specific for the management of CILVD exists, therefore, management of cancer survivors with history of CILVD is based on the existing clinical guidelines established by the American College of Cardiology/ American Heart Association (Hunt et al., 2005) and the Heart Failure Society of America (Lindenfeld et al., 2010) recommending that patients continue taking HF medications indefinitely, even after they have attained LVEF recovery. These guidelines are supported by data from clinical trials that did not include patients with cancer. It is unknown whether cancer survivors with history of CILVD and LVEF recovery should be managed the same as those patients with HF and do not have a history of cancer. Cancer survivors with history of HF are advised to continue taking HF medications indefinitely, even after they have attained LVEF recovery and are no longer receiving cancer therapy. There is a paucity of published evidence-based studies to support the lifelong pharmacologic therapy with beta blockers, angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) in cancer survivors with a history of CILVD and recovered LVEF. Thus, there is a need to investigate whether LVEF can remain normal in these patients after HF medications are discontinued and would clearly benefit this therapeutic dilemma. This will relieve the cancer survivors from the financial burden of the added cost of prescription and the trouble of taking the medications. For these reasons, it is paramount to determine whether cancer survivors with a history of CILVD and LVEF recovery need to continue taking HF medications for life. In this pilot study, the study investigators propose to examine whether cancer survivors with a history of CILVD resulting in HF who achieve LVEF recovery with recommended HF medications for at least 6 months will maintain their LVEF if HF medications are discontinued. The findings from this pilot study will provide the baseline information for planning a larger confirmatory trial to support evidenced- based practice for the pharmacological management of cancer survivors with a history of CILVD.

4.0 Eligibility

Inclusion Criteria:

1) Cancer survivors with no evidence of disease for at least 6 months as determined by the oncologist and no longer receiving cancer treatment.
2) Prior diagnosis of CILVD with recovered LVEF (i.e. improved to ≥ 50%) for at least 6 months with recommended HF medications (ACE-I or ARB and/or B-blocker).
3) Absence of other causes of cardiomyopathy (e.g. ischemia, hypertension, amyloidosis, or hemochromatosis) per chart review of the clinician's documentation.

4) Documented normal LVEF of ≥50% for at least 6 months after the initiation of recommended HF pharmacological therapy.
5) Age 18 - 80 years. HF clinical guidelines is supported by evidenced-based data from clinical trials which includes individuals up to 80 years of age.
6) Reside within the United States
7) Able to read and write English, because the MD Anderson Symptom Inventory – Heart Failure (MDASI-HF) instrument (Fadol et al., 2008) has been validated in English language only.

Exclusion Criteria:

1) Cancer recurrence that requires anti-cancer treatment
2) A documented history of hypertension, coronary artery disease, myocardial infarction,
   diabetes mellitus, amyloidosis or hemochromatosis.
3) Presence of HF symptoms (e.g. shortness of breath, edema).
4) Pregnancy

5.0 Study Plan

The study will be conducted at the MD Anderson Cancer Center Department of Cardiology cardiomyopathy clinic where patients will have clinic follow up while enrolled in the study.
Prior to data collection, approval to conduct the study will be obtained from the Institutional Review Board of the University of Texas MD Anderson Cancer Center (MDACC). Potentially eligible cancer survivors will be identified in the outpatient cardiomyopathy clinic in the Department of Cardiology at MDACC by attending cardiologists and midlevel providers. The research staff will be notified and will meet with eligible patients in the clinic to describe the study and ask participants to give informed consent. If the patient agrees, the research staff will obtain informed consent and enroll the patient in the study. The participants will be registered in the study at the Cardiopulmonary Center of the MD Anderson Cancer Center. The investigator will comply with the Health Insurance Portability and Accountability guidelines at all times. The patient study records will be will be kept in storage for 5 years after completion of protocol and after the protocol is closed. After the participant has signed the informed consent, instructions will be

provided regarding the following activities that are expected to occur at different time points of clinical follow-up during the study (Table 1).

