5TH GLOBAL CARDIO-ONCOLOGY SUMMIT

São Paulo, Brazil - October 3–4, 2019

frontiers Event Abstracts

5TH GLOBAL CARDIO-ONCOLOGY SUMMIT

ISBN: 978-2-88963-090-5
DOI: 10.3389/978-2-88963-090-5
Citation: Alexander Lyon, Artur Katz, Christine Brezden-Masley, Cristina Salvadori Bittar, Gustavo dos Santos Fernandes, Isabela Bispo Santos da Silva Costa, Marilia Harumi Higuchi dos Santos, Michael Fradley, Susan Dent, Roberto Kalil Filho, Daniel Lenihan, Ludhmila Abrahão Hajjar. (2019). 5th Global Cardio-Oncology Summit

October 3-4, 2019, WTC-Sheraton Hotel, São Paulo, Brazil

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Welcome to the 5th Global Cardio-Oncology Summit

The 5th GCOS is a world congress of cardio-oncology, focused on the care of cancer patients and survivors, or with multiple risk factors for cardiovascular disease, including the toxic effects of treatment such as chemotherapy, radiotherapy, immunotherapy and cell transplantation. The program will address the latest research in the field, to better understand how cancer affects heart and vessels, trying to identify mechanisms and strategies to prevent and to treat heart disease in cancer patients.

These abstracts were selected based on originality, clinical significance and transalational ability.

LIST OF ORGANIZERS

Alexander Lyon
Artur Katz
Christine Brezden-Masley
Cristina Salvadori Bittar
Gustavo dos Santos Fernandes
Isabela Bispo Santos da Silva Costa
Marilia Harumi Higuchi dos Santos
Michael Fradley
Susan Dent
Roberto Kalil Filho
Daniel Lenihan
Ludhmila Abrahão Hajjar

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IN COLLABORATION WITH

Programme

Thursday, 3 October 2019

7:30-8:00 am Registration

8:00-8:20 am Opening session: Welcome and opening remarks

Dr. Roberto Kalil Filho, Brazil
Dr. Ludhmila Hajjar, Brazil
Dr. Daniel Lenihan, USA
Dr. Susan Dent, USA

8:20-8:50 am Plenary lecture # 1: The evolving field of cardio-oncology: Perspectives

Chairs: Dr. Ludhmila Hajjar, Brazil and Roberto Kalil Filho, Brazil
Dr. Daniel Lenihan, USA

8:55-9:55 am Session 01

CARDIOTOXICITY-Part I. Left ventricular dysfunction and heart failure in cardio-oncology

Chairs: Dr. Jean-Bernard Durand, USA and Dr. Ludhmila Hajjar, Brazil

(a) 8:50-9:05 am The use of biomarkers for prediction of cardiotoxicity

Dr. Daniela Cardinale, ITA

(b) 09:05-9:20 am Clinical phenotypes associated with cardiac injury during cancer therapy

Dr. Anne Blaes, USA

(c) 09:20-09:35 am **Multimodality imaging to ensure early detection of cardiotoxicity**

Dr. Jennifer Liu, USA

(d) 09:35-09:50 am **Prevention and monitoring of cardiac dysfunction in survivors of adult cancers**

Jean-Bernard Durand, USA

Discussion 5 minutes

9:55-10:10 am **Coffee break**

10:10-11:10 am **Part II. Breast cancer: Cancer therapy monitoring and treatment planning – what should we be doing to minimize cardiotoxic risk?**

Chairs: Dr. Gustavo dos Santos Fernandes, Brazil and Dr. Susan Dent, USA

(a) 10:10-10:20 am **Case presentation**

Dr. Isabela Bispo Santos da Silva Costa, Brazil

(b) 10:20-10:35 am **Contemporary cancer therapy and cardiac impact: Are anthracyclines still necessary?**

Dr. Christine Brezden-Masley, CAN

(c) 10:35-10: 50 am **Radiotherapy: What is the cardiovascular risk?**

Dr. Samir Abdallah Hanna, Brazil

(d) 10:50-11:05 am **Is there an effective strategy for cardioprotection?**

Dr. Ludhmila Hajjar, Brazil

Discussion 5 minutes

11:10-12:00 am **Session 02**

Vascular toxicity associated with oncology treatments

Chairs: Dr. Artur Katz, Brazil and Dr. Ariane Macedo, Brazil

(a) 11:10-11:20 am **Case presentation**

Dr. Carolina Carvalho Silva, Brazil

(b) 11:20-11:35 am **Thromboembolism and anticoagulation in cancer patients**

Dr. Chiara Melloni, USA

(c) 11:35-11:50 am **Vascular events encountered in cardio-oncology**

Dr. Joerg Herrmann, USA

Discussion 10 minutes

12:00-12:50 pm **Satellite symposium bayer challenges and recommendations in anticoagulation in cancer patients: Venous thromboembolism (VTE) and stroke prevention in atrial fibrillation (AF)**

Chairs: Dr. Ludhmila Abrahão Hajjar, Dr. Isabela Bispo Santos da Silva Costa, Dr. Gustavo Fernandes.

12:00-12:20 pm **Treatment and prophylaxis of venous thromembolism in patients with cancer**

Dr. Ludhmila Abrahão Hajjar, Brazil

12:20-12:40 pm **Stroke prevention in atrial fibrillation in patients with cancer**

Dr. Chiara Melloni, USA

Discussion 10 minutes

12:50-1:20 pm **Lunch**

1:20-2:05 pm **Session 03**

Cardiovascular risk alert in heme malignancies

Chairs: Dr. Vanderson Rocha, Brazil and Dr. Juliana Pereira, Brazil

(a) 1:20-1:40 pm **Stem cell transplant and cardiotoxic exposures: Early and late effects**

Saro Armenian, USA

(b) 1:40-2:00 pm **Multiple myeloma and amyloidosis: New treatments and cardiovascular challenges**

Dr. Daniel Lenihan, USA

Discussion 5 minutes

2:05-3:05 pm **Session 04**

Coronary artery disease in oncology patients

Chairs: Dr. Cristina Bittar, Brazil, Dr. Filomena Galas, Brazil and Dr. Jean-Bernard Durand, USA

(a) 2:05-2:15 pm **Case presentation**

Dr. Isabela Costa, Brazil

(b) 2:15-2:30 pm **Intervention in cancer patients: Individualizing the techniques**

Dr. Carlos Campos, Brazil

(c) 2:30-2:45 pm **Does radiation exposure affect coronary revascularization?**

Dr. Anju Nohria, USA

(d) 2:45-3:00pm **Cardiotoxicity of 5-Fluoropyrimidines**

Dr. Thomas Suter, GER

Discussion 5 minutes

3:05-3:50 pm **Session 05**

Valvular disease

Chairs: Dr Joerg Herrmann, USA and Dr. Isabela Costa, Brazil

(a) 3:05-3:15 pm **Case presentation**

Dr. Cristina Bittar, Brazil

(b) 3:15-3:30 pm **Aortic stenosis and transcatheter aortic valve implantation**

Dr. Fábio Sândoli, Brazil

(c) 3:30-3:45 pm **Carcinoid heart disease**

Dr. Ludhmila Abrahão Hajjar, Brazil

Discussion 5 minutes

3:50-4:00 pm **Coffee break**

4:00-4:35 pm **Young investigator competition-top 3 abstracts for presentation**

Chairs: Dr. Sebastian Szmit, POL and Dr. Eric Harrison, USA

Discussion 5 minutes

4:35-5:25 pm **Thomas force lecture**

Dr. Joseph Carver, USA (50 min)

5:25-6:30 pm **Posters**

Dr. Alex Lyon, UK
Dr. Susan Dent, USA
Dr. Roohi Ismail-Khan, USA
Dr. Michael Fradley, USA

6:30-7:30 pm **JACC CO Journal-Meet the editors reception**

Friday, 4 October 2019

8:00-8:15 am **Recap of Day 1-Opening remarks and day 1 overview**

Dr. Ludhmila Hajjar, BRA

Presentation of young investigator awards

Chairs: Dr. Sebastian Szmit, POL; Dr. Eric Harrison, USA

8:15-8:55 am **Plenary #2**

Chairs: Dr. Susan Dent, USA and Dr. Javid Moslehi, USA

The importance of immunotherapy in cancer treatment

Dr. Gustavo Fernandes, Brazil

Immunotherapy and adverse cardiac events: How to recognize and manage?

Dr. Tomas Neilan, USA

8:55-9:50 am **Session 06**

New scientific advances in cardio-oncology

Chairs: Dr. Alexander Lyon, UK and Mr. Carlos Negrão, Brazil

(a) 8:55-9:10 am **Vascular tone and function in tumors**

Dr. Roger Chammas, Brazil

(b) 9:10-9:15 am **Cancer cachexia: Effects of aerobic training upon skeletal muscle atrophy and metabolism**

Dr. Patricia Chakur Brum, Brazil

(c) 9:15-9:30 am **Genetic susceptibility to anthracycline cardiomyopathy – genes and environment**

Dr. Paul Burridge, USA

Discussion 10 minutes

9:50-10:00 am **Coffee break**

10:00-11:10 am **Session 07**

Cardiac imaging

Chairs: Dr. Cesar Nomura, Brazil, Dr. Bruna Leal, Brazil and Dr. André Almeida, Brazil

(a) 10:00-10:30 am **Debate: Strain for everybody?**

- Yes: Dr. Juan Plana, USA
- No: Dr. Ronald Witteles, USA

(b) 10:30-10:45 am **Cardiac magnetic resonance – when to use, new protocols**

Dr. Dinesh Thavendiranathan, CAN

(c) 10:45-11:00 am **Coronary tomography in cancer patients**

Dr. Carlos Rochitte, Brazil

Discussion 10 minutes

11:10-12:00 am **Session 08**

Research and training programs

Chairs: Dr. Joseph Carver, USA and Dr. Carolina Carvalho Silva, Brazil.

(a) 11:10-11:25 am **Fellowships in cardio-oncology**

Dr. Ana Barac, USA

(b) 11:25-11:40 am **Building a program**

Dr. Alexander Lyon, UK

(c) 11:40-11:55 am **Facilitating international collaboration – roles and future projects**

Dr. Susan Dent, USA

Discussion 5 minutes

12:00-12:50 pm **Satellite symposium ferring**

Prostate cancer: Cardiovascular risk awareness and what can we do to minimize cardiotoxic risk on the patient under ADT

Dr. Ariane Macedo, Brazil
Dr. Diogo Bastos, Brazil

12:50-1:20 pm **Lunch**

1:20-1:55 pm **Session 09**

Advanced heart failure in cancer patients

Chairs: Dr. Ludhmila Hajjar, Brazil and Dr. Roberta Saretta, Brazil

(a) 1:20-1:30 pm **Case presentation**

Dr. Stéphanie Rizk, Brazil

(b) 1:30-1:50 pm **Criteria for heart transplantation and ventricular assist devices in cancer patient**

Dr. Mônica Avila, Brazil

Discussion 5 minutes

1:55-3:05 pm **Session 10**

Cardiovascular effects of tyrosine kinase inhibitors for various solid and liquid tumors

Chairs: Dr. Chiara Melloni, USA and Laleh AmiriKordestani, USA

(a) 1:55-2:10 pm **Overview of targeted therapy for cancer and possible cardiovascular impact**

Dr. Javid Moslehi, USA

(b) 2:10-2:25 pm **Cardiovascular toxicities of TKIs for CLL and other B-cell malignancies (BTK inhibitors)**

Dr. Michael Fradley, USA

(c) 2:25-2:40 pm **Cardiovascular toxicities of TKIs for melanoma (BRAF and MEK inhibitors)?**

Dr. Rodrigo Munhoz, Brazil

Discussion 10 minutes

2:50-3:20 pm **Coffee break**

3:20-3:55 pm **Session 11**

Survivorship programs

Chairs: Dr. Veronica Santos, Brazil and Dr. Silvia Moulin Ribeiro Fonseca, Brazil

(a) 3:20-3:35 pm **CVD prevention and treatment during survivorship**

Dr. Gregory Armstrong, USA

(b) 3:35-3:50 pm **Building a survivorship program**

Dr. Joseph Carver, USA

Discussion 5 minutes

3:55-4:25 pm **Session 12**

Physical activity and cancer

Chairs: Dr. Cristina Bittar, Brazil, Patricia Oliveira, Brazil and Dr. Amanda Rodrigues, Brazil

(a) 3:55-4:10 pm **Evaluation before exercise programs and exercising during treatment**

Dr. Carlos Negrão, Brazil

(b) 4:10-4:25 pm **Exercise in the follow up of oncology patients**

Dr. Laura Testa Brazil, Brazil

Discussion 5 minutes

4:30-4:55 pm **Session 13**

Social media in cardio-oncology: Impact, tips and cautions

Chairs: Dr. Marcio Sommer, Brazil and Dr. Jennifer Liu, USA
Dr. Javid Moslehi, USA

Discussion 5 minutes

4:55-5:30 pm **Session 14**

Future of cardio-oncology

Chairs: Dr. Christine Bresden-Masley, CAN; Dr. Dinesh Thavendiranathan, CAN and Dr. Ludhmila Hajjar, Brazil

How do we move forward?

Bonnie Ky, USA

Discussion 10 minutes

Room 2

14:00-14:40 pm **BRAVADO registry investigator's meeting**

Carlos Augusto Homem de Magalhães Campos MD, PhD
Ludhmila Abrahão Hajjar, MD PhD
Isabela Bispo Santos da Silva Costa, MD
Vinicius Bocchino Seleme, MD
Diego Carter Campanha Borges, MD
Roberto Kalil Filho, MD, PhD

Room 2

15:20-17:20 pm **Satellite symposium GE**

The role of strain echocardiography in the management of cancer patients: A practical approach

- Main indications of myocardial strain by echocardiography
- Strain imaging: Optimization and pitfalls
- Case discussions and image analysis with Echo Pac

Coordinators

Dr. Cecília Beatriz Bittencourt Viana Cruz, Brazil
Dr. Bruna Morhy Borges Leal Assunção, Brazil

Speakers

Dr. Adenalva Lima de Souza Beck, Brazil
Dr. Alex dos Santos Felix, Brazil
Dr. Diego Ribeiro Garcia, Brazil
Dr. Juliana Barbosa Sobral Alves, Brazil
Dr. Marcelo Dantas Tavares de Melo, Brazil
Dr. Maria Estefânia Bosco Otto, Brazil

5:20-5:35 pm **Closing remarks**

Aortic dissection in a case of multiple myeloma treated with bortezomib

Edielle de Sant'Anna Melo*, Mariana Lemos, Iran Gonçalves Júnior, Henrique Luiz dos de Godoy

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BACKGROUND

Cardiotoxicity is one of the most significant adverse effects of oncological treatment. This study presents the case of a patient with multiple myeloma treated with bortezomib. The patient presented with acute thoracoabdominal aortic dissection after the sixth chemotherapy cycle. Information on this case was obtained by reviewing the patient's clinical record and the existing literature.

CASE

A 65-year-old female with anemia was admitted. Hematological follow-up was initiated and a bone marrow biopsy was performed because the anemia worsened. She was diagnosed with multiple myeloma. Chemotherapy was initiated using the VCD regimen (bortezomib, cyclophosphamide, and dexamethasone) plus zoledronic acid (Zometa®).

Between the third and fourth cycles, the patient was referred to a cardiologist due to systemic hypertension and significant concentric left-ventricular hypertrophy on echocardiography.

