First annual Canadian Cardiac Oncology Network conference

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ABSTRACT

The inaugural Canadian Cardiac Oncology Network conference was held at the Ottawa Convention Centre, Ottawa, Ontario, May 13, 2011. The learning objectives of the meeting were to

- understand and appreciate the importance of cardiac toxicity in the treatment of cancer patients.
- review current guidelines, recommendations, and ways to prevent and treat cardiac toxicity in cancer patients.
- develop potential research initiatives and collaboration across Canada.

Although the cardiac toxicities associated with conventional systemic therapy agents are well established, the short- and long-term cardiac toxicities associated with targeted agents are less understood. In addition, the effects of exposing patients to multiple targeted therapies, and potentially compounding multiple cardiac toxicities, are unknown. This meeting report includes highlights from presentations at the conference.



The Canadian Cardiac Oncology NETWORK

KEY WORDS

Cancer treatment, targeted therapies, cardiac health, cardiac toxicities, solid malignancies

1. INTRODUCTION

The inaugural Canadian Cardiac Oncology Network conference, held May 13, 2011, was chaired by Dr. Susan Dent from The Ottawa Hospital Cancer Centre, Ottawa, Ontario, and was attended by health care professionals from across Canada. Conference highlights included presentations from keynote speaker Dr. Thomas Suter of Switzerland and a number of Canadian experts who reviewed the current understanding of cardiac toxicity as it pertains to traditional systemic agents and the effects of the newer targeted agents on cardiac health.

The meeting also focused on novel imaging techniques and strategies—including computed tomography, positron-emission tomography (PET), and two-dimensional echocardiography (ECHO)—to detect cardiac toxicity at an earlier stage. Several novel investigator-led research projects were presented. The meeting concluded with a productive discussion identifying the need for a collaborative national approach to the cardiac management of oncology patients and a recognition that prospective studies of targeted therapies should include cardiac toxicity as a clinical endpoint.

2. SESSIONS

2.1 Plenary Lecture: Cardiovascular Side Effects of Cancer Treatment—What We (Think We) Know, What We Should Know

Presenter: Thomas Suter, Bern University Hospital, Bern, Switzerland

Cancer treatment is associated with several cardiovascular side effects, including arrhythmias, QT

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prolongation, cardiac dysfunction, thromboembolism, angina pectoris, myocardial infarction, hypertension, and renal toxicity. Cytotoxic chemotherapy drugs that have typically been associated with cardiovascular side effects include anthracyclines, paclitaxel, antimetabolites, cyclophosphamide, and cisplatin, with incidences that range between 2% and 12% [1]. The adoption of signalling inhibitors into the treatment of many malignancies has led to improvements in cancer care; however, those agents also bring with them concerns about cardiovascular side effects. In particular, agents against the human epidermal growth factor receptor 2 (HER2)—for example, trastuzumab, lapatinib—have been associated with congestive heart failure, with incidences ranging from 3% to 28% [2,3]. Angiogenesis inhibitors such as bevacizumab and sunitinib have been reported to contribute to hypertension (5%–20%) [4], QT prolongation (3%–17%) [5], and higher risks of venous thromboembolic events (12%) [6].

Unlike the cardiovascular toxicity associated with traditional cytotoxic chemotherapy, the cardiac dysfunction associated with targeted therapies tends to be reversible upon cessation of therapy (as with trastuzumab, for instance) or treatable with medical management (for example, hypertension with bevacizumab). As cancer therapies evolve, traditional cytotoxic agents will be combined with one or more targeted therapies. The potential cardiovascular consequences of those combinations, both short- and long-term, are unknown. Thus, it will become increasingly important to identify early biomarkers for cardiac dysfunction in the patients being treated.