Table 1. Data collection timeline for patients

Data Collected	Day 1 Study enrollment	Month 1 +/- 7 days	Month 2 +/- 7 days	Month 3 +/- 7 days	Month 4 +/- 7 days	Month 5 +/- 7 days	Month 6 +/- 7 days	Month 12 +/- 7 days	Month 18 +/- 7 days	Month 30 +/- 7 days
Telephone follow-up				X		X				
Clinic Visit (Physical Assessment)	X	X	X		X		X	X	X	X
Demographic information	X									
Antineoplastic agent received/total dosage	X									
Labs (Na, K, Cl, CO2,BUN, Creat, TSH*, T4*, BNP, TnI, Pregnancy Test*)	X	X	X		X		X	X	X	X
Echocardiogram with contrast and GLS measurement (if not done within a month prior to study enrollment)	X		X		X		X	X	X	X
MDASI-HF	X	X	X		X		X	X	X	X
Weaning of HF medications	X	X	X							

Legend: Na=sodium; K=potassium; Cl= Chloride; CO2= Carbon dioxide; BUN=Blood Urea Nitrogen; Creat = Creatinine; TSH= Thyroid stimulating hormone; T4= Thyroxine; BNP = B-type Natriuretic Peptide; TnI= Troponin I; GLS= Global longitudinal strain; MDASI-HF= MD Anderson Symptom Inventory- Heart Failure; HF = Heart Failure.

* Will be drawn with labs at study enrollment (Day 1) only. Pregnancy test will be performed for women of childbearing age only.

Demographic data to be collected from the patients will include age, marital status, race, education in years, and employment status. Disease and treatment data such as tumor type, cancer treatment received (type and total dosage of chemotherapy, radiation therapy, biologic and targeted therapies), left ventricular ejection fraction (LVEF) with global longitudinal strain measurement per echocardiogram, cardiac medications (Angiotensin converting enzyme inhibitor (ACE-I), Angiotensin receptor blocker (ARB) and beta blockers) will be collected. To maintain security of the database, access will be limited to the principal investigator, research nurse and research data coordinator specifically assigned

to the study using a protected password. The completed data collection forms will be kept in storage in the department of nursing locked in a cabinet and the key will be kept by the principal investigator. After completion of protocol and after the study is closed, the study documents will be kept in storage for 5 years.

Weaning of HF medications will start at study enrollment date (Day 1). A summary of the steps for the weaning procedure is outlined in Table 2. The participants will be instructed to decrease their HF medications by one half the current dose each week and measure their BP and pulse rate daily and record in a log (Appendix A), and bring to clinic with each visit. If the BP is >140/90 mm Hg or pulse rate >110 beats per minute or they develop HF symptoms (shortness of breath, lower extremity edema, increased abdominal girth, orthopnea or paroxysmal nocturnal dyspnea), the participants will be instructed, on weekdays to call the clinic nurse (713-792-4050) who will subsequently notify the attending cardiologist and the principal investigator, and on weekends or holidays to call the cardiologist on call at 713-792-2121.

Table 2: Steps for Weaning Participants Off HF Medications

HF Meds	**Weaning Procedure**
On ACE I & Beta-blockers o ACE I o Beta-blockers	o Gradually wean ACE I first before Beta-blockers o Decrease to half the current dose Q week until off unless BP>140/90 mm Hg o Decrease to half the current dose Q week until off unless BP>140/90 mm Hg or HR>110 bpm
On Beta-blockers only	o Decrease to half the current dose Q week until off, unless BP>140/90 mm Hg or HR >110bpm
On ACE I only	o Decrease to half the current dose Q week until off unless BP>140/90 mm Hg
On ARB & Beta-blockers o ARB o Beta-blockers	o Gradually wean ARB first before Beta-blockers o Decrease to half the current dose Q week until off unless BP>140/90 mm Hg o Decrease to half the current dose Q week until off unless BP>140/90 mm Hg or HR>110 bpm
On ARB only	o Decrease to half the current dose Q week until off, unless BP>140/90 mm Hg or HR >110bpm

If the participant's HF medications include ACE-I and beta-blockers, the ACE-I inhibitor will be weaned first (e.g. if current dose of Lisinopril is 40 mg by mouth daily, it will be decreased to 20 mg by mouth daily for the first week, then 10 mg daily for the second week, then 5 mg daily for the third week, then discontinue), unless the BP is > 140/90 mm Hg. or if HF symptoms develop.

If the participant tolerates the weaning of the ACE-I and the BP<140/90 mm Hg and pulse rate <110 beats per minute, and with no signs or symptoms of HF exacerbation, then will proceed with weaning the beta blocker at one-half the

current dose each week. This will continue until medication is off (e.g. if current dose of Carvedilol is 25 mg by mouth twice daily, decrease to 12.5 mg by mouth twice daily, then 6.25 mg by mouth twice daily, then 3.125 mg by mouth twice daily, then off) unless the BP is > 140/90 mm Hg or pulse rate >110 beats per minute. If this occurs, the participants will be instructed to call the clinic nurse or cardiologist on call at the telephone numbers provided to the participant as stated above.