A thoracic computed tomography (CT) was performed evidencing a dilatation of the descending aorta to 4.3 cm. Scans performed before chemotherapy initiation had not revealed any changes in the diameter of the aorta. The scheduled treatment and chemotherapy sessions were maintained.

After the sixth chemotherapy cycle, a new CT scan revealed aortic dissection. This was later confirmed by angiography, which evidenced thoracoabdominal

aortic dissection, with an intimal flap extending from the aortic root to the abdominal aorta. Intimal flap appeared to reach the origin of the right coronary artery, with diffuse dilatation of the dissected thoracoabdominal aorta, reaching a caliber of 5.5 cm in the ascending aorta.

The patient was referred for surgery and received postoperative care in the intensive care unit. She remained hemodynamically unstable and progressed to cardiorespiratory arrest during the immediate postoperative period.

DISCUSSION

Heart failure due to systolic ventricular dysfunction is the most frequent harmful effect of chemotherapeutic agents. However, reports of systemic hypertension in patients using bortezomib are lacking in the literature. Further research is needed to develop new strategies for preventing and treating cardiotoxicity associated with chemotherapeutic agents.

Myocardial metastasis of neuroendocrine tumor

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BACKGROUND

Neuroendocrine tumors (NET) are rare slow-growing tumors that express somatostatin receptors and are usually diagnosed with metastatic disease. The most common metastatic sites are lymph nodes, bone and liver. Myocardial metastasis are rare and related more frequently to disseminated disease and primary bowel tumors. There are few studies about prevalence, clinical presentation and treatment of heart metastatic disease, however, new modern techniques have resulted in the increase in diagnosis of these rare metastatic presentations.

CASE PRESENTATION

A 64-year-old female patient was diagnosed in 2015 with primary small bowel neuroendocrine carcinoma with liver and pancreatic metastasis, initially treated with somatostatine analogue and interferon up until 2017. The disease progressed and she developed carcinoid syndrome. OctreoScan (Whole-Body Scintigraphy 111In-Octreotide) was used for new staging, which showed disease dissemination to several bone segments and uptake in the right ventricule. Transthoracic echocardiogram showed increased echogenicity of the interventricular septum in its right ventricular portion, with normal aspect and mobility of the heart valves. A radionuclide therapy was employed with 400mCi of 177Lu-DOTATATE. Echocardiogram was repeated 6 months after the end of treatment, showing a reduction of the hyperechogenic material.

DISCUSSION

The nuclear imaging techniques using somatostatin analogue radiotracer are able to identify early metastasis of NET being more sensitive than other

imaging modalities, resulting in more accurate treatment, prognosis and follow up planning. NET myocardial metastasis can progress with severe complications such as malignant arrhythmia and cardiac arrest as a consequence of infiltration of the conduction structures of the heart, so once identified it becomes clear that the treatment should be evaluated according to the extent of the disease and the clinical presentation. Several therapeutic modalities may be employed such as the use of somatostatin analogues, chemotherapy, radiotherapy and surgical intervention. Radionuclide therapy is used as first or second line therapy for NETs, but little is known about its applicability and effects on myocardial metastasis.

Comprehensive angiographic assessment of coronary disease in oncologic patients presenting acute coronary syndromes: Distribution of plaque rupture, anatomical complexity and total burden

Vinicius B. Seleme[1]*, Carlos M. Campos[1], Isabela Bispo S. da S. Costa[2], Diego Carter Borges[1], Cristina S. Bittar[2], Carolina Maria D. C. e Silva[2], Silvia Moulin R. Fonseca[2], Giovani Henrique Pinto[2], Expedito E. Ribeiro da Silva[1], Roberto Kalil Filho[1], Ludhmila Hajjar[1,2]

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BACKGROUND

Differently from other clinical scenarios, oncologic patients have prothrombotic states, vasospasm and vascular injuries that may precipitate acute coronary syndromes (ACS). We aim to provide a description of the atherosclerotic burden and lesion complexity of oncologic patients presenting ACS.

METHODS

Prospective study that enrolled patients of two tertiary care centers collecting all consecutive cases of ACS in oncologic patients. The number and location of coronary lesions with obstructions greater than 50% were recorded. Each lesion was classified based on Ambrose's, Goldstein complexity, Leaman and SYNTAX scores.

RESULTS

From 2012 to 2018 a total of 516 lesions from 100 oncologic patients with ACS were assessed. The mean age was 69.4$\pm$7.9 years old, 66% were male, 35% were diabetics, 12% did not have significant coronary artery disease and 71% had multivessel disease. The mean Leaman and SYNTAX Scores were 14.3$\pm$11.1 and 19.3$\pm$14.7, respectively. About the morphology of the lesion, it was found that 35% were at least Ambrose type II (high complexity).

Regarding the distribution of complex lesions (thrombus, ulceration, haziness or impaired flow) in coronary tree, it was found that plaque rupture occurred predominantly in proximal segments.

CONCLUSION

Although secondary causes of infarction are described in these patients, such as those related to types of cancer and their respective treatments, oncologic patients presenting ACS have high atherosclerotic burden and lesions with complex morphology were frequently found, demonstrating that type I myocardial infarction is still frequent in these individuals.

Osimertinib-induced cardiomyopathy

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BACKGROUND

Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has been approved for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) with EGFR mutations. We report a series of cases of newly developed cardiomyopathy with subsequent heart failure exacerbation after the initiation of osimertinib.

CASES

An 84-year-old woman with Stage IVa lung adenocarcinoma presented with hypotension and hyponatremia 4 weeks after dose escalation to 80mg osimertinib. Echocardiogram showed an ejection fraction (EF) of 20% with severe generalized left ventricular hypokinesis (prior EF: 63%) and no evidence of ischemia. Osimertinib was replaced with erlotinib and patient was started on cardio-protective medications. Echocardiogram was repeated shortly after this visit and showed an improvement of EF to 41%.

A 71-year-old male with recurrent lung adenocarcinoma was initiated on osimertinib 80 mg daily. 12 days later, he presented with acute dyspnea. Echocardiogram showed an EF of 39% (prior EF: 52%). Ischemic etiology was ruled out and cardiomyopathy was attributed to osimertinib. The patient was diuresed, and osimertinib treatment was stopped. Osimertinib was re-initiated 16 days later with no recurrence in symptoms.

A 72-year-old fema le with recurrent lung adenocarcinoma was started osimertinib 80 mg daily. One month later, she presented with progressive dyspnea. Echocardiogram revealed an EF of 38% (Prior EF: 67%). Patient initiated on

treatment with an ACE inhibitor and beta blockers. Osimertinib was replaced with erlotinib. A follow-up echocardiogram two months later demonstrated normalization of EF to 57%.

DISCUSSION

Our case series highlights a rare but important cause of cardiomyopathy that needs to be considered in patients that have started treatment with osimertinib despite history of coronary artery disease. It demonstrates that cardiotoxicity from osimertinib is likely reversible with the use of cardioprotective medications and based on our observation, it occurs 80 mg daily. Based on our case series, erlotinib could be an option for patients with this osimertinib associated complication. These cases illustrate the independent risk of acute cardiomyopathy associated with osimertinib.

Acute coronary syndrome due to an invasive thymoma with blood supply by circumflex artery

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BACKGROUND

Thymomas are usually located in the anterior mediastinum. These tumors have a slow growing behavior, but with potential to invade nearby structures. Most patients are asymptomatic; however, in some cases there are signs and symptoms associated with the involvement of surrounding organs, including the heart.

CASE REPORT

A 56-year-old female patient diagnosed with Thymoma B2 Masaoka IVa since 2013 had been previously submitted to oncologic treatment with local radiotherapy and different chemotherapy regimens. In 2015, the patient performed a cardiac magnetic resonance (CMR) that evidenced invasion of the left ventricle and progression of disease (Figure 1). Systemic treatment was indicated, but the patient refused new chemotherapy treatment and only maintained clinical follow-up with the oncology team. At the end of 2018, she came to the emergency care with typical precordial pain. The initial electrocardiogram (ECG) showed inverted T wave in the avL and DI leads, with no subsequent ECG changes. There was an elevation in the myocardial necrosis markers during hospitalization. Transthoracic echocardiogram showed left ventricle (LV) with discrete systolic impairment due to diffuse hypokinesia and atypical movement of the ventricular septum, left ventricular ejection fraction of 50% and presence of an extensive mass adjacent the free wall of the LV, with a discrete compressive effect in the heart, without hemodynamic repercussion.

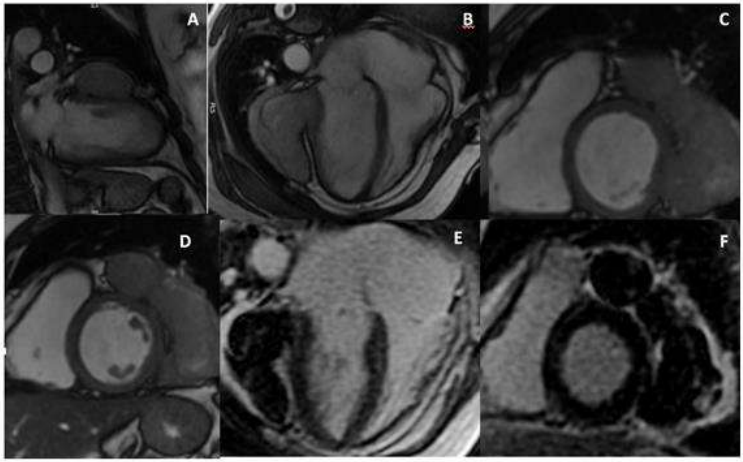

FIGURE 1: Cardiac magnetic resonance imaging showing the thymoma invading the left ventricle. (**A**) Cine MRI 2 chamber. (**B**) Cine MRI 4 chamber. (**C, D**) Cine MRI short axis. (**E, F**) Late gadolinium enhancement showing an heterogeneous contrast captation.

The coronary computed tomography angiography (CCTA) showed a heterogeneous expansive lesion located between the LV and the left lung that shows signs of myocardial invasion and presents a macroscopic neovascularization irrigated by the left circumflex coronary, marginal branches and posterior ventricular branch artery. The current chest pain of the patient was attributed to an acute myocardial infarction type 2.

DISCUSSION

This case highlights a unique and rare case of a thymoma Masaoka IVa that involves the heart with signs of myocardial invasion and presents a macroscopic neovascularization irrigated by the left circumflex coronary and its branches, causing typical angina due to compromised coronary blood flow by the mass causing ischemia.

Management of chemotherapy-related cardiac dysfunction in the cardio-oncology clinic at south health campus

Maria Anwar*

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**maria.anwar@ahs.ca*

BACKGROUND

The Cardio-Oncology Clinic at South Health Campus (SHC) consists of a multidisciplinary team that provides care for patients experiencing chemotherapy-related cardiotoxicity.

OBJECTIVES

Describe patients referred for chemotherapy-related cardiac dysfunction, identify management strategies, and determine the impact on LVEF and/or HF symptoms during follow up.

DESIGN

A retrospective chart review was performed on 101 adult patients from Nov 1, 2013 to July 1, 2017. Information was gathered on patient demographics, cancer histories, cardiac risk factors, LVEF reduction and recovery, and heart failure symptoms.

RESULTS

Chemotherapy regimens contained anthracyclines (53%), trastuzumab (10%) or both (29%). Common cardiac risk factors consisted of tobacco use (40%), hypertension (30%) and dyslipidemia (22%). Over half of the population was managed with evidence-based HF therapy, including angiotensin-converting enzyme inhibitors (53%), angiotensin II receptor blockers (21%) and/or beta-blockers (53%). Additional strategies involved chemotherapy interruption (36%)

or close monitoring only (30%). Sixty-nine patients had an LVEF reduction of 5% or more and 58% achieved partial or full recovery.

CONCLUSION

The Cardio-Oncology Clinic at SHC manages a diverse population, with the individualized use of medications and non-pharmacological strategies. Reassuringly, the findings of this study reveal improvements in LVEF and HF symptoms during follow up.

DOACs for stroke prevention in patients with atrial fibrillation and cancer

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BACKGROUND

Atrial fibrillation (AF) is present in a significant number (4%) of cancer patients (1). Stroke prevention is an important aspect of management in patients with AF. Currently there is limited evidence for the use of direct oral anti-coagulants (DOACs) in cancer patients for stroke prophylaxis in AF (SPAF). However, small prospective studies and subgroup analyses have not demonstrated negative implications on safety or efficacy in comparison with warfarin and low molecular weight heparin (LMWH) (2-5). A lack of specific prescribing guidance results in variable clinical practice with the adoption of multiple anti-coagulation strategies. Here we analyse DOAC prescribing in AF and cancer at a single tertiary-care institution over a 6-month period.

METHODS

All outpatient DOAC prescriptions at St Bartholomew's Hospital between November 2018 and April 2019 were reviewed, as well as all inpatient orders of DOACs on the oncology wards. From this, all patients with an active diagnosis of cancer who were prescribed a DOAC for SPAF were identified.

RESULTS

29 cancer patients who had received a DOAC for SPAF were identified. 38% of patients had a haematological malignancy and 62% had solid tumour

malignancies. The mean duration of DOAC therapy was 10.9 months. DOACs used included apixaban (55%), edoxaban (21%) and rivaroxaban (24%). There were no embolic strokes or transient ischaemic attacks (TIAs) identified in any of the patients following commencement of DOAC. 5 patients suffered from minor bleeding complications including gastrointestinal bleeding and haematuria. 4 of these patients had gastrointestinal or genitourinary cancer. There were no major bleeding events.

CONCLUSION

There appears to be encouraging evidence from a limited data set that DOACs are efficacious and relatively safe in the prevention of embolic stroke in cancer patients with AF. These data highlight the need for randomised control trials to evaluate DOACs against warfarin and LMWH in cancer patients, and also support the recent guidance issued by the International Society for Thrombosis and Haemostasis suggesting an individualised approach to anticoagulation in cancer based on stroke and bleeding risk, drug-drug interactions and patient values.

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Regional cardiac function for identification of radiation therapy induced cardiac dysfunction and effect of genetic profile

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BACKGROUND

The impact of radiation therapy (RT) on the heart is not well understood and is of increasing importance as cancer patients are living longer. In this study, we present preliminary results of using MRI to identify cardiotoxicity in rat models of breast cancer RT with different genetic profiles.

METHODS

Salt-sensitive (SS) and Brown Norway rats were bred to produce SS.BN3 consomic rats, which are genetically identical to SS rats except for chromosome 3. The SS.BN3 rats have previously shown to exhibit different vascular dynamics versus SS. Both SS and SS.BN3 adult female rats received whole-heart RT to 24 Gy using 3 equal fields. The rats were scanned on 9.4T MRI scanner at 8-weeks (n=11) and 10-weeks (n=13) post-RT. The MRI exam included cine, tagging, and T1/T2 mapping sequences. The images were analyzed to generate parameters of global function (ejection fraction (EF) and mass), contractility (longitudinal (Ell) and circumferential (Ecc) strains, %wall thickening), and tissue characteristics (T1/T2 values).