Traditional biomarkers such as brain natriuretic peptide (BNP), creatinine kinase, and troponin are elevated in the face of cardiomyopathy or myocyte cell death; however, those markers may be normal in the earlier phases of cardiac dysfunction. Thus, new markers and imaging modalities are needed for the assessment of cardiovascular dysfunction at earlier stages when preventive strategies can be initiated. Future studies evaluating the role of targeted therapies with or without cytotoxic chemotherapy agents should explore novel assessment tools to evaluate cardiac dysfunction.

2.2 Cardiac Toxicity: View of an Oncologist

Presenter: Christine Brezden–Masley, University of Toronto, St. Michael's Hospital, Toronto, Ontario, Canada

Dr. Christine Brezden–Masley presented an overview of the acute and chronic cardiac toxicities associated with anthracyclines and the potential strategies for preventing toxicities (for example, iron-chelating agents, cardioprotective agents, longer infusion rates). Brezden–Masley also discussed cardiac toxicities that have been observed with targeted therapies. The initial trials of trastuzumab were conducted in combination with anthracyclines in women with metastatic breast cancer, resulting in a 27% increase in cardiac dysfunction [7]. That finding led to a change in clinical practice whereby clinicians administered trastuzumab after anthracyclines ("sequential treatment"). Rates of cardiac toxicity (congestive heart failure) reported with trastuzumab in early-stage breast cancer trials have varied from 0.4% to 3.9% [8–11]. The median duration of follow-up in those trials is relatively short (3–5 years), although to date, there has been no signal that heart failure rates will increase with time.

Recent breast clinical trials have investigated the roles of one or more targeted agents (for example, pertuzumab, trastuzumab, or both) sequentially or concurrently with anthracyclines, and to date those trials have not demonstrated significant short-term cardiac toxicity. However, the long-term cardiac consequences of those treatment modalities are still unknown. Some of the newer agents, including angiogenesis inhibitors (for example, bevacizumab), have been associated with increased rates of hypertension, and management of treated patients will also be important to avoid long-term cardiac-related events.

Given this variability in treatment strategies and the various surveillance strategies adopted in clinical trials, a Canadian expert panel (cardiologists, oncologists, surgeons) developed Canadian practice guidelines on cardiac management and published them in *Current Oncology* in 2008 [12]. Those guidelines will need to be updated on a regular basis as novel targeted therapies are adopted into clinical practice.

To summarize, cardiac toxicity is an important clinical problem in breast cancer and other solid tumours. Thus, it is necessary to recognize the risk factors associated with developing cardiac toxicity and to try to minimize those factors as the clinical development of novel targeted agents advances. It will become increasingly important to establish cardiology–oncology partnerships to lower the burden of cardiac toxicities caused by newer therapeutic modalities.

2.3 Cardiac Toxicity: View of a Cardiologist

Presenter: Christopher Johnson, University of Ottawa, The Ottawa Hospital, Ottawa, Ontario, Canada

To prevent the development of cardiac toxicity, a good understanding of the pathophysiology of heart failure in patients undergoing cancer treatment is important. Identifying patients with early-stage cardiac dysfunction would allow for earlier intervention to prevent the development of overt congestive heart failure. All patients undergoing cardiotoxic cancer treatment should be screened for risk factors such as hypertension, coronary artery disease, diabetes, obesity, metabolic syndrome, cardiotoxins, and family history

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of cardiomyopathy. It is also important to identify cancer patients in the early stages of heart disease (stage A: high risk for heart failure without structural heart disease of symptoms; stage B: structural heart disease without signs or symptoms of heart failure) so that earlier intervention and close monitoring can be instituted [13]. Cancer patients with cardiovascular risk factors undergoing systemic therapy require a multidisciplinary approach that optimizes the balance between their cancer treatment outcome and cardiac health: "The cured cancer patient of today does not want to become the heart failure patient of tomorrow" [14].

To summarize, cardiac risk assessments in cancer patients receiving cardiotoxic agents are complex. Cardiac risk factors must be manageable, detectable, and modifiable if the patient is to benefit from the best possible cancer treatment. It is important that medical oncologists, cardiologists, and family physicians collaborate to optimize cardiac health in this population. New Canadian guidelines are needed to facilitate the collaboration between those parties.