For those participants who are on ARB and beta blockers, the ARB will be weaned first, then the beta-blockers with the same stepwise process and the same BP and pulse rate parameters as stated above with the weaning of ACE-I and beta blockers until completely off. We anticipate approximately a total of 6 weeks for the weaning of the HF medications.

The activities for each of the time points during the data collection are outlined below.

Day 1 (Study enrollment)

1. Clinic visit for baseline physical assessment, review of medical history including demographic information, antineoplastic agents received, risk factors, and for any signs and symptoms of HF.
2. Collection of blood specimen for laboratory works (BNP, Troponin I, Electrolyte (Sodium, Potassium, Chloride, and CO2), BUN, Creatinine, TSH and T4).
3. 2-D echocardiogram with contrast to measure LVEF and strain, if not performed within a month prior to enrollment in the study.
4. Pulse rate and blood pressure measurement using a sphygmomanometer (calibrated at the clinic), and recording on a diary that will be brought to every clinic visit.
5. Completion of the MDASI-HF symptom assessment instrument.
6. Instructions regarding monitoring for the following signs and symptoms and report to contact numbers provided (weekdays 713-792-4050; weekends and holidays -713-792-2121).
    a. Blood pressure > 140/90 mm Hg
    b. Pulse rate >110 beats per minute
    c. Shortness of breath
    d. Lower extremity edema or increased abdominal girth
    e. Paroxysmal nocturnal dyspnea (waking up at night with difficulty breathing)
    f. Orthopnea (problem with lying flat)

Month 1

1. Clinic visit for follow up physical assessment, review of medical history, review of systems, and evaluate for any signs and symptoms of HF.
2. Review of BP and pulse rate diary
3. Collection of blood specimen for laboratory works (BNP, Troponin I, Electrolytes (Sodium, Potassium, Chloride, CO2) , BUN, and Creatinine).

Month 2

1. Clinic visit for follow up physical assessment, review of medical history, review of systems, and evaluate for any signs and symptoms of HF.
2. Review of BP and pulse rate diary.
3. Collection of blood specimen for laboratory works (BNP, Troponin I, Electrolytes (Sodium, Potassium, Chloride, CO2), BUN, Creatinine).
4. 2-D echocardiogram with contrast to measure LVEF and strain and evaluate for early signs of change in cardiac function.
5. Symptom assessment using the MDASI-HF instrument.

Month 3

1. Telephone follow-up with a member of the research team, review of medical history, and evaluate for any signs and symptoms of HF.
2. Review of BP and pulse rate diary.

Month 4

1. Clinic visit for follow up physical assessment, review of medical history, review of systems, and evaluate for any signs and symptoms of HF.
2. Review of BP and pulse rate diary.
3. Collection of blood specimen for laboratory works (BNP, Troponin I, Electrolytes(Sodium, Potassium, Chloride, CO2), BUN, Creatinine).
4. 2-D echocardiogram with contrast to measure LVEF and strain and evaluate for early signs of change in cardiac function.
5. Symptom assessment using the MDASI-HF instrument.

Month 5

1. Telephone follow-up with a member of the research team, review of medical history, and evaluate for any signs and symptoms of HF.
2. Review of BP and pulse rate diary.

Month 6

1. Clinic visit for follow up physical assessment, review of medical history, review of systems, and evaluate for any signs and symptoms of HF.
2. Review of BP and pulse rate diary.
3. Collection of blood specimen for laboratory works (BNP, Troponin I,

Electrolytes [Sodium, Potassium, Chloride, CO2], BUN, Creatinine).
4. 2-D echocardiogram with contrast to measure LVEF and strain and evaluate for early signs of change in cardiac function.
5. Symptom assessment using the MDASI-HF instrument.

Month 12

1. Clinic visit for follow up physical assessment, review of medical history, review of systems, and evaluate for any signs and symptoms of HF.
2. Collection of blood specimen for laboratory works (BNP, Troponin I, Electrolytes (Sodium, Potassium, Chloride, CO2), BUN, Creatinine).
3. 2-D echocardiogram with contrast to measure LVEF and strain and evaluate for early signs of change in cardiac function.
4. Symptom assessment using the MDASI-HF instrument.

Month 18

1. Clinic visit for follow up physical assessment, review of medical history, review of systems, and evaluate for any signs and symptoms of HF.
2. Collection of blood specimen for laboratory works (BNP, Troponin I, Electrolytes (Sodium, Potassium, Chloride, CO2), BUN, Creatinine).
3. 2-D echocardiogram with contrast to measure LVEF and strain and evaluate for early signs of change in cardiac function.
4. Symptom assessment using the MDASI-HF instrument.