RESULTS

All animals showed normal EF (>50%) and wall thickening (>50%). Cardiac hypertrophy was observed (mass~0.5 g), especially in SS rats at 10-weeks. Figure 1 shows strain and T1/T2 results. All animals showed depreciated strain (mean Ell < 16%, mean Ecc < 18%). Although Ell did not show large differences

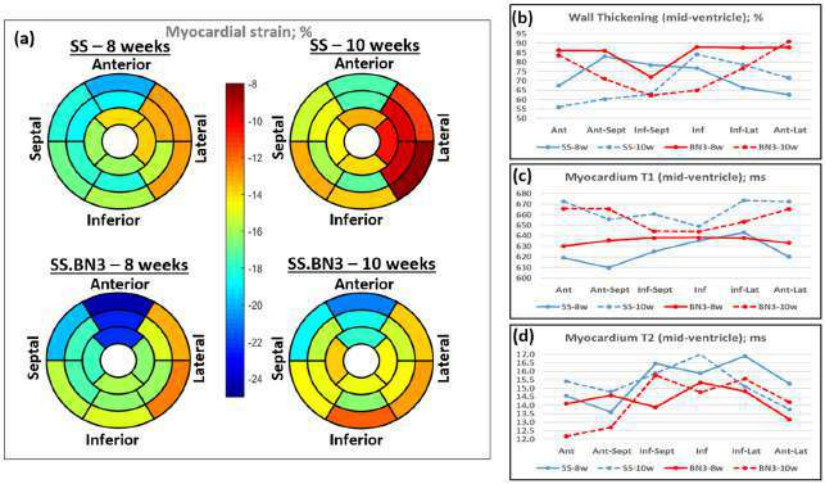

FIGURE 1: (**a**) AHA 17-segment maps showing circumferential strain distribution in SS and SS.BN3 rats at 8-weeks and 10-weeks timepoints post-RT. (**b-d**) Segmental % wall-thickening, TI, and T2 values, respectively, at mid-ventricular short-axis position in both rat groups and two imaging timepoints. Note depreciated strain, especially in SS rats, at 10-weeks, and in the lateral and inferior regions. Note also T1 and T2 variations between the two rat types and the two imaging timepoints.

between SS and SS.BN3 rats, Ecc showed more depreciation in SS, especially at 10-weeks. On a regional basis, strain was more depreciated in the lateral and inferior walls. Average T1 values increased from 619/636 ms at 8-weeks to 676/658 ms at 10-weeks in SS/SS.BN3, respectively. Average T2 values decreased and slightly increased in SS.BN3 and SS rats, respectively, between 8- and 10-weeks in the anterior/septal regions. Large positive correlations ($R > 0.8$) occurred between Ell and EF; Ecc and mass; and EDV and T1. Large negative correlations ($R < -0.75$) occurred between %thickening and both Ecc and mass.

CONCLUSION

In conclusion, MRI have the potential for early detection and characterization of RT-induced cardiotoxicity development on a regional basis and differentiating between different genetic profiles, which would allow for prompt intervention to reduce cardiotoxicity.

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An optimized cardiac MRI exam for early detection of cardiotoxicity in small-animals

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BACKGROUND

Cardiac MRI of rat models of cancer provides important information about cardiotoxicity development. Nevertheless, a comprehensive cardiac functional exam would be challenging for such sick animals. In this study, we developed and evaluated an optimized MRI exam for measuring both global and regional cardiac function in rat models of radiation therapy (RT).

METHODS

Adult salt-sensitive rats (8 rats, 8-10 weeks post whole-heart RT of 24Gy; and 2 control rats) were scanned on 9.4T MRI scanner. The scan included cine (long-axis (LAX) & 6 short-axis (SAX) slices) and tagging (1 LAX & 3 SAX slices). The effects of imaging parameters on image quality were investigated. Optimal imaging parameters for cine were: TR = 7 ms, TE = 2.1 ms, flip angle = 15°, matrix = 176x176, FOV = 40x40 mm^2, slice thickness = 1 mm, bandwidth = 526 Hz/pixel, #averages = 2, #phases = 20. Optimal parameters for tagging were same as in cine, except for: TE = 2.5 ms, matrix = 256x256, bandwidth = 376 Hz/pixel, #averages = 3. The cine and tagging images were analyzed to measure global function (ejection fraction (EF), end-diastolic volume (EDV), mass) and myocardial strain.

RESULTS

Total scan time was ~30 minutes, which was tolerable for all animals. Global function was normal in all animals; however, RT rats showed reduced strain. EF/EDV/mass were $60\pm1.2\%$ / 0.28 ± 0.01 ml / 0.39 ± 0.05 g in controls;

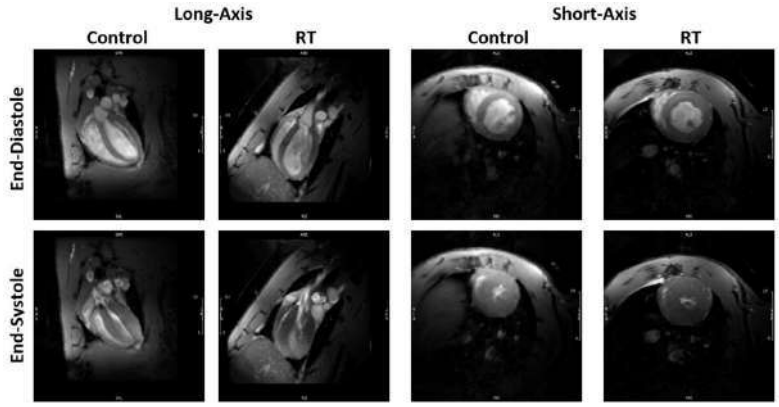

FIGURE 1: Long-axis and short-axis cine images at end-diastole and end-systole of both control and RT rats. The images show ventricular remodeling, as illustrated by change in ventricular shape, to maintain EF. Note increased hypertrophy in RT.

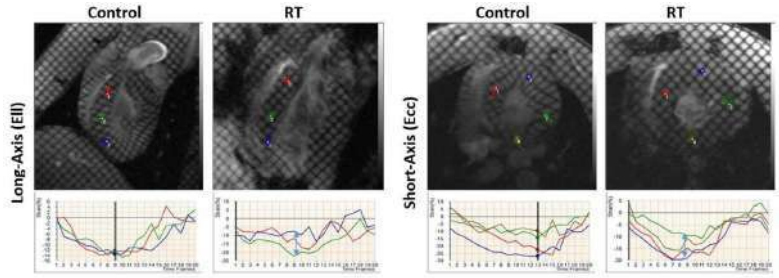

FIGURE 2: Long-axis and short-axis tagged images of both control and RT rats, showing longitudinal (Ell) and circumferential (Ecc) strains, respectively. Note reduced strain in RT (arrows).

and 78.6±2.6% / 0.26±0.02 ml / 0.52±0.05 g in RT. Longitudinal/radial/circumferential strains were -18±1.4% / 61.5±16.3% / -12.5±0.7% in controls; and -14.1±1.5% / 43.1±10.2% / -9.8±2.4% in RT. The results showed that tissue contrast and artifacts in the cine images significantly affect EF and other global function measurements, whereas resolution has less effect on the results. On the other hand, reduced resolution in the tagged images has significant

effect on strain values, whereas tagline density has less effect on strain, as long as more than one tagline intersects the myocardium.

CONCLUSION

In conclusion, this study provides an optimized comprehensive cardiac MRI protocol for imaging rat models of cancer, which provides accurate measurements of both global and regional function parameters while minimizing artifacts and reducing scan time to be tolerated by sick animals.

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Effects of chemotherapy on myocardial glycolytic metabolism in patients with lymphoma

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BACKGROUND

The progress of chemotherapeutic treatment has triggered an increase in the exposure of cancer patients to the adverse effects of cancer therapy, especially to cardiotoxicity (CTX). Due to its clinical complications and its prognosis, it is recommended the rigorous follow-up of patients undergoing chemotherapy, through imaging, for CTX screening and diagnosis. The standardized test is the echocardiogram, but it is based on the decrease of the left ventricular ejection fraction (LVEF), an event that usually occurs late after extensive myocardial damage. More recent studies have highlighted the role of ^{18}FDG PET/CT as a useful tool for the early diagnosis of cardiac dysfunction, since it evaluates myocardial metabolic changes that may reflect chemotherapy-induced toxicity. The aim of this study was to investigate alterations of cardiac glycolytic metabolism in patients with lymphoma evaluated through ^{18}FDG PET/CT before, during and/or after chemotherapy.

METHODS

Seventy patients with lymphoma who underwent baseline ^{18}FDG PET/CT (before chemotherapy) and control (after its onset) were evaluated retrospectively. Of the total of the sample, 30 underwent basal and interim examination (during chemotherapy), and 66, baseline and final (shortly after the end of chemotherapy). The SUV of the heart (left ventricle – LV), liver and aorta were measured in all exams.

RESULTS

There was an increase in the maximum LV SUV of 3.5±1.9 to 5.6±4.0 ($p<0.05$) between the baseline and interim examination and an increase in the maximum LV SUV of 4.0±2.2 to 6.1±4.2 ($p<0.001$) between baseline and final examination. A percentage increase of LV ≥30% maximum SUV occurred in more than half of the sample (57.6%). The elevation of cardiac SUV during and after chemotherapy was accompanied by an increase in the values of the following rates: LV Maximum SUV/Aorta Maximum SUV and LV Mean SUV/Liver Mean SUV.

CONCLUSION

In conclusion, the present study showed an increase in cardiac glycolytic metabolism in patients with lymphoma, verified by ^{18}FDG PET/CT during and/or after chemotherapy. The relevance of this study lies in the fact that this change in myocardial uptake of ^{18}FDG may be an early indication of CTX and, therefore, be related to unfavorable outcomes and prognosis.

Keywords: cardio-oncology, cardiotoxicity, chemotherapy, ^{18}FDG PET/CT

Toxicity of Vinorelbine

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BACKGROUND

Vinorelbine is a vinca alkaloid used to treat neoplasia such as ovarian cancer, breast cancer, hematologic neoplasia and lung cancer. Vinorelbine cardiotoxicity is rare and when it occurs it is presented by chest pain, pulmonary edema, arrhythmias and acute myocardial infarction. We present a case of acute coronary syndrome in a patient using vinorelbine alone as chemotherapy.

CASE

E.C.F.S, 47 year-old female, with hypertension, diabetes mellitus and breast cancer, diagnosed in 2015. Previous use of anthracyclic, taxol and fluoracil. Vinorelbine alone was started at a dose of 25 μg/m^2. After two doses, patient sought emergency service due to chest pain and electrocardiogram was performed without changes. Serial blood tests of negative myocardial necrosis markers were performed. Patient received aspirin, clopidogrel and sublingual nitrate and the pain improved. Patient was hospitalized and underwent coronary angiography showing severe obstructive lesion in the right coronary artery and in the anterior descending artery. Patient underwent angioplasty of both coronary arteries successfully. There were no other obstructive lesions. After discharge, patient restarted her oncologic treatment with vinorelbine and after two doses the chest pain recurrence. Clinical treatment optimization with oral nitrate and amlodipine was chosen. Patient evolved with improvement and no symptoms.

DISCUSSION

The pathophysiology of vinorelbine toxicity is still unclear, but possible explanation in the literature are vasoconstriction, coronary spasm and cell hypoxia.

In this case study, even after treating the patient's severe coronary lesions, a recurrence of chest pain after restarting vinorelbine, favors the hypothesis that this medication may be the cause of chest pain. Clinical treatment with nitrates and calcium channel blockers were chosen and the cancer treatment was maintained. Patient's chest pain improved with no further symptoms. The real case above demonstrates the importance of the team work among cardiologists and oncologists in order to provide, to cancer patients, the continuity of their therapies contributing to longer survival.

Second generation tyrosine kinase inhibitors are associated with a worse lipoprotein profile in individuals with chronic myeloid leukemia

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BACKGROUND

The treatment of Chronic Myeloid Leukemia (CML) was revolutionized by the use of tyrosine kinase inhibitors (TKIs). However, newer generation TKIs have been associated with cardiovascular events, through unclear mechanisms. In the present study, we evaluated the differences in the lipoprotein levels and composition in a CML population exposed to different TKI regimens.

METHODS

Consecutive CML patients on treatment with Imatinib, Dasatinib and Nilotinib at the Instituto do Cancer do Estado de Sao Paulo were prospectively included, and clinical and laboratory information, including lipid panel and apolipoprotein A and B1 levels, were collected. We compared the differences in metabolic panel across the three TKIs available in our center. Multivariable models were constructed using linear regression.

RESULTS

Among 173 patients (53% males, 71% white, mean age 51 years), 86 were using a first-generation TKI (Imatinib) and 87 on second-generation TKI

(63 on Dasatinib; 24 on Nilotinib). The median TKI treatment time was 7.7 years. The use of second generation TKIs was associated with higher LDL-C levels ($p<0.001$) and higher HDL-C ($p=0.008$) when compared to those using imatinib. The use of second generation TKIs was associated with higher levels of both apoA1 and apoB ($p<0.001$). After adjustment for age, sex and lipid lowering medication use, dasatinib was associated with higher HDL-C and apoA1 levels ($p=0.003$ and $p<0.001$), but nilotinib was not. Both second generation TKIs were associated with higher LDL-C and apoB levels ($p<0.01$ for all). Finally, while both second generation TKIs were associated with higher ApoB/ApoA1 ratio, this effect was more pronounced for nilotinib ($p=0.003$ for dasatinib and $p=0.01$ for nilotinib).

CONCLUSION

While both dasatinib and nilotinib are associated with worse LDL-C and apoB levels, dasatinib is associated with higher HDL-C and apoA1 levels. Collectively, those differences might explain the higher cardiovascular event rates with second generation TKIs, as well as difference in between the two drugs in this category.

Keywords: cardiovascular risk, chronic myeloid leukemia, tyrosine kinase inhibitors

Case report—quimio/radiotherapy in patient with left bundle branch block and atrial septal defect

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BACKGROUND

Patients are at risk of LV dysfunction and HF when submitted to quimio and radiotherapy. The occurrence and intensity of the myocardial damage and clinical manifestation is variable, depending on drugs used as well as cardiovascular risk factors. Thus, patients, oncologists and cardiologists must be aware of this scenario that is becoming more prevalent in clinical practice.

CASE

E.R.O, 62 y/o, white, Ituiutaba-MG

Incidental LBBB and A.S.D 12 mm was diagnosed in 2017. In April 2018 a breast cancer was detected (carcinoma ductal). Doxorubicin, cyclophosphamide, paclitaxel and radiotherapy were applied in low dosage. One year later she felt exercional dyspnea and fatigue. HR 90 bpm, no murmur, BP 150-100 mmHg. No congestion. EKG in sinus rhythm, LBBB. All blood tests normal. TT 3D echo and strain were requested. Treatment was started with sacubitril/valsartana 24-26 bid, bisoprololol 5 mg/day, spironolactone 25 mg/day. She was without symptoms in the first month and echo parameters showed improvement four months later (table). Higher dosage caused hypotension.