2.4 Biomarkers and Preclinical Determination of Cardiac Toxicity

Presenter: Angeline Law, University of Ottawa, The Ottawa Hospital, Ottawa, Ontario, Canada

There are no definitive guidelines for the early detection of cardiac toxicity in patients undergoing systemic therapy and no well-established tools for screening those patients. Most screening strategies used today—for example, ECHO or multigated acquisition imaging—detect cardiac toxicity at a later stage. Ideally, screening strategies should be used at an earlier stage to identify patients at high risk of experiencing cardiac toxicity. The approaches currently used to identify early cardiac toxicity include

- estimation of baseline risk of cardiac complications,
- detection of temporary events, and
- identification of subclinical changes (for example, diastolic function, and two-dimensional strain and strain rate imaging).

Reduction of cardiac toxicity can be accomplished with

- early detection and treatment of heart problems or factors that increase cardiac stress (for example, hypertension, pre-existing cardiac disease);
- serial ECHO (especially for patients on anthracyclines), and
- early initiation of cardiac medication (such as angiotensin converting-enzyme inhibitors and beta-blockers).

Evaluations of left ventricular (LV) ejection fraction by ECHO or multigated acquisition imaging show cardiac dysfunction only when functional impairment is already present [15]. Current screening techniques are unable to detect early cardiac dysfunction, thus limiting the ability to institute preventive strategies in a timely fashion. Advanced ECHO techniques such as strain and strain rate imaging measure myocardial deformation and, compared with conventional measures of LV function, may help to identify preclinical changes in global and regional myocardial function earlier.

Biomarkers—for example, troponins and BNP—may detect early cardiac toxicities. Tests for these substances have the advantage of being noninvasive, less expensive than imaging, easily reproducible, and lacking in radiation exposure and inter-observer variability. Increased troponin levels after high-dose systemic therapy have been correlated with cardiac events in a large prospective study with long-term follow-up [16]. Troponin elevation can also predict patients who are unlikely to recover LV function. Increased BNP is useful in determining both prognosis and diagnosis of early asymptomatic LV dysfunction. Multiple small studies have demonstrated an association between increased BNP and cardiac toxicity. Currently, a multicentre trial from MD Anderson, the PREDICT trial (http://clinicaltrials.gov/ct2/results?term=NCT01311843) is investigating the efficacy of biomarkers in identifying and preventing cardiac toxicity in cancer patients. Larger prospective trials are needed to determine the predictive and prognostic value of biomarkers before they can be implemented in regular practice.

2.5 Novel Imaging Modalities for Cardiac Assessment

Presenter: Narinder Paul, University of Toronto, Toronto General Hospital, Toronto, Ontario, Canada

Dr. Narinder Paul presented an overview of current cardiac imaging technologies, the applications of those technologies, and future developments in the field. The discussion focused primarily on the clinical and research applications of cardiac magnetic resonance imaging (MRI) as a powerful tool for a comprehensive cardiac assessment. The utility of cardiac MRI was illustrated using clinical examples demonstrating

- a detailed structural assessment of the vessels, myocardium, and pericardium;
- an accurate functional assessment of ventricular volumes, ejection fraction, and flow quantification;
- physiologic evaluation with wall stress, motion, and perfusion indices; and
- tissue characterization for myocardial fibrosis, edema, and iron deposition.

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As newer oncology treatments prove effective in disease management, the longer-term cardiac consequences of those treatments need to be accurately detected and quantified. Cardiac MRI is the most versatile and powerful imaging tool currently available for this purpose, and future developments include global T1 mapping for diffuse fibrosis, and PET:MRI for assessing the metabolic activity of the heart.