Month 30

1. Clinic visit for follow up physical assessment, review of medical history, review of systems, and evaluate for any signs and symptoms of HF.
2. Collection of blood specimen for laboratory works (BNP, Troponin I, Electrolytes (Sodium, Potassium, Chloride, CO2), BUN, Creatinine).
3. 2-D echocardiogram with contrast to measure LVEF and strain and evaluate for early signs of change in cardiac function.
4. Symptom assessment using the MDASI-HF instrument.

Heart failure will be defined as an LVEF < 50%, or a decrease of >10% from baseline LVEF, at any time during the weaning and after completely off of HF medications while enrolled in the study.

The baseline and follow up echocardiograms will be interpreted by the same two cardiologists who are collaborators in the study to ensure consistency of interpretation. If the participants' echocardiography reveals a decrease in the LVEF (<50% or >10% lower than baseline LVEF), the attending cardiologist will be notified immediately, and the participant will be evaluated if they have met the

endpoint considered as failure for the study. The participant will be carefully monitored, and HF medication will be titrated as clinically indicated and followed closely as clinically necessary until LVEF return to baseline and symptoms resolved.
If the participant develops HF symptoms even with normal LVEF from previous echocardiogram during a regular follow up per study protocol, an echocardiogram may be repeated as clinically indicated at any time point in addition to the study time points. Should the LVEF drop after the HF medications has been completely discontinued, the attending cardiologist will be notified and HF medications will be restarted and gradually uptitrated until normal baseline LVEF is achieved.

6.0 Criteria for Removal from the Study

On the basis of clinical observation and the experience of clinicians involved in the management of CILVD, we predict that 20% of the participants will experience a decrease in their LVEF when the HF medications are completely discontinued. The demographic characteristics, types of prior chemotherapy received, total dosage of chemotherapy (for participants previously treated with anthracyclines), cardiac biomarkers (i.e. BNP, troponin I), and echocardiography findings of these participants will be identified.

The participants will be removed from the study if any of the following conditions occur:

1) Echocardiography which reveals a decrease in the LVEF (<50% or >10% lower than baseline LVEF).
2) Occurrence of any cardiac related adverse events including acute coronary syndrome, malignant ventricular dysrhythmias (e.g. ventricular tachycardia or ventricular fibrillation) or new onset atrial fibrillation or atrial flutter.
3) Patients that cannot tolerate weaning of HF medications because of hypertension or increased pulse rate will be removed from the study and replaced.

7.0 Protocol Monitoring

To ensure patient safety, we will implement continuous monitoring for excessive heart failure using a design developed by Thall, et. al.,(1995). Specifically, we will terminate enrollment into a particular stratum if $\Pr[\pi_{HF} > 0.20 \mid \text{data}] > 0.92$. To use this rule, we will assume that π_{HF} has a prior distribution of *B* (0.4, 1.6). The rule will be applied separately to each stratum because we are concerned that response will not be homogenous across strata. Table 3 gives the specific stopping rules, and Table 4 has the operating characteristics of this rule. Tables 3 & 4 were developed using a Stata program designed by Bryan Fellman.

Table 3. Rules for stopping for excessive occurrence of heart failure

# of Patients with Heart Failure	# of Patients Enrolled in Stratum
3	5
4	6, 7, 8, or 9 patients
5	10, 11, or 12 patients
6	13, 14, or 15 patients

Table 4. Operating Characteristics of Early Stopping Rule

P(True Toxicity Rate)	P(Stop Early)	p10	p25	p50	p75	p90	Avg # pts	Avg # toxicities
0.10	0.0156	15	15	15	15	15	14.87	1.46
0.15	0.0551	15	15	15	15	15	14.57	2.18
0.20	0.1284	9	15	15	15	15	14.03	2.76
0.25	0.2365	7	15	15	15	15	13.25	3.31
0.30	0.3772	5	9	15	15	15	12.21	3.67
0.40	0.6561	5	5	9	15	15	9.92	3.97
0.50	0.8620	5	5	7	9	15	7.93	3.94

To illustrate this stopping rule, let's say that 10 patients have been enrolled in a particular stratum and that only 4 have had heart failure. The 11th patient is now enrolled and he/she develops heart failure. Enrollment to this stratum will be terminated because $\Pr[\pi_{HF} > 0.20 \mid \text{data}] = 0.96$. Under this stopping rule, we will terminate enrollment early 13% of the time when the proportion of patients who have subsequent heart failure is truly 20%. We will terminate enrollment early 86% of the time when the proportion of patients who have subsequent heart failure is 50%. It should be noted that the stopping rule will be applied for a decrease in LVEF (<50% or >10%

decrease from baseline LVEF), or occurrence of any cardiac related adverse events including acute coronary syndrome, malignant ventricular dysrhythmias (e.g. ventricular tachycardia or ventricular fibrillation) or new onset atrial fibrillation or atrial flutter. These conditions will count as failure for both the primary endpoint and for the safety monitoring rule.