ECHO	3D DV	3D SV	3D EF	CIRCUNF STRAIN	GLS	L.A.V.	S.P.P.	E/E'
FIRST	64	40	36%	19	15	30	32	17
SECOND	60	32	46%	24	17	28	25	9

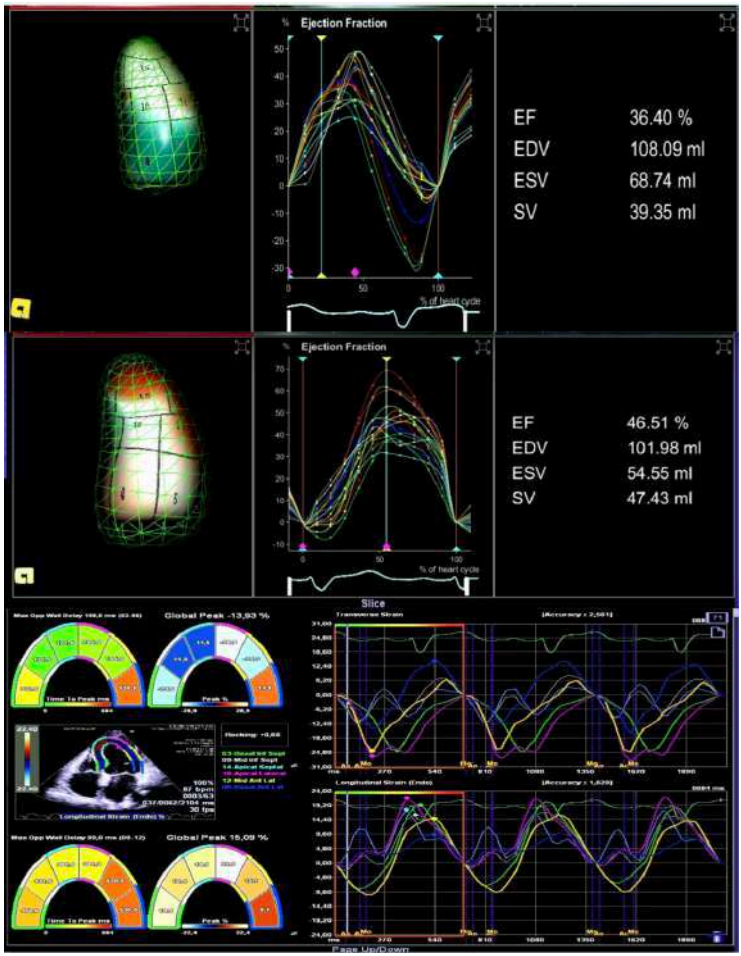

FIGURE 1

DISCUSSION

The EF by m-mode is the main parameter used to detect myocardial dysfunction during quimio, 10% below the normal inferior value or 15% by GLS. In this case EF decreased from 65% to 50%, but 3D EF was 36% and GLS -15

showing worse dysfunction. The correlation with NYHA-3 clinical status and reproducibility four months later was better by 3D and strain. In HF, LBBB increased mortality compared with patients without LBBB (Swedish register). It is also associated with less LV recovery in comparison with patients without LBBB (Duke University echo data Center). The option for sacubitril/valsartan instead of ACEI, took into account the results of Paradigm trial which showed reduction in mortality and hospitalizations.

In spite of the risk factors she was not informed of the need of a cardiological consultation. Once the cancer diagnoses is confirmed, should be mandatory the risk stratification. The earlier the patient is referred to the cardiologist, the sooner HF is identified and the prognosis improved.

Use of the cardiac risk score to predict cardiotoxicity in HER-2 positive breast cancer patients undergoing trastuzumab chemotherapy

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BACKGROUND

Trastuzumab (TTZ) improves survival for women with HER-2-positive breast cancer, but increases risk for cardiotoxicity. A clinical score with a high negative predictive value (NPV) for cardiotoxicity would better select those patients that the long term monitoring is recommended. Cardiac Risk Score (CRS) includes age and baseline left ventricular ejection fraction (LVEF) and was developed for the prediction of cardiac event (NYHA III/IV congestive heart failure or possible/probable cardiac death) in HER-2 positive initial breast cancer patients undergoing AC-T or AC-TH chemotherapy protocols. The aim of this study was to evaluate the performance of this score in predicting only cardiotoxicity in HER-2 positive initial breast cancer patients undergoing any chemotherapy protocol including TTZ.

METHODS

Retrospective cohort study including all patients followed at the institution's oncology outpatient clinic between 2016 and 2018. The CRS was calculated for each patient: [7.0 + (0.04 x age in years) - (0.1 x baseline percent LVEF by echocardiogram)] x 100/4.76. AUC was calculated to evaluate the ability of the score in predicting cardiotoxicity (decrease in LVEF of at least 10 percentage points from baseline to a value < 50%). The best cutoff point was identified through the Youden index.

RESULTS

We studied 79 patients during a 75.0 patients-year follow-up (median 0.9 [IQR: 0.7-1.1] year). Mean age was 52.5±12.3 years and baseline LVEF was 64.3±4.6%. AC-TH was the most frequent chemotherapy protocol (67.1%), followed by TCH (13.9%). The incidence of cardiotoxicity was 8.9% (95%CI: 2.6-15.2%). Median CRS was 57.4 (IQR: 47.1-66.4) points and the AUC was 0.65 (95%CI: 0.46-0.85; P = 0.181). A score > 70.8 points showed a sensitivity of 42.9% and a specificity of 90.3% to predict cardiotoxicity. The positive predictive value was 30.2% and the NPV was 94.2%.

CONCLUSION

CRS score showed a good NPV for the development of cardiotoxicity. Nevertheless, a better risk score is necessary to safely select patients to intensive cardiac monitoring.

Use of a clinical risk score to predict cardiotoxicity in non-elderly HER-2 positive breast cancer patients undergoing trastuzumab chemotherapy

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BACKGROUND

Trastuzumab (TTZ) improves survival for women with HER-2-positive breast cancer, but increases risk for heart failure (HF) and cardiomyopathy (CM). A clinical score with a high negative predictive value (NPV) for cardiotoxicity would better select those patients that the long term monitoring is recommended. A risk prediction model for older patients after adjuvant TTZ therapy was able to predict 3-year risk of HF/CM in patients ≥ 67 years. This model calculates risk based on age, adjuvant chemotherapy and the presence of comorbidities. The aim of this study was to evaluate the performance of this score in predicting cardiotoxicity in younger patients.

METHODS

Retrospective cohort study including all patients < 67 years with initial HER-2 positive breast cancer followed at the institution's oncology outpatient clinic between 2016 and 2018 that underwent chemotherapy protocols including TTZ. The risk score was calculated for each patient. A score 0-3 was considered low risk; 4-5, moderate risk; and ≥6, high risk. Cardiotoxicity was defined as a decrease in left ventricular ejection fraction (LVEF) of at least 10 percentage points from baseline on follow-up echocardiography to a value < 50%.

RESULTS

We studied 68 patients during a 64.8 patients-year follow-up (median 0.9 [IQR: 0.7-1.1] year). Mean age was 49.5 $\pm$ 10.3 years. AC-TH was the most frequent chemotherapy protocol (72.1%). Median score was 2.0 (IQR: 2.0-3.0) points. In applying the risk score, 61 patients (89.7%) were considered at low risk, 6 (8.8%) at moderate risk, and 1 (1.5%) at high risk to develop HF/CM. The incidence of cardiotoxicity was 10.3% (95%CI: 4.2-20.1%), being 9.8% in the low risk and 14.3% in the moderate-high risk group (P = 0.550). Score $\geq$ 4 points (moderate-high risk) had a positive predictive value of 14.3% (95%CI: 2.3-54.4%), and a NPV of 90.2% (95%CI: 87.0-92.6%) to predict cardiotoxicity.

CONCLUSION

The score demonstrated a good NPV for the development of cardiotoxicity in a younger population than that studied in the original risk score derivation cohort. Nevertheless, a better risk score is necessary to safely select patients to intensive cardiac monitoring.

Development of a cardio-oncology service in Lithuania

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BACKGROUND

Advances in cancer therapy have dramatically improved outcomes for cancer patients (pts). However, cancer treatment can cause severe cardiovascular (CV) complications which affect cardiac mortality and morbidity of cancer pts and cancer survivors. As a result, new cardiology subspecialty – cardio-oncology (CO) – has developed. The goals of CO are an understanding of the mechanism of the cardiotoxicity (CT) of cancer therapies and to invent the best monitoring and treatment strategies.

METHODS

We performed a retrospective observational study reporting on the almost 5 years of experience of the CO service in Lithuania.

Cancer pts were consulted by a single part-time specialist at Vilnius University hospital. All new pts had blood tests including biomarkers and TTE (with stress protocol if indicated). We evaluated age, gender, reasons for referral, cancer location and stage, CV risk factors (RF), rates of CT and treatment in consulted pts.

RESULTS

A total of 274 pts (63% females) were referred to our service in a 4.5 year period between December 2014 and June 2019.

Patients' median age was 66, ranging 24–92 years. The most common reasons for referral were cancer treatment complications and pre-chemo/

pre-operation risk assessment (45% and 42% of pts). Stress test was performed for 45% pts.

Pts with 24 cancer types were referred: 29% pts had breast, 22% gastrointestinal, 13% genitourinary, 13% hematological, 10% gynecological, 8% lung and 5% other type of cancer.

More than half had advanced stage of cancer.

CV RF were common: 77% of pts had hypertension, 35% – dyslipidemia, 29% were obese, 25% were smokers and 10% had diabetes.

TnI elevation was determined in 17% then reduced GLS was measured in 39% pts undergoing cardiotoxic therapies. However, early mixed CT was found in 4% of pts.

BB were administered to 70% of pts, then ACEI/ARB to 63% of pts. 19% of pts received loop diuretics and 16% MRA.

CONCLUSIONS

CO is a rapidly growing subspecialty of cardiology which aims to remove cardiac disease as a barrier to effective cancer treatment and to prevent, reduce and reverse cardiac damage of cancer therapies. To establish a CO service at least one cardiologist with an interest in oncology is needed. Continuous education, medical training and clinical research are key to success.

Myocardial and pericardial complication after allogenic hematopoietic stem cell transplantation

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BACKGROUND

Hematopoietic stem cell transplantation (HSCT) provokes several adverse cardiac events through direct toxicity of conditioning chemoradiation and indirect effects through graft versus host disease (GVHD) and immunosuppressive therapy. In addition, anthracyclines which also have cardiotoxicity are often administrated as a first-line or an induction chemotherapy. There are few systematic reports evaluating cardiotoxicity after HSCT including myocardial and pericardial complication.

METHOD

Consecutive 168 cases with hematopoietic disease who underwent allo-HSCT during January 2014 and December 2018 in Kyushu University Hospital were retrospectively surveyed about the incidence of cancer therapy related cardiac dysfunction (CTRCD) and pericardial effusion (PE). In addition, predictors of CTRCD and PE, and overall survival in several groups were evaluated. CTRCD was defined as left ventricular (LV) ejection fraction (EF) of below 53% and over 10% decrease from baseline.

RESULTS

Primary diseases were acute myeloid leukemia (n = 69, 41.1%), acute lymphocytic leukemia (n = 24, 14.3%), other type leukemia (n = 20, 11.9%), lymphoma (n = 24, 14.3%), myelodysplastic syndrome (n = 19, 11.3%), and others (n = 12, 7.2%). Median follow-up duration was 1534 days (95%, CI 605 days - n.r). Patients with non-CTRCD and CTRCD were 128 (76.2%) and 40

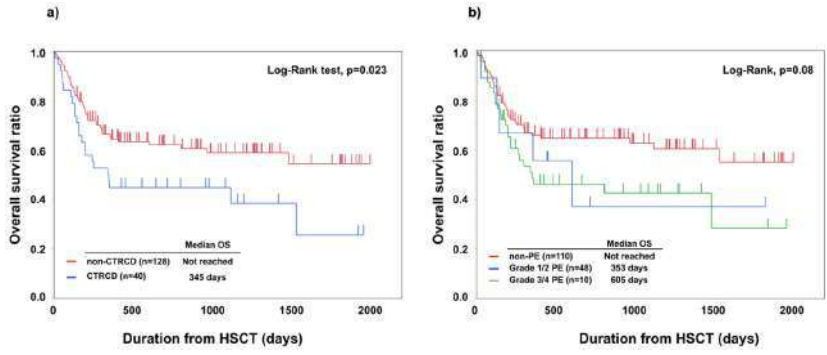

FIGURE 1

(23.8%), respectively. Non-PE, Grade 1 or 2 PE, and Grade 3 or 4 PE were 110 (65.5%), 48 (28.6%) and 10 (6.0%), respectively. The predictor of CTRCD was LV asynergy with EF $\geq$ 53%) before HSCT ($p = 0.015$) and high anthracycline cumulative dosage ($p < 0.01$). The predictor of PE was conditioning total body irradiation ($p = 0.037$).

Conditioning myeloablative regimen using cyclophosphamide and acute GVHD did not have significant association to the incidence of PE ($p = 0.13$ and 0.50, respectively). Median overall survival (OS) of patients with non-CTRCD and those with CTRCD were not reached and 345 days, respectively (Log-Rank test, $p = 0.023$) [Figure 1a]. Median OS of patients with non-PE were not reached. Median OS of patients with Grade 1 or 2 PE, and those with Grade 3 or 4 PE were 353 days and 605 days, respectively. [Figure 1b], Six cases with PE (60% of Gr3/4 PE) required pericardial drainage.

CONCLUSION

CTRCD after HSCT is associated with poor prognosis of hematopoietic disease patients. High dose anthracycline and local LV wall motion abnormality with preserved LVEF can be useful predictors of CTRCD after HSCT.

The cardio-oncology concerns of combining Tamoxifen and Ribociclib based on the TEEL trial

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BACKGROUND

The TEEL Study was an open labeled, non-randomized; phase I dose escalation followed by a planned phase Ib dose expansion trial of Tamoxifen (Tam) with Ribociclib (Ribo) in adult patients with advanced ER+ (HER2 negative) breast cancer. Ribo is an inhibitor of cyclin D1/CDK4 and CDK6 and has been successfully combined with Letrozole to improve PFS. This trial was done to examine the safety of the combination of Tam and Ribo in pre- and post-menopausal pts. The goal of the phase 1 expansion was to help confirm safety and develop a daily dosing schedule. Both Tam and Ribo were known to cause QTC prolongation and this was a major safety concern of the study.

METHOD

This was an open labeled, non-randomized, phase I escalation study with a phase Ib dose expansion. The phase I portion of the study was a ***dose escalation*** to determine the safety of the combination and to determine the MTD and the RP2D for Ribo with Tam. Breast cancer patients with HR+/HER2- locally advanced or metastatic breast cancer with any prior endocrine therapy and up to two lines of prior cytotoxic chemotherapy regimens administered in the metastatic or locally advanced setting. The planned Phase Ib dose expansion was not done but was planned to better characterize the toxicity profile and assess the anti-tumor activity Ribo + Tam and to further evaluate the safety of the combination. Triplicate EKG were done at baseline, at C1D1, C1D15, C1D22, and then every subsequent cycle at day 1.

RESULTS

A total of 12 patients were screened and 7 patients were enrolled (with 5 screen failures). Ribociclib was given at 400 mg po daily for 21 days on and 7 days off. Tamoxifen was given per standard at 20 mg daily. The best response was partial response. Each cycle was 4 weeks and 1 patient remained on this combination for at least 12 cycles with PR, after cycle 3 and SD thereafter. Two patients developed significant QTC prolongation. Pt. #3 was taken off study for QTC prolongation after cycle 8 with QTC >501. Prior to that, her treatment had been interrupted twice due to QTC prolongation. Her First EKG was manually calculated at: QT 370 ms, QTcb 427 ms, QTcf 407 ms. Her Longest EKG: QT 402 ms, QTcb 514 ms, QTcf 473 ms. Pt #12 was also taken off study during cycle 6 due to QTC>501. Her first EKG: QTc382 ms, QTcb 480 ms, QTcf 445 ms. "Longest ekg" QTc 432 ms, QTcb 496 ms, QTcf 473 ms. Both of these patients had prolonged QTC based on manual EKG. Dose limiting toxicity was noted in patient #10 who was noted to develop progression of disease (new leptomeningeal disease) after cycle 1 and subsequently had a CVA off study, thought to be associated with progressive disease. Table 1 describes highest QTC vs. cycle of therapy and there does not appear to be evidence of worsening prolongation with the number of cycles on study drugs. Other AEs were noted – please see Table 2 for AEs.

Table 1: Clinically relevant adverse events

CTCAE Term	Grade		
Adverse Events	2	3	Grand Total
Acute kidney injury		1	1
Alanine aminotransferase increased	2	2	4
Anemia	1		1
Aspartate aminotransferase increased	2		2
Cardiac disorders - Other, specify	1		1
Cholesterol high	1		1
Dehydration	1		1

(*Continued*)

Table 1: (*Continued*)

Diarrhea		1	1
Dizziness	1		1
Electrocardiogram QT corrected interval prolonged	2	1	3
Fall	1		1
Gastrointestinal disorders - Other, specify		1	1
Hypokalemia	1		1
Hypophosphatemia	1	2	3
Hypotension	1	1	2
Lymphedema	1		1
Mucositis oral	1		1
Myalgia	1		1
Neutrophil count decreased	4	1	5
Otitis media	1		1
Sinus bradycardia	1		1
Stroke		1	1
Syncope		4	4
Upper respiratory infection	2		2
Urinary tract infection	1		1
Vomiting	1		1
White blood cell decreased	4	3	7
Grand Total	32	18	50

Table 2: QTC by cycle on ribociclib

Subject	Cycle	Highest QTc
1	1	475
1	2	472
1	3	475
1	4	448
1	5	469
1	6	465
1	7	465
1	8	474
1	9	477
1	10	457
1	11	481
1	12	483
1	13	477
1	EOT	489
2	1	446
2	2	426
2	3	421
2	4	427
3	1	582
3	2	458
3	3	462
3	4	479
3	5	494
3	6	463
3	7	689
3	8	450
3	9	479
8	1	452
8	2	451
8	EOT	450
10	1	452

(*Continued*)

Table 2: (*Continued*)

10	EOT	436
11	1	460
11	2	451
11	3	435
11	4	454
11	EOT	459
12	1	495
12	2	495
12	3	476
12	4	508
12	5	513
12	6	509
12	7	527
12	EOT	450

CONCLUSIONS

The combination of Tam and Ribo was not considered to be safe and there were two DLTs in the phase 1 part of the study, leading to the early stopping. The phase I expansion was not completed. There were 5 events of prolonged QTC, one event was determined to be a DLT. The other DLT was a CVA described above (associated with CNS disease). Unfortunately, the combination was limited by the synergistic effects of QTC prolongation of both Tam and Ribo. The importance of manually calculating the EKGs and utilizing the Fridericia formula was noted in this study. The Fidercicia is more accurate in oncology patients as it demonstrates less overcorrection than the Bazzett formula at faster heart rates which a were re quite common in cancer patients. Rational limits must be implemented to ensure patient safety without unnecessary withholding of potentially lifesaving cancer therapies. The relative risk of arrhythmia is 1.2 for QT intervals >500 ms and is exceedingly low at QT intervals less than 500 ms.

Pulmonary stenosis caused by external compression of hodgkin lymphoma: An unusual clinical presentation

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BACKGROUND

Hodgkin lymphoma (HL) is a hematologic neoplasia derived from B lymphocytes and classical HL (cHL) accounting for approximately 95% of all HL. Ten-year survival rate for HL is estimated to be 80% and cardiovascular death is the prevalent cause for a non-malignant death among these HL survivors. We present a woman diagnosed with mediastinal HL and an unusual cardiovascular complication.

CASE

A 49-year-old woman, without comorbidities, contrast allergy, diagnosed with cHL CS IVB. In her first evaluation was identified ejection systolic murmur pancardic 3+/6+ more audible on the left sternal border with back and cervical irradiation associated with digital clubbing, suggested pulmonary stenosis. The PET CT 18 FDG showed lymph node enlargement at levels III to V on the right and III and V on the left, measuring up to 5.2 x 3.8 cm and 3.6 x 2.3 cm, respectively. Chest anterior mediastinal mass, measuring 12.6 x 11.0 cm, corresponding to 2/3 of the thoracic diameter, with invasion of the pulmonary parenchyma in the left upper lobe. Thoracic lymph node enlargement: upper and lower right paratracheal, left inferior paratracheal, pre-vascular, subcarinal and pericardial, measuring 3.5 x 2.0 cm. The echocardiogram

(echo) showed mass adjacent to the right ventricle, with direct contact with the great vessels, causing compression of the pulmonary artery that generates flow acceleration and a maximum systolic RV-TP gradient of 33 mmHg. She started chemotherapy.

DISCUSSION

Symptomatic pulmonary artery stenosis (PAS) in adults is rare and is mainly due to external compression by mediastinal tumors. A few cases of PAS secondary to HL has been reported in the literature. The symptoms are chest pain and dyspnea. It is uncommon for mediastinal masses to compress the pulmonary artery sufficiently to produce murmurs. Thoracic CT is the gold standard for the detection of mediastinal masses and evaluation of vascular invasion, but it cannot assess the hemodynamic severity of great vessel compression. Echo enables dynamic investigation of cardiac and paracardiac structures and it may visualize the severity of great vessel compression ranging from minimal changes in velocity to severe pressure gradient abnormalities.

Cisplatin-related atrial fibrillation in young people: Case report

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BACKGROUND

Chemotherapy treatment of testicular cancer has some standard regimens, which include cisplatin as one of the drugs. Cisplatin may lead to cardiovascular toxicity increasing the risk of thromboembolic events and arrhythmias. Atrial fibrillation is among the most prevalent arrhythmias in cancer patients and may represent a poor prognosis. The mechanisms possibly related to the occurrence of atrial fibrillation in cancer patients are electrophysiological remodeling, oxidative stress, cellular apoptosis, inflammation and regulation of the immune system. The incidence of cisplatin-associated atrial fibrillation can reach 15.5%. We describe the case of a young patient undergoing treatment for testicular cancer with cisplatin.

CASE

An 18-year-old male with no previous comorbidities was diagnosed with testicular cancer and started chemotherapy with the BEP regimen (bleomycin, etoposide and cisplatin). During infusion of the second cycle of chemotherapy, the patient had an episode of atrial fibrillation with high heart rate detected on the vital signs evaluation, later confirmed by 12-lead electrocardiogram. The patient had no symptoms. Intravenous amiodarone was infused at an attack dose followed by a maintenance dose with reversal of arrhythmia to sinus rhythm. The electrolyte dosage was normal. Transthoracic echocardiography was normal, with all normal-sized cardiac chambers. The patient was exposed to a new cycle of chemotherapy using oral amiodarone. Anticoagulation with direct oral anticoagulant was started. After the end of the chemotherapy treatment, the echocardiogram and 24-hour Holter

finding no abnormality and, for this reason we decided to discontinue the pharmacological treatment for atrial fibrillation.

DISCUSSION

We describe a case of a young patient with no heart disease who developed two episodes of cisplatin-related atrial fibrillation. All other etiologies were excluded. This case shows the importance of cardiac monitoring during cisplatin infusion, since it can happen even in patients without cardiovascular risk factors and without symptoms. Atrial fibrillation, although uncommon in young people, can complicate or delay cancer treatment.

Androgen Deprivation Therapy (ADT) and its association with Cardiovascular (CV) disease mortality in men with early-stage Prostate Cancer (PC) receiving curative Radiation Therapy (RT)

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BACKGROUND

ADT in combination with RT is effective treatment for men with localized PC, but may impact non-oncologic mortality including mortality related to CV causes. We explored the associations between ADT and CV death among men receiving RT for localized PC in the National Program for Cancer Registry's (NPCR) Breast and Prostate Cancer Patterns of Care (POC) study.

METHODS

From NPCR POC's databases of cases diagnosed in 2004 from 7 population-based cancer registries, we selected men with localized PC treated with definitive RT followed through 2009. Comorbidity was quantified using the Adult Comorbidity Evaluation 27 and included CV disease (e.g. myocardial infarction and stroke), and CV-risk factors (e.g. hypertension). National Death Index data and linkage with vital statistics data were used to determine cause and date of death. Rates of CV death were compared between RT versus RT+ADT in univariate and multivariable analyses.

RESULTS

Among 2,413 men with mean age 68 years (range 39-94) and 55% white non-Hispanic, 997 (41%) received RT alone and 1,416 (59%) received RT+ADT. CV death occurred in 2.3% of RT patients and 3.4% of RT+ADT patients at 8 years post-diagnosis. In univariate analysis, receipt of ADT was associated with higher CV death in those with: age <60, white, insured by Medicare, living in mixed urban-rural area, higher education level, high socioeconomic status, no or mild comorbidity level, low PSA (<4 ng/ml), and Gleason score 7. In multivariable analysis, use of ADT did not significantly predict hazard of death from CV disease (HR 1.21, p=0.28) or PC (HR 0.76, p=0.34) among those receiving RT; however, those with pre-existing CV disease had higher rates of CV death (HR 2.51, p <0.01) and patients with mild (HR = 1.6, p = 0.02) and high (2.39, p = 0.03) levels of comorbidity were more likely to suffer CV death.

CONCLUSIONS

In a geographically diverse population of men with localized PC who received RT as definitive therapy, receipt of ADT was not associated with increased risk of CVD mortality or PC mortality after controlling for confounding variables. Pre-existing CV disease was associated with higher risk of CV death.

Risk factors and outcome of patients with cancer associated Venous Thromboembolism

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BACKGROUND AND AIM

Venous Thromboembolism (VTE) is second leading cause of death in cancer patients. In the Indian population VTE is under-reported in patients with malignancy. We studied the clinical profile and outcome of patients with cancer associated VTE registered in Cancer thrombosis clinic, Tata Memorial hospital, a tertiary cancer institute.

METHODS

This is a retrospective analysis of prospectively collected data of patients with VTE for period of one year (2017-2018) who were referred to Cancer thrombosis clinic. The demographic data, details of cancer, co-morbidities, details of VTE, and treatment given for VTE and their outcomes were recorded and analyzed.

RESULTS

307 cancer patients were diagnosed to have VTE. The median age was 52 years. Females were predominant 53.1%. In females gynecologic malignancies (41.7%) and in males Thoracic malignancy (34%) were the commonest sites. 212/307 (69.05%) had advanced stage cancer. VTE was detected incidentally in 25.4% patients. Most patients had proximal lower limb DVT (60.8%). The associated risk factors included recent chemotherapy 182/307 (59.67%), recent surgery 34/307 (11.14% range) and catheter related thrombosis 20/307. The median duration of follow up was 6 months. 148 (51.74%) patients received long term anticoagulation 78.32% received Low molecular weight heparin and 1.7% Non-Vitamin K oral anticoagulants (NOAC). 2 patient had massive PE, one underwent pulmonary thrombectomy and other systemic

thrombolysis. 6 patients under went IVC filter insertion. 39 patients required indoor admission. 19 patients had bleeding on anticoagulation out of which 11 patients had major bleeding requiring intervention. 26 (9%) had Recurrent DVT on anticoagulation. Median survival was 7 months (Range 2 to 11 months). No fatal PE was observed.

CONCLUSION

Most patients with cancer associated VTE had advanced stage of cancer and VTE was incidental. Significant proportion of patients had developed VTE while on chemotherapy in which high proportion was found in platinum based chemotherapy. Long term anticoagulation with LMWH is well tolerated. NOACS are being used in selected patients. Further research on risk stratification for VTE and primary prophylaxis in the ambulatory cancer patient on chemotherapy is required. Rate of recurrent VTE despite treatment is high.

Outcome of chemotherapy related Grade 4 cardiac dysfunction—experience of a single center cardio oncology clinic

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INTRODUCTION

Life expectancy after the diagnosis and treatment of cancer has increased significantly in the past 2 decades however cancer therapy induced cardiotoxicity is responsible for considerable morbidity and mortality.

OBJECTIVE

To study the clinical profile of patients diagnosed with chemotherapy induced Grade 4 cardiac dysfunction (CRCD) and factors affecting their response to heart failure (HF) therapy.

METHODS

This is a retrospective analysis of prospectively collected data of patients with chemotherapy related cardiac dysfunction (CRCD) Grade 4, registered in the cardio oncology clinic at a tertiary cancer center in period 2015-2018. CRCD GRADE 4 was diagnosed by 2 DECHO as left ventricular ejection fraction (LVEF) <20% in patients who have received cardio toxic chemotherapy as per NCI CTCAE (v-4) criteria. The patients were considered as responders when LVEF increased at least 10 absolute points and non-responders when LVEF increased fewer than 10 absolute points or deteriorated after starting anti failure treatment. The Kaplan-Meier method was used to determine cause specific survival. Univariate analysis was performed by comparing groups with log-rank test.

RESULTS

38 patients were diagnosed with Grade 4 CRCD. 57.9% were breast cancer patients, 15.7% Bone and Soft Tissue and 13.2% NHL. 98% patients received anthracyclines. The median dose of doxorubicin was 400 mg/m^2. The median time to development of grade 4 CRCD was 14 months after last dose of anthracycline. Median clinical follow up duration was 19 months. 23 (60.5%) were responders of which 10 (26.31%) patients LV function recovered completely. The two-year survival was 78.00% in non-responders and 100.00% in responders. (95% CI; 45.52% to 92.46%). There was a significant difference between responder and non-responders (p-value= 0.032) in survival curves. The median survival was not reached. Descriptive statistics were used to display clinical data. Higher number of non-responders received >200 mg/m^2 doxorubicin dose.

CONCLUSIONS

There was a higher frequency of non-response in patients who received doxorubicin more than 200 mg/m^2. LV function recovered completely in 26.31% of responders. Systematic monitoring of LV function in patients receiving cardio toxic chemotherapy will lead to prevention, early detection and treatment of CRCD.

The utility of cardiac MRI (CMR) in a tertiary cardio-oncology centre

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BACKGROUND

The demand for more sensitive and reproducible imaging markers for diagnosis and monitoring of cardiotoxicity is rising, alongside an expanding spectrum of cardiovascular presentations. CMR offers gold standard assessment cardiac function as well as tissue characterization and perfusion, and therefore can help guide clinical management in the cardio-oncology setting. We assessed the clinical value of CMR in a tertiary cardio-oncology centre.

METHODS

We retrospectively reviewed CMR scan requests in cardio-oncology patients at Barts Heart Centre between June 2017 to December 2018 and evaluated the impact of the results on management using previously published criteria-[1]however metal artifact can degrade images. We evaluated the clinical impact of LGE CMR incorporating a device-dependent metal artifact reduction strategy in patients with CIEDs. Methods: 136 CMR studies were performed in 133 consecutive patients (age 56±19 years, 69% male.

RESULTS

199 CMR scans were requested in 172 patients (mean age 57, range 18-91, 50% females). 60% of patients had solid malignancies and 40% haematological. 22% of requests were for cardiotoxicity screening whilst on therapy

(14% HER2 monoclonal antibodies, 4% anthracyclines, 4% fluoropyrimidines), 18% risk stratification prior to chemotherapy, 16% cardiac malignancies/infiltration, 32% for late effects post treatment and 14% for investigation of cardiac complications during therapy. The most common indications for CMR were monitoring of LVEF where echocardiography was non-diagnostic/discordant between studies (34%), ischaemia assessment (27%), LV dysfunction etiology (17%) and tissue characterization (23%) for amyloid (23 patients), cardiac masses (8), cardiac metastases (1), myocarditis (7) and iron loading (3). CMR findings led to a management change in 132 (66%) cases and a new diagnosis in 66 (33%). Of those receiving anthracycline/HER2 therapy, 72% had a management change attributed to the CMR but 81% were able to continue with anthracycline/HER2 therapy due to CMR showing stable LV function (echocardiography showed reduced LV function in 80%). In 19% of cases, chemotherapy was withheld based on CMR findings of reduced LV function. In 3 patients avoidance of fluoropyrimidines was recommended after perfusion CMR and in 4 allowed to continue.

CONCLUSION

CMR can be used to risk stratify and monitor for cardiotoxicity during and after cancer care and is helpful to guide management in up to two thirds of cases.

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Driving knowledge of cardiotoxicity from CAR T cell therapies in the right direction

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INTRODUCTION

CD19-specific chimeric antigen receptor (CAR) T cell therapies have unveiled unprecedented promise in the treatment of refractory or relapsing haematological malignancies in paediatric and adult populations, including acute lymphoblastic leukaemia (ALL) and large B cell lymphoma. Whilst cytokine release syndrome (CRS) and neurotoxicity are the most widely appreciated adverse effects of this potent therapy, the true extent and characteristics of cardiovascular involvement remain poorly defined.

DISCUSSION

Observed cardiovascular problems include sinus tachycardia and other arrhythmias, as well as well left ventricular systolic dysfunction (LVSD), profound hypotension, and shock requiring intensive therapy unit (ITU) admission and inotropic support. Two retrospective studies by the team at The Children's Hospital of Philadelphia have assessed the cardiovascular adverse effects of CAR T cell therapies, specifically in paediatric populations. In their 2017 analysis of 39 patients, Fitzgerald et al demonstrated cardiotoxicity in 36% (14 patients) as defined by either fluid-refractory vasoplegic shock treated with inotropic agents or LVSD. A further analysis of 93 patients in 2018 by Burstein et al supported earlier evidence, with 24% (24 patients) meeting the primary endpoint of hypotension requiring inotropic support. Of these patients, 41% (10 patients) had LVSD, and 18% (six patients) had ST-segment abnormalities on ECG. LVSD persisted at discharge in 7% (7 patients), and just 1% (one patient) at six months. Both studies demonstrated dramatic clinical improvement with the use of tocilizumab.

CONCLUSION

The ability to harness the life-saving potential of CAR T cell therapies is dependent on counteracting on-target, off-tumour toxicities. Our review highlights the need for prospective studies to define the cardiac safety of CAR T cell therapies in the acute and longer term. Surveillance must encompass the breadth of biomarkers and advanced cardiac imaging parameters including global longitudinal strain and diastolic assessment on echocardiography, as well as magnetic resonance imaging, that have informed other areas of cardio-oncology.

Treating the treatment-chemotherapy induced multi-organ toxicity

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BACKGROUND

Adjuvant chemotherapy consisting of capecitabine and oxalipatin in colorectal cancer decreases the incidence of disease recurrence. Whilst improving disease-free survival in patients, this chemotherapy regime has rare but significant complications. In this article we report on a previously fit and healthy patient who developed both common and uncommon side effects from this chemotherapy regime.

CASE

A 40-year-old gentleman presented to his local hospital with a two-day history of dyspnoea having been started on adjuvant chemotherapy five days prior (250 mg of Oxaliplatin as an infusion and a cumulative oral dose of 20 g of Capecitabine) for colorectal cancer.

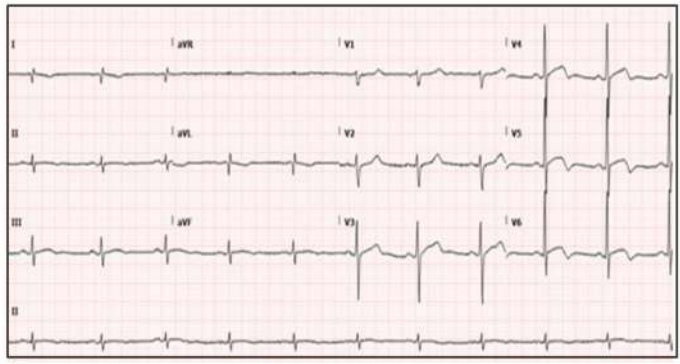

FIGURE 1

His electrocardiogram (ECG) on presentation is depicted in Figure 1. He developed central chest tightness within several hours of arriving in hospital and a repeat ECG is depicted in Figure 2. His troponin was elevated.

An echocardiogram was performed and showed an LVEF of 26%. His global longitudinal strain (GLS) was –7.7% (Figure 3a).

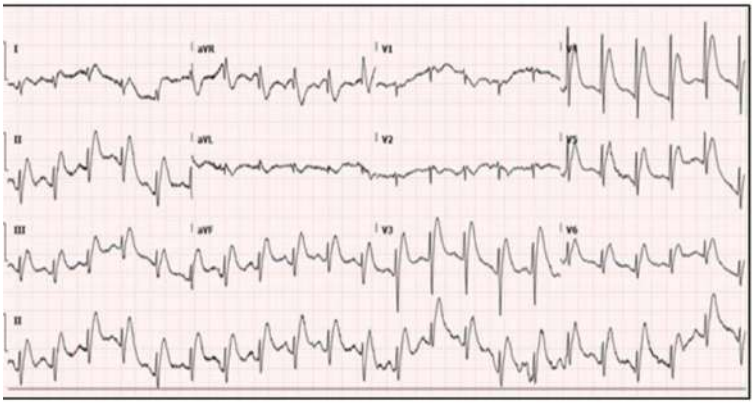

FIGURE 2

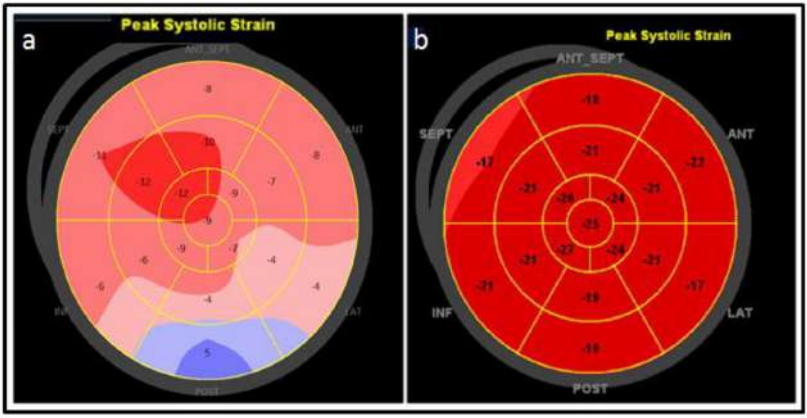

FIGURE 3

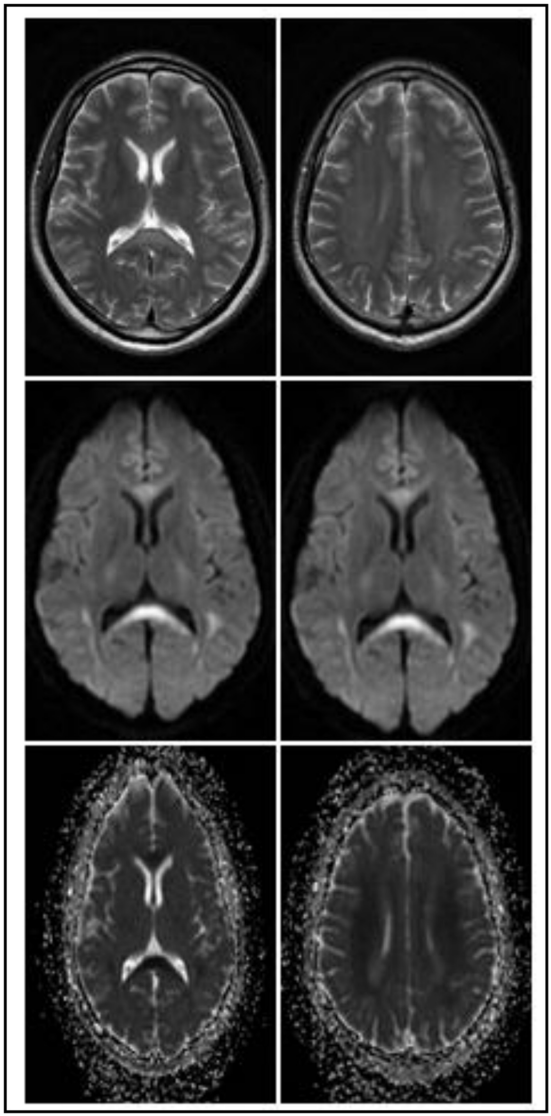

FIGURE 4

He also developed intermittent dysarthria and dysphasia, with a sensation of feeling disoriented. A magnetic resonance image (MRI) scan of his head showed diffused subcortical and callosal white matter signal change and restricted diffusion consistent with a toxic leukoencephalopathy (Figure 4).

A CT pulmonary angiogram (CTPA) was performed as he remained hypotensive which showed bilateral pulmonary emboli.

Over the next few days, he improved haemodynamically and small doses of bisoprolol and ramipril were introduced. He went on to have a cardiac MRI which showed mild LV systolic impairment (LVEF 53%). There was no abnormal late gadolinium enhancement and T1 and T2 values were in the normal range. No stress perfusion defects were seen.

On discharge, TTE demonstrated an LVEF of 56% and a GLS of -21.4% (Figure 3b). Follow up was arranged in the thrombosis, neurology and cardio-oncology clinics.

DISCUSSION

The key to the successful use of chemotherapy agents is dependent on the clinician's awareness of the potential toxicity profile, and the prompt recognition and management of side effects. This requires close co-operation between medical working together in a multidisciplinary Cardio-Oncology setting.

Heart failure with preserved ejection fraction and pulmonary hypertension secondary to a left atrium myxoma: A case report

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BACKGROUND

Primary heart tumors are rare. 80% are benign with myxomas being the most common. They are more incident from 40 to 60 years of age, preferring female sex (3:1) and the left atrium.

CASE

M. L. R., 59 years old, female, appeared for a pre-op evaluation for uterine myoma surgery. She had been undergoing treatment for Type 2 diabetes, dyslipidemia, heart arrhythmia and hypertension. In anamnesis she revealed progressive dyspnea for the previous 3 years during exercise and everyday activities. She also described symptoms like palpitations, orthopnea and episodes of paroxysmal nocturnal dyspnea.

The cardiology team quested a 2-D echocardiograph, which showed a mass inside the left atrium blocking the entrance of the left ventricle, with 6 cm in its greater diameter suggestive of left atrium myxoma. The exam revealed a pulmonary artery pressure of 74mmHg and ejection fraction of 71%. She was now diagnosed with heart failure with preserved ejection fraction (NYHA III) and pulmonary hypertension secondary to the tumor. Then the tumor was evaluated with a chest CT scan and surgery was planned.

The procedure occurred without complications. She evolved well and left ICU four days later. A chest X-ray showed an elevation of left hemidiaphragm. She was discharged clinically stable and with referrals to follow up.

DISCUSSION

The pathological mechanism of cardiac tumors is more related to their location than their histology. Left atrial myxomas frequently present with heart failure, as with our patient. This is caused by the mass blocking the circulation through the heart or heart valves, simulating a mitral stenosis. Another complication is elevation of pressure inside the left atrium during diastole leading to secondary pulmonary hypertension.

Prognosis for the patient following surgery depends on how much damage the myxoma caused during its growth. If heart failure was established before the procedure, the patient will continue with this because of cardiac remodeling. She is now in follow-up because myxomas have a high recurrence rate. The elevation of left hemidiaphragm is probably secondary to phrenic nerve injury during the surgery. She has reported no complaints and for now requires no intervention.

Ventricular dysfunction in a patient with hypereosinophilic syndrome

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BACKGROUND

Hypereosinophilic Syndrome is a myeloproliferative disease defined by an absolute count greater than 1500 eosinophils/micromol in the peripheral blood for at least 6 months associated with tissue infiltration, resulting in organ damage. It most commonly affects men aged between 20 and 50 years and has an estimated prevalence of 0.36-6.3/100.000 patients. The etiology may be primary (clonal eosinophil expansion) or secondary (parasitoses, collagen diseases, medications). The most affected organs are: skin (37%), lung (25%), gastrointestinal tract (14%), and the heart is affected only 5% of the time. The main cardiovascular manifestations are ventricular dysfunction, restrictive cardiomyopathy, valve and tendon chordae alterations, and endomyocardial fibrosis. The treatment aims to reduce eosinophilia to control symptoms.

CASE

MALS, male, 60 years old, ex-smoker. Began in 2012 dyspnea on the moderate efforts associated with wheezing and orthopnea. Treatment for Asthma was started, but without improvement. There was progressive worsening of dyspnea for minimal effort. Transthoracic echocardiogram showed ejection fraction (LVEF) of 29% and diffuse hypokinesia with severe diastolic dysfunction. Coronary angiography did not show coronary lesions. Persistently

elevated eosinophilia has been identified. In 2017, performed a bone marrow biopsy that identified T-cell lymphoproliferative disease. Pulmonary biopsy with eosinophilic infiltrate and cardiac magnetic resonance showed biventricular diastolic dysfunction, reduced LVEF, without a scar (Figure 1). Endomyocardial biopsy without eosinophilic infiltrate. Chemotherapy was initiated with fludarabine and drugs for heart failure, with reduction of peripheral blood eosinophilia and stabilization of pulmonary and cardiac symptoms.

DISCUSSION

Despite the rare cardiac involvement due to hypereosinophilic syndrome, in the case above, the patient had symptomatic ventricular dysfunction concomitant with eosinophilia. After exclusion of other causes of heart failure, the diagnosis was made for the initiation of specific chemotherapeutic treatment, and an important clinical improvement was obtained.

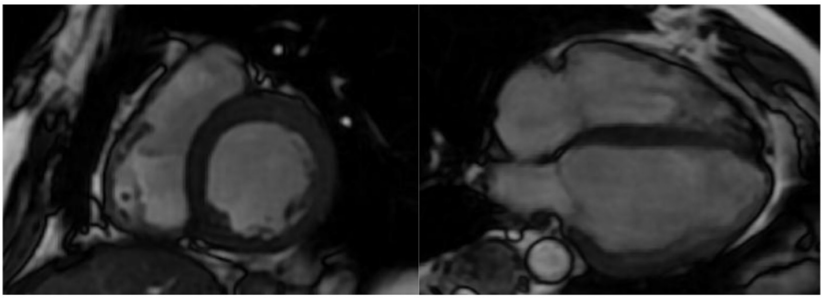

FIGURE 1: Cine-cardiac magnteic resonance imaging showing biventricular dysfunction.

The cardio-oncology MDT: A constructive collaboration between two medical specialties

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BACKGROUND

Cardiovascular disease (CVD) and cancer are the leading causes of morbidity and mortality (M+M) in the developed world. With increasing life-expectancy and better cancer treatment, CVD is a principal determinant of M+M in cancer patients.

Cardio-oncology (C-O) services provide cardiac care for cancer patients and survivors. Multi-disciplinary team meetings (MDTMs) are an invaluable way to facilitate discussions between cardiologists, oncologists and allied health professionals. Cardiologists are educated about cancer care, and oncologists can better understand the rationale behind the management of cardiac issues.

Here we evaluate the role of the C-O MDTM in optimising the management of cardio-oncology patients.

METHODS

We analysed the healthcare records of all consecutive patients discussed at a dedicated C-O MDTM in a tertiary centre in London between October 2018 to July 2019. Clinical data, reason for discussion and the MDT outcome were recorded.

MDT members were cardiologists, oncologists, trainees, cardiac physiologists and specialist nurses. Where necessary, members from other specialities were included to aid decision making.