2.6 Cardiac Toxicity: Can We Prevent It?

Presenter: Sean Hopkins, The Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada

The combination of systemic therapy agents (such as anthracyclines) with targeted therapies (such as trastuzumab) has been shown to increase cardiac dysfunction (27%), as reported with trastuzumab and anthracyclines in the metastatic setting [3]. As a result, anthracyclines and targeted therapies have traditionally been given sequentially. Interestingly, recent breast studies in the neoadjuvant setting have shown dramatically higher rates of pathologically complete responses, without significant cardiotoxicity, when anthracyclines were given concurrently with trastuzumab in women with locally advanced breast cancer. Those findings may reflect a more selective population of women with no baseline cardiac risk factors.

A number of interventions are available to prevent cardiac toxicities. They include

- prolonged infusion of systemic therapy drugs,
- use of antioxidants, and
- use of iron chelators (such as dexrazoxane), which reduce the production of reactive oxygen species and free radicals.

Liposomal formulations of systemic therapy drugs such as pegylated doxorubicin have also been associated with a reduced risk of cardiac toxicity.

Carnitine has been shown to improve mitochondrial function and to lower the release of cytochrome C, which in turn decreases the activation of caspase-9. Activation of intrinsic apoptotic pathway is thus decreased, preventing cell death. A phase II trial at the Ottawa Hospital Cancer Centre treated women receiving anthracycline as systemic therapy for stage II breast cancer with either carnitine or a placebo. The study was closed early because of poor accrual, but the results may provide some insight into the potential role of compounds such as carnitine in the prevention of cardiac toxicity.

Ultimately, current strategies to address cardiac toxicity typically deal with exposure to a single cardiotoxic drug. With the development of standalone and combination targeted therapies, which may have their own cardiac toxicity implications, additional research into preventive strategies will be needed.

2.7 Management of Cardiac Toxicity in Oncology Patients

Presenter: Michele Turek, University of Ottawa, The Ottawa Hospital, Ottawa, Ontario, Canada

The mechanisms by which traditional cancer treatments lead to cardiac toxicity include

- direct effects on the heart (LV dysfunction, ischemia),
- effects on the coagulation system,
- hypertension, and
- atrial fibrillation or arrhythmias.

The chemotherapy drugs most associated with LV dysfunction are the anthracyclines and alkylating agents. Chemotherapy drugs associated with ischemia include capecitabine and 5-fluorouracil. Less-common cardiac adverse effects such as bradycardia and QT prolongation have been associated with the taxane group.

Targeted therapies that have been associated with cardiac toxicity include bevacizumab, trastuzumab, and small tyrosine inhibitors such as erlotinib and sorafenib. Trastuzumab blocks the "anti-stress" mechanism of HER2 in myocytes, leading to LV dysfunction, usually reversible upon therapy cessation.

Trastuzumab-related cardiac toxicity occurs, on average, 4.5 months [17] after commencement of treatment and, clinically, often leads to asymptomatic low ejection fraction. Such changes can result in trastuzumab being delayed or stopped for patients being treated with curative intent. The uncertainty surrounding a decision about when or if to stop trastuzumab in such patients led to the development of a dedicated cardiac oncology clinic at The Ottawa Hospital. The clinic is attended by 3 cardiologists in consultation with a medical oncologist and a pharmacist. From its inception in October 2008 to the time of writing, 258 consultations were conducted, together with 344 follow-up and surveillance visits. The initial referral base consisted of women with HER2-positive early-stage breast cancer, but the clinic population has now expanded to include all cancer patients receiving any potentially cardiotoxic therapy, including angiogenesis inhibitors and tyrosine kinase inhibitors.

Several guidelines have been developed to assist in the management of patients experiencing cardiac toxicity related to their cancer treatment, including one from the United Kingdom [17] and one from Canada [12]. A better understanding of the incidence and prevalence of cardiac toxicity in oncology patients can be effectively achieved through the establishment of a registry and the development of clinical practice guidelines that will help to disseminate best practices. As the complexity of cancer treatment increases, particularly with the introduction of combinations of targeted therapies, closer surveillance of patients will

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be needed to prevent and treat early cardiac toxicity and to provide evidence-based cardiac management. A multidisciplinary approach between allied health professionals such as cardiologists, oncologists, and pharmacists will be essential to that surveillance.