Data management

Patient confidentiality will be maintained at all times. Patients will be assigned a study identification number by the study coordinator. All identifiers matching the questionnaire to the participant will be stored in a password-protected database. This information will be accessible to only the study coordinator, principal investigator, co-principal investigator, and collaborators in the Department of Cardiology.

8.0 Statistical Considerations

This study has two specific aims: to examine how many patients continue to maintain their LVEF after discontinuing HF medications (beta-blockers, ACE-I and/or ARBs) for 6 months while enrolled in the study and to describe the characteristics of patients who successfully maintain their LVEF and those who have a decrease in their LVEF during the weaning process and after discontinuing HF medications.

Failure is defined as an LVEF < 50%, or > 10% decrease from baseline LVEF or occurrence of any cardiac related adverse events including acute coronary syndrome, malignant ventricular dysrhythmias (e.g. ventricular tachycardia or ventricular fibrillation) or new onset atrial fibrillation or atrial flutter**.** Incidences of premature discontinuation from the study because of a decrease in the participant's LVEF will be considered a HF medication withdrawal failure. Patients who discontinue early for reasons not related to heart failure will be replaced. We anticipate only a 20% failure rate. Failure rate, and its corresponding 90% confidence interval, will be calculated separately for each stratum, and this information will be used to plan a larger, confirmatory controlled trial. If the failure rate is 20%, the 90% confidence interval will extend from 13% to 37%.

We will also describe characteristics of participants who have a decrease in their LVEF and those who maintain their LVEF using means, standard deviations, graphs and contingency tables. We will examine risk factors, such as increased troponin I, and B-type natriuretic peptide concentrations or abnormal echocardiographic strain that increase the possibility of withdrawal failure, as well as other clinical/demographic factors, as described in Sections 4 and 5. No hypothesis testing will be completed. The study results will be used to calculate power and sample size for the planning of a larger confirmatory trial.

Sample Size: The study will include 45 cancer survivors who meet the inclusion criteria, are followed up in the MD Anderson Cancer Center cardiology clinic, and agree to participate in the study. Patients will be stratified by type of chemotherapy, enrolling 15 patients who were treated for their cancer with anthracyclines, 15 who were treated with Herceptin, and 15 who were treated with a combination of agents or who had HF secondary to sepsis or stress induced cardiomyopathy.

9.0 References

Akechi, T., Okuyama, T., Endo, C., Sagawa, R., Uchida, M., Nakaguchi, T., et al. (2010). Anticipatory nausea among ambulatory cancer patients undergoing chemotherapy: prevalence, associated factors, and impact on quality of life. *Cancer Sci, 101*(12), 2596-2600.

Bird, B. R., & Swain, S. M. (2008). Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res, 14*(1), 14-24.

Carver, J. R., Shapiro, C. L., Ng, A., Jacobs, L., Schwartz, C., Virgo, K. S., et al. (2007). American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol, 25*(25), 3991-4008.

Cohen, M., Kronzon, I., & Lebowitz, A. (1982). Reversible doxorubicin-induced congestive heart failure. *Arch Intern Med, 142*(8), 1570-1571.

Ewer, M. S., Swain, S. M., Cardinale, D., Fadol, A., & Suter, T. M. (2011). Cardiac dysfunction after cancer treatment. *Tex Heart Inst J, 38*(3), 248-252.

Ewer, M. S., Vooletich, M. T., Durand, J. B., Woods, M. L., Davis, J. R., Valero, V., et al. (2005). Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol, 23*(31), 7820-7826.

Fadol, A. (2006). Management of acute decompensated heart failure in patients with cancer. *Clin J Oncol Nurs, 10*(6), 731-736.

Fadol, A., Mendoza, T., Gning, I., Kernicki, J., Symes, L., Cleeland, C. S., et al. (2008). Psychometric testing of the MDASI-HF: a symptom assessment instrument for patients with cancer and concurrent heart failure. *J Card Fail, 14*(6), 497-507.

Haq, M. M., Legha, S. S., Choksi, J., Hortobagyi, G. N., Benjamin, R. S., Ewer, M., et al. (1985). Doxorubicin-induced congestive heart failure in adults. *Cancer, 56*(6), 1361-1365.

Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, W, W., et al. (2011). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute, Bethesda, MD.

Thall, P.F., Simon, R.M., Estey, E.H. (1995). Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. 14. 357-379.