RESULTS

85 patients were discussed over a period of 10 months (median age 66 y; 42% female). The most common malignancies were haematologic (49%), followed by breast (14%) and lung (7%) cancers. The most common reasons for discussion were left ventricular dysfunction (39%), multiple cardiac comorbidities (17%) and ischaemic heart disease (8%). 64% of patients had known CVD prior to their cancer diagnosis.

69% of patients were able to continue/complete their cancer treatment, facilitated by meticulous cardiac monitoring in C-O clinics. 11% of patients were awaiting further diagnostic evaluation. The MDT did not support the continuation of cancer treatment in 20% of patients due to extensive comorbidities and poor prognosis. 8 patients (9%) had died at follow up (only 1 was actively being treated for cancer and died of neutropaenic sepsis).

CONCLUSION

The C-O MDTM is integral to the management of complex cardio-oncology patients, providing a consensus view to allow the appropriate management of these patients to optimise cancer outcomes and minimise cardiac M+M.

Metastatic leiomyosarcoma for myocardium

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BACKGROUND

Primary cardiac neoplasia is rare, but cardiac metastasis (CM) is relatively more common and can occur in up to 8% of cases. In females, the main primary sites are: melanoma, pulmonary and renal neoplasia. Other solid tumors, commonly associated with CM, include: breast cancer, soft tissue sarcomas, esophageal cancer, hepatocellular carcinoma and thyroid cancer.

CASE

T.N.S, 23 years old, female, diagnosed with low-grade leiomyosarcoma in the shoulder in 2011 and has done the resection in the same year. Frist line of Chemoterapy (CT) adjuvance: Doxirrubicin 300 mg/m^2. Progression of disease was detected by pulmonary and lymphnode metastasis, so Gencitabine associated to Docetaxel was started as a second line CT. She was not responsive to the second line. Therefore third CT was perfomed with Pazopanibe. Nevertheless it had to be discontinued in October / 2017 due to pregnancy. She has not completed prenatal care afraid of aborting your child. Cesarean section was performed at term. On the second postoperative day, the patient developed cardiac tamponade and was subjected to pericardiocentesis that drained 200 ml of citrus liquid. Echocardiogram showed large heterogeneous mass adhered to the right ventricle with expansion to the right atrium, vascularized at doppler, with an interventricular gradient of 28mmHg, measuring 54x25 mm. Tomography showed an intracardiac mass intrinsically adhered to the myocardium, with no surgical cleavage point. Since then, the patient has experienced rapid deterioration and died within a few days.

DISCUSSION

We can observe that even a indolent tumor may progress aggressively under CT suspension condition overlapping immunosuppression, in this case pregnancy. Abandonment of treatment, ignoring a medical advice about contraindication to pregnancy endangered the woman's life, culminating in a tragic outcome, a despite early treatment attempt.

Transcatheter aortic valve replacement in a patient with renal cell carcinoma: A case report

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BACKGROUND

The average cancer patient survival has increased over de last decades due to improvement in cancer treatment. As a result, these patients are older and dealing with others health problems, especially cardiovascular disease. In this context, severe aortic stenosis (AS) often represents a cause of concern, because its incidence rises with age and it's becoming more common to diagnose AS in cancer patients.

CASE

A 72- year-old man was referred to cardio-oncology service due to dyspnea (New York Heart Association class III) and chest pain. His past medical history revealed metastatic renal cell carcinoma (RCC) to bone, subcutaneous tissue and lymph nodes. He was diagnosed with RCC in 2008 and underwent a right radical nephrectomy. After 4 years of post-operative surveillance metastatic lesions were treated as they were identified. Echocardiography showed severe AS (aortic valve area 0,7cm^2 and mean aortic pressure gradient 65mmHg). The heart team decided to perform TAVR and the procedure was successfuly done in june 26th, 2019. A 26-mm Inovare valve was implanted under fluoroscopic guidance, using transapical approach, without major complications.

DISCUSSION

Surgical Aortic Valve Replacement (SAVR) remains the gold standard therapy for symptomatic severe AS. However, Transcatheter Aortic Valve Replacement (TAVR) has been showing excellent results and reducing complication rates. Therefore, TAVR has become an effective and non-inferior treatment option in comparison to SAVR with the advantage of being less invasive, allowing a shorter hospital length of stay. The perioperative risk assessment is a cornerstone of a well-planned treatment. In the beginning, TAVR was indicated only for high-risk surgical patients. Nowadays, the advances in technology allowed the development of new evidences, expanding TAVR indications for a wider range of patients, regardless of their surgical risk. Another interesting point is that the currently used risk scores do not take into account the cancer diagnosis and were not designed for it, hence they are underpowered to predict events in this particular group of patients.

Seizure as first manifestation of endocarditis in a patient with metastatic pancreatic adenocarcinoma: A case report

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BACKGROUND

Nonbacterial thrombotic endocarditis (NBTE) associated with malignancy it's a rare condition. Cancer patients used to be immunocompromised and often need a central venous catheter for chemotherapy which rise their chances to acquire endocarditis. In addition, these patients can present atypical manifestations what makes diagnoses difficult.

CASE

A 46-year-old man diagnosed with metastatic pancreatic adenocarcinoma presented to the emergency department with first episode of seizure just before chemotherapy. His past medical history revealed deep vein thrombosis in his right leg 3 months prior for which he was treated with rivaroxaban. After initial medical support, a brain magnetic resonance image was performed revealing several ischaemic lesions probably due to cardiac embolism. A transesophageal echocardiogram (TEE) was requested and showed slightly mobile two echogenic foci in native mitral valve associated with moderate regurgitation.

Blood cultures were carried out and antibiotic treatment was initiated for suspected bacterial endocarditis. Despite the lesions in CNS, his neurological exam did not show serious damage. Moreover, the blood cultures were negative with no growth. Regarding to diagnose of endocarditis, the patient did not fulfill the Duke's criteria, due to the lack of others clinical signs, symptoms or laboratorial findings. Although the histological exam has not been performed, the hypothesis of NBTE was reinforced and the patient was kept under anticoagulation with low molecular weight heparin.

DISCUSSION

The absence of bloodstream bacterial infection is the cornerstone of NBTE. This condition generally is associated with hypercoagulable states like in malignancies scenario. NBTE affects mostly left sided heart valves, mainly mitral valve. In terms of diagnose, TEE is the preferred imaging modality to detect the vegetations. Concerning to the treatment, anticoagulation therapy is the most important intervention and surgical valve replacement should be considered, if appropriate.

Cardiac metastasis of fibrolamellar hepatocellular carcinoma: Report of a rare case with unique images on 3D echocardiography and contrast echocardiograhy

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BACKGROUND

Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare malignancy, and comprises less than 1% of all primary liver tumors[1]. It is more prevalent in adolescents and young adults without underlying liver diseases and most cases presents at advanced stage. Initial stage of disease is one of the most important determining factors associated with prognosis. Lymph node involvement, distant metastasis, vascular invasion, and inoperable FLHCC are markers of less favorable response to chemotherapy, and these patients have a very poor prognosis. The most common extra-hepatic metastatic sites are the lung in 55%, lymph nodes in 41%, and bone in 28% of patients, while cardiac metastasis are very rare[2]. Intra-atrial tumor growth in autopsied cases of FLHCC ranged from 1 to 4.8%[3], and carries a dismal prognosis with a median survival ranging from 1 to 4 months in some case series[4-6].

CASE

A 21-year-old female, previously healthy, referring history of back pain in the last nine months, treated initially only with analgesics, evolved in the last 5 months with hyporexia, increased abdominal volume and weight loss (10 kg). Sought specialized care in the past week and started imaging investigation, performing a computed tomography angiography (angio-CT) that showed

hypervascular hepatic lesions, hepatic hilum lymph node enlargement, peritoneal carcinomatosis, multiple pulmonary metastatic implants, paratracheal lymph node enlargement and metastatic lesions in pancreas and left adrenal. CT showed lytic lesions on spine, aspect of metastatic bone lesions and also contrast filling defects on IVC, pointing to the possibility of associated intracavitary thrombosis or mass. Sorologies for viral hepatitis were all negative. The patient was anemic (Ht: 27%), and had augmented levels of CA-125, CA 19-9 and CA 15-3. AST, ALT and bilirrubines were all normal. The patient underwent three-dimensional transesophageal echocardiogram (3DTEE), that showed a large lobulated and echogenic mass firmly attached to the right atrial (RA) wall, with part of the mass extending from the IVC, causing obstruction to the inflow. There was no clear separation between the mass and the RA wall, indicating possible direct invasion. Intravenous infusion of microbubble contrast agent (Sonovue) was performed during the TEE, revealing a unique 3D visualization of the vascularization framework

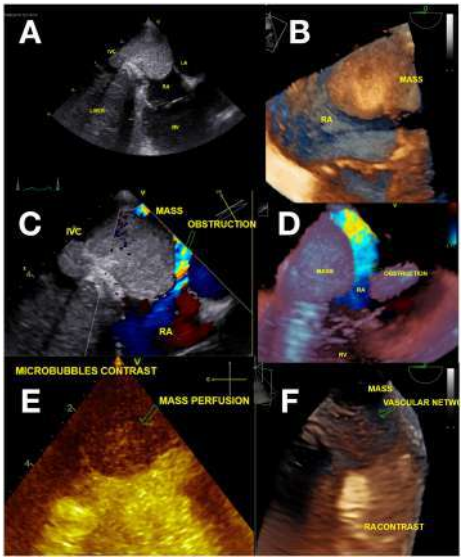

FIGURE 1: Echocardiographic investigation of the right atrial (RA) mass. (**A**) Transesophageal echocardiography (TEE) showing a large RA mass extending from the inferior vena cava (IVC), attached to the RA wall. (**B**) 3D TEE rendered images showing the large and echogenic mass attached to the roof of the RA. (**C**) Color 2D TEE showing the mass causingobstruction to the flow coming from the IVC. (**D**) Color 3D TEE rendered images showing obstruction to the flow coming from the IVC. (**E**) Microbubbles contrast enhanced TEE, showing contrast uptake inside the mass (perfusion). (**F**) Contrast enhanced 3DTEE showing the vascularization framework inside the malignant lesion.

inside the lesion (Figure 1). The patient underwent percutaneous liver biopsy, and histopathology showed a typical pattern of FLHCC. After four cycles of Gencitabine in combination with Oxaliplatine, and a short course of Sorafenib, chemotherapy rendered no significant response, and the progression of disease continued accelerated, with marked clinical deterioration. The patient was kept in palliative care.

DISCUSSION

We report a case of FLHCC who presented at a very advanced stage, with extensive extrahepatic and cardiac metastasis. Using 3D echocardiography and contrast enhanced echocardiography we could depict in details a large echogenic mass extending from the IVC to the RA, very adherent to the RA wall, with an invasive aspect. The 3D echocardiographic features had additional value for the correct evaluation of this case, ruling out thrombus and showing a vascularized mass, depicted by an unique view by contrasted 3DTEE, pointing out to a metastatic implant.

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Angiotensin receptor-neprilysin inhibitor used in a patient with late anthracyclic cardiotoxicity

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INTRODUCTION

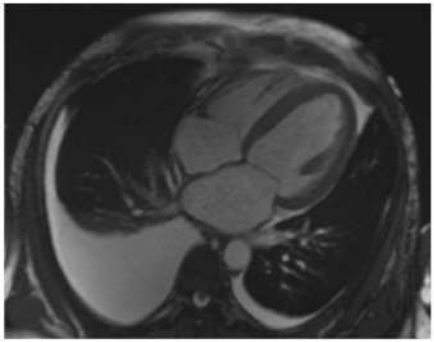
Sacubitril-valsartan is an angiotensin receptor-neprilysin inhibitor with label indication for symptomatic heart failure with reduced ejection fraction and effective in reducing the risk of death from cardiovascular causes and hospitalization. In this case report, angiotensin receptor–neprilysin inhibitor was used in the HF and may be related with chemotherapy cardiotoxicity.

CASE REPORT

Male, 38 years old, hypertension, diabetes, chronic dialytic kidney disease and Hodgkin's Lymphoma treatment with anthraciclic in 1986. Arrives at the emergency with dyspnea with limitation for physical activity. Transthoracic Doppler Echocardiography revealed dilated cardiac chambers and left ventricular ejection fraction (LVEF) of 31%. Cardiovascular Magnetic Resonance showed biventricular dysfunction RVEF 44%, LVEF 39%, without areas of fibrosis or myocarditis (Figure 1). Coronary computed tomography angiography without obstructive lesions. A diagnosis of late anthracyclic cardiotoxicity was then made. Heart failure (HF) treatment started with carvedilol, aldactone, hydralazine, monocordil and ivabradine. After 7 days, the patient still presents HF symptoms, choosing to initiate sacubitril-valsartan. Patient tolerated the medication well and evolved with significant clinical improvement. Echocardiography showed improvement in systolic and diastolic diameters in addition to LVEF 68%.

DISCUSSION

Diagnosis of cardiotoxicity is difficult to establish as there is no specific pattern of heart disease at the present time. A temporal relationship between treatment and cardiac dysfunction should be established and other potential causes must be excluded. The anthracyclic cardiotoxicity diagnosis was made and the treatment was started. The good clinical response to sacubitril-valsartan, as observed, lead us to the hypothesis that this drug could bring great benefit to cancer patients associated with heart failure, but further studies should be performed for such confirmation.



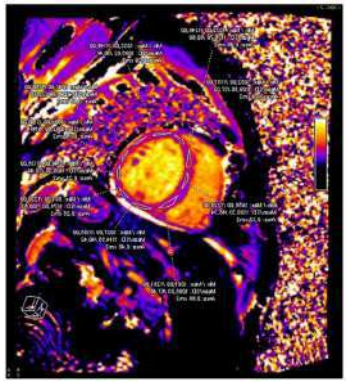


FIGURE 1: (**A**) Four-chamber SSFP image shows significant increase of left chambers, bilateral pleural effusions. (**B**) T1-mapping – values were higher (1001~1056 ms) = interstitial fibrosis.

Ejection fraction dysfunction during abiraterone treatment

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INTRODUCTION

Prostate cancer continues to be a significant burden on men's health. Suppression of gonadal testosterone synthesis represents the standard first line therapy for treatment of locally advanced and metastatic prostate cancer. Recently, new testosterone synthesis inhibitors such as abiraterone have shown to increase survival in patients with castration resistant disease. This treatment is characterized by a broad spectrum of toxicities. Cardiotoxicity related to this testosterone synthesis inhibitors can manifest in several ways, including hypertension in up to 22% of cases, arrhythmias and left ventricular dysfunction.

CASE REPORT

Male, 68 years old, former smoker, with hypertension, diabetes and metastatic prostate adenocarcinoma in use of Gosserelin and Abiraterone. The patient entered the emergency room complaining of progressive dyspnea on the last 2 weeks. Physical examination revealed crackling crackles and tachycardia. Troponin I and CKMB were positive and NT pro-BNP 11202 pg/mL. Electrocardiogram showed sinus rhythm, anterior T-wave inversion and corrected QT (*Bazett's formula*) 519 msec. Transthoracic Doppler Echocardiography with ejection fraction (LVEF) of 21% and diffuse hypokinesia. Cardiac catheterization diagnosis without obstructive lesions.

Cardiac Magnetic Resonance showed non-ischemic mesocardiac fibrosis in the mid-basal portion of the left ventricular anteroseptal and septal walls of the left ventricle anterior wall with 25% LVEF (Figures 1 and 2).

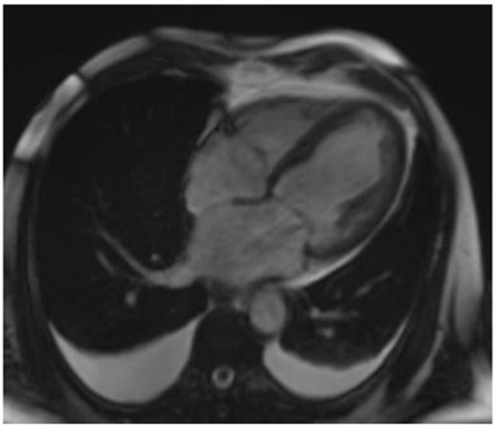

FIGURE 1: Four-chamber SSFP image shows significant increase of left chambers, bilateral pleural effusions and pericardial effusion.

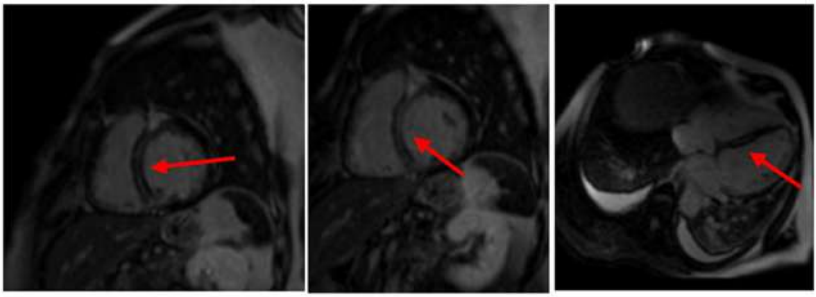

FIGURE 2: (**A-B**) Short-axis delayed enhancement and (**C**) Four-chamber delayed enhancement (DE): the arrow points extensive midmyocardial DE along interventricular septum (fibrosis) – nonischemic myocardial disease.

DISCUSSION

In the case report, we demonstrated abiraterone cardiotoxicity. Current safety studies show few adverse effects on the cardiovascular system, but most clinical trials generally exclude patients with cardiovascular comorbidities and are not representative of real life. Thus, cardiovascular changes during treatment should be extensively investigated and reported in order to increase vigilance and stimulation of symptom-seeking beyond early treatment.

Rationale and design of the prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA II) trial: A randomized, placebo-controlled, multicenter trial

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BACKGROUND

Cardiotoxicity due to anthracycline-containing chemotherapy and/or trastuzumab during breast cancer treatment may lead to ventricular dysfunction and to dose-reduction or halt in potentially life-saving cancer therapy. This reduction in left ventricular ejection fraction (LVEF) may be attenuated by angiotensin blockade. In chronic systolic heart failure, neprilysin inhibition with Sacubitril/Valsartan is superior to traditional angiotensin blockade, but whether it can prevent reduction in LVEF after anthracycline-containing chemotherapy has not been evaluated previously. The primary hypothesis of the PRADA II trial is that Sacubitril/Valsartan compared to placebo can prevent reduction in LVEF associated with anthracycline-containing chemotherapy.

METHODS

PRADA II (ClinicalTrials.gov Identifier: NCT03760588) is a randomized, placebo-controlled, double blind, multi-center clinical trial. 300 breast cancer patients from four university hospitals in Norway, scheduled to receive chemotherapy with anthracycline epirubicin with or without trastuzumab, will be randomized 1:1 to Sacubitril/Valsartan or placebo. The target dose is 97/103 mg b.i.d. The patients will be examined with cardiovascular magnetic resonance (CMR), echocardiography, cardiovascular biomarkers and functional testing at baseline, at end of anthracycline treatment and at 18 months (Figure 1). The primary outcome is change in LVEF by CMR. Secondary outcomes are change

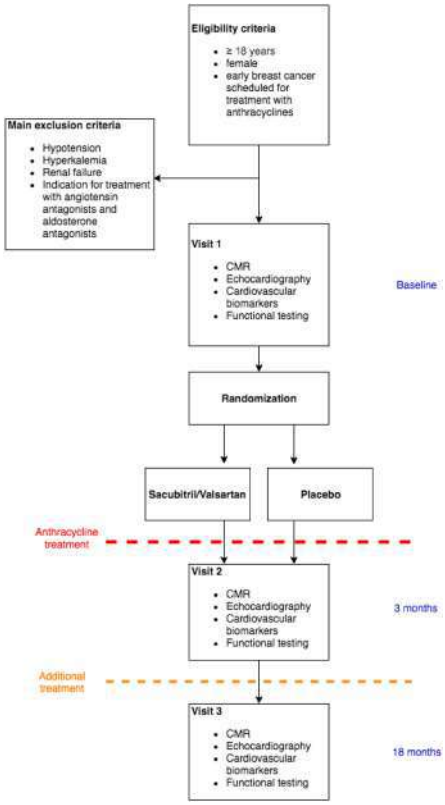

FIGURE 1: Flow chart of the PRADA II trial.

in LV function by global longitudinal strain and LVEF by echocardiography, and cardiovascular biomarkers.

CONCLUSION

PRADA II is the first randomized, placebo-controlled study of Sacubitril/Valsartan in the cardio-oncology setting and may provide important new insights in preventive cardioprotective strategies in cancer patients receiving anthracyclines with or without trastuzumab.

The trial will further enable identification of patients at higher risk of developing cardiotoxicity and those most likely to respond to cardioprotective therapy.

Cardio-oncology awareness among cardiologists and oncologists in Florida: Survey from the Florida chapters of the American College of Cardiology (ACC) and American Society of Clinical Oncology (ASCO) work group

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BACKGROUND

The lack of knowledge in cardio oncology (CO) results in suboptimal patient care. ACC CO Council Advocacy Work Group and the Florida (F) Chapter of ACC (FCACC) collaborated with the F Chapter of ASCO (FLASCO) to assess CO knowledge amongst cardiologists (CAR) and oncologists (ONC) in F (USA) and to determine needs at state level.

METHODS

An 18 questions web based survey was delivered over 3 weeks to all members of FCACC and FLASCO using their respective membership platforms. Data was analyzed for each surveyed group.

RESULTS

165 of 2800 ONC and 138 of 2500 CAR responded to their surveys.

Question in the Survey	Oncologists	Cardiologists
	N=165	N=138
Very Comfortable treating CO patients	14%	16%
CO services in their communities	46%	42%
Refers to CO services if available	93%	34%
Excellent cooperation between CAR and ONC	34%	34%
Lack of local CO educational resources	64%	20%
Attended < 1 educational session in CO (past 3 years)	65%	55%

58% of ONC consult general cardiology and 38% consult CO for possible cancer treatment related cardio-toxicity (CT).

29% of ONC treat patients with potential CT > once/week and 35% < once/month.

The most common CT seen in ONC practices were: CHF/reduced LVEF 84%, arrhythmias/atrial fibrillation 43%, VTE and arterial thromboembolism 42%, QT prolongation 36%.

ONC were not familiar with CT of proteasome inhibitors (PI): 4%, multi-targeted tyrosine kinase inhibitors (TKI): 33%; 5 fluorouracil (5-FU): 30%; cisplatin (C): 35%; check point inhibitors (CPI): 23%.

Cardiac evaluations were triggered by anthracyclines (A): 95%; trastuzumab (T): 88%; C: 33%; 5 FU: 28%; vascular endothelial growth factor inhibitors: 55%, TKI: 47%, PI: 35%, CPI: 39%.

CONCLUSIONS

This surveys were unique in assessing the same questions in CO resources and knowledge to both CAR and ONC. Even this selective group exhibited lack of CO knowledge, available services, cooperation between CAR and ONC and lack of awareness of CT effects of cancer therapies. To address this knowledge gap we established CO committees at FCACC and FLASCO and started a project on basic education in CO to improve state wide patient care.

Cardiac tamponade as the first manifestation of Erdheim-Chester disease: A rare case in literature

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BACKGROUND

Erdheim-Chester Disease (ECD) is a rare entity classified as inflammatory myeloid neoplasia with an unknown incidence that occurs preferentially in men after 50 years. In general, it is multisystemic. Cardiovascular manifestations are present in more than half of the patients, with infiltration of the aorta and atrial pseudotumor being the most common forms.

CASE

A 55-year-old female patient presented with short-term syncope with sphincter release, progressive dyspnea to minimum efforts, orthopnea and limb edema within 3 months. She underwent to a transthoracic echocardiography in an emergency department, which found signs of cardiac tamponade. Pericardial drainage with pericardial fluid analysis, bacterial cultures, fungi and negative AARB tests were performed. Pericardial biopsy was also performed, which showed no changes. An etiological investigation was carried out with cardiac magnetic resonance imaging (CMRi), which detected: right atrium (RA) with enlarged dimensions; presence of irregular contoured tissue formation infiltrated in RA wall, affecting the interatrial septum, aorta, right coronary artery and vena cava; presents hypersignal in double-IR sequence and isosignal in triple-IR sequence; discreet perfusion and heterogeneous late gadolinium enhancement are observed; presence of suggestive image

of thrombus adjacent to the wall tissue formation of the RA; absence of myocardial fibrosis; such findings on CMRi are suggestive of non-Langerhans cell histiocytosis, which are characteristic of ECD. Adrenal biopsy confirmed histiocytic proliferation, confirming the diagnosis of ECD.

DISCUSSION

ECD is a rare disease that is difficult to diagnose. Cardiac involvement in ECD gives a worse prognosis. The case illustrated shows a serious and rare complication of the disease, such as cardiac tamponade. The most characteristic finding is aortic involvement and is associated with cardiac tamponade; an adjacent myocardial, endocardial, pericardial, valvular and perivascular infiltration may also occur. Cardiologists' knowledge about this disease allows early diagnosis in these situations.

Progressive evolution of carcinoid heart disease: A case report

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BACKGROUND

Neuroendocrine tumors (NET) are rare, 35% have Carcinoid Syndrome (CS) at diagnosis and of these 40% have Carcinoid Heart Disease (CHD). Patients with CHD develop symptoms of heart failure (HF) and represent the major cause of morbidity and mortality of patients diagnosed with NET.

CASE

In 2017, a 60-year-old female patient had abdominal pain and diarrhea. It progressed with worsening diarrhea, significant weight of loss, flushing episodes and dyspnea. Ten months after the onset of the condition, she was referred to the oncology department, where PET-CT showed terminal ileum thickening, lymph node cluster near the ileum and liver lesions. Liver biopsy found metastatic NET. She started treatment with octreotide, with partial improvement of symptoms and was referred to cardiology. Initial transthoracic echocardiography (TTE) showed thickened tricuspid valve (TV) with slight opening reduction and moderate tricuspid regurgitation (TR). Diuretic therapy was started, with initial improvement of symptoms; however, due to the worsening of diarrhea and nausea, she began to use it irregularly and develop ascites, worsening dyspnea, high levels of 5-hydroxyindolacetic (5-HIAA) and decompensation of HF. In 2018, a new TTE showed significant disease progression, with right chamber dilatation, thickened TV, reduced

opening, failed cusp coaptation and important TR; as well as pulmonary valve stenosis and pulmonary hypertension. Currently, the patient is not able to undergo intestinal resection and hepatic embolization, performs paracentesis every 15 days and presents dyspnea to moderate to small efforts.

DISCUSSION

The goal to slowing the evolution of CHD is controlling the progression of CS. Follow-up with biomarkers (5-HIAA and NT-ProBNP) provide us with diagnostic and prognostic data. TTE is a good tool for CHD assessment. Cardio-oncologists play an important role in the management of HF symptoms and in assessing the most appropriate time for valve replacement and perioperative assistance.

Malignant thymoma causing secondary pulmonary hypertension and left atrium invasion

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BACKGROUND

Thymoma is the most common neoplasm of the anterior mediastinum, and accounts for 20-25% of all mediastinal tumors. Most patients are asymptomatic, being diagnosed on the basis of incidental findings on imaging studies. The involvement of middle and posterior mediastinum is rare, with fewer cases involving left atrium invasion.

CASE

A 58-year-old male with hypertension, presented with progressive exertional shortness of breath. Echocardiogram showed a large heterogeneous mass in the middle mediastinum, involving the aorta, leading to an extrinsic compression of the pulmonary trunk and the left atrium, apparently invading the latter. The left ventricle showed normal dimensions, with preserved systolic function and no wall abnormalities. The right chambers showed severe enlargement with moderate dysfunction due to diffuse hypokinesia of the right free wall, with severe tricuspid regurgitation. The pulmonic valve was normal. The Doppler in the pulmonary artery showed a maximum velocity of 3,91m/s (peak gradient 61 mmHg), due the extrinsic compression of the pulmonary trunk. The mass biopsy suggested a type AB thymoma, that turned out to be inoperable even after radiotherapy and chemotherapy.

DISCUSSION

Thymomas are malignant primary tumors of the anterior mediastinum and have strong association with myasthenia and other systemic syndromes,

not present in our patient. The intravenous affinity of invasive thymomas can lead to intracardiac metastases involving the right atrium and the superior vena cava. Extrinsic compression of pulmonary trunk and left atrium invasion due to a malignant middle mediastinum thymoma is a rare occurrence. Complete surgical excision is the preferred treatment approach whenever technically feasible. Thymomas are usually chemotherapy sensitive. Chemotherapybefore and/or after surgery and radiation therapy may be useful in appropriately selected patients.

CONCLUSION

Thymoma can mimic a variety of diseases, including those with compressive symptoms and paraneoplastic diseases, as well as mediastinal widening. Hence the importance of this case to expand diagnostic reasoning for a tumor in the middle mediastinum, since it is a rare differential diagnosis to be considered.

Renal cell carcinoma with extension to the heart

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BACKGROUND

Renal cell carcinoma (RCC) is an aggressive and lethal tumor that has a high frequency of metastatic spread to unpredictable sites. Most cases of RCC are discovered as incidental findings on imaging studies for other reasons. Intravascular tumor growth into the renal vein and inferior vena cava reported to be seen in about 15% of patients with extension into right atrium in approximately 1% of cases.

CASE

A 67-year-old male presented with progressive lower extremities swelling, ascites and exertional shortness of breath. Echocardiogram showed a large mass within the inferior vena cava with its extension into the right atrium. The segment of the mass inside the atrium measured 5.0 cm×3.0 cm, was heterogenous, pedunculated, and mobile. The left chambers showed moderate enlargement, with moderate left ventricular eccentric hypertrophy, diffuse hypokinesia and moderate systolic disfunction with ejection fraction of 37%. The diastolic function analysis showed grade I disfunction. The inferior vena cava appeared to be dilated and was almost completely filled up by the heterogeneous mass, likely malignancy. The findings were most consistent with the extension of a metastatic mass within the right atrium. The mass biopsy suggested a renal cell carcinoma.

DISCUSSION

Common sites of renal cell carcinoma metastasis include the lungs, adrenals, intestines, brain, and most intra-abdominal organs, but there have been

several reported cases of rare metastatic sites. Renal cell carcinoma can invade local vasculature into the renal vein and grow as a solid column of cells that can sometimes extend up to, as in our patient, the right atrium via inferior vena cava. Other than primary or metastatic tumors, thrombus and tricuspid valve vegetations, rare causes of a right atrial mass include anatomic variants, coronary fistula, paced wires and indwelling catheters.

CONCLUSION

Renal cell carcinoma typically metastasizes to unpredictable sites and presents with atypical symptoms. Classic presentation of RCC is rare and majority of cases are diagnosed as incidental findings on imaging studies for other reasons. A RCC extension to the heart is a rare occurrence.

Constrictive pericarditis due to tuberculous etiology in active lymphoproliferative disease: Diagnostic challenge