3. RESEARCH INITIATIVES

3.1 MANTICORE (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) 101—Breast

Presenter: Ian Paterson, University of Alberta, Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada

The MANTICORE study (http://clinicaltrials.gov/ct2/results?term=NCT01016886) will enrol 159 patients with histologically confirmed HER2+ breast cancer. This parallel 3-arm, randomized, placebo-controlled double-blind trial is designed to determine if conventional pharmacotherapy for heart failure (that is, angiotensin converting-enzyme inhibitors, beta-blockers) can prevent trastuzumab-mediated LV remodelling, as measured by the 12-month change in LV end-diastolic volume by cardiac MRI. Secondary objectives include understanding the evolution of LV remodelling on cardiac MRI; the mechanism of trastuzumab-mediated cardiac toxicity (by assessing for the presence of myocardial injury and apoptosis with serum biomarkers and cardiac MRI); and correlating cardiac biomarkers of myocyte injury and extracellular matrix remodelling with LV remodelling on cardiac MRI in patients with HER2-positive early breast cancer. This trial was activated in October 2010 in Edmonton, and 22 patients have consented. Additional investigational sites across Canada are being recruited.

3.2 A Prospective Evaluation of the Cardiac Side Effects of HER2± Breast Cancer Adjuvant Therapy Using Cardiac Positron-Emission Tomography and Speckle-Tracking Echocardiography

Presenter: Jean-Michel Caudrelier, The University of Ottawa, The Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada

This prospective exploratory study is being jointly conducted by the departments of radiation and medical oncology and the cardio-oncology clinic of the Ottawa Hospital, and by the department of nuclear medicine at the Ottawa Heart Institute. It will evaluate the potential of cardiac PET and speckle-tracking ECHO for identifying and monitoring cardiac dysfunction during standard adjuvant therapy for HER2-positive breast cancer.

Eligible patients will receive FEC (5-fluorouracil–epirubicin–cyclophosphamide) plus docetaxel adjuvant chemotherapy and whole-breast radiation therapy (46–50 Gy) in addition to 12 months of trastuzumab. Patients will undergo cardiac PET and speckle-tracking ECHO at baseline and during and after adjuvant therapies. This recently opened trial has so far accrued 1 patient (minimum target: 30 patients).

3.3 Determining the Cardiac Biomarkers Profile in Breast Cancer Patients Receiving Adjuvant Trastuzumab Therapy

Presenter: Bindi Dhesy–Thind, McMaster University, Juravinski Cancer Centre, Hamilton, Ontario, Canada

This prospective single-centre pilot study will evaluate cardiac biomarkers (troponin T, high-sensitivity troponin, and N-terminal pro-BNP) in patients with stages I–III breast cancer undergoing trastuzumab treatment. Marker results will be compared with results of standard cardiac imaging. Currently, 8 of a proposed 25 patients have been accrued.

4. SUMMARY

The inaugural Canadian Cardiac Oncology Network conference held at the Ottawa Convention Centre in May 2011 brought together a multidisciplinary group of health care professionals interested in the cardiac health of cancer patients undergoing systemic therapy. The meeting provided opportunities to discuss current treatment approaches in the management of cardiac toxicity and the importance of prevention and early intervention. It also provided an excellent forum for research collaboration. We extend our thanks to all those who made this first meeting such a success, including our pharmaceutical sponsors. Based on positive feedback received, we look forward to seeing even more participants at the second Canadian Cardiac Oncology Network conference, which will take place in Ottawa in June 2012.

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6. CONFLICT OF INTEREST DISCLOSURES

TS: consultant and advisory role—Hoffmann–La Roche (uncompensated), GlaxoSmithKline (uncompensated), Merck, Astex Pharmaceuticals; honoraria—Sanofi–Aventis, Chugai Japan, Hoffmann–La Roche; research funding—Hoffmann–La Roche;

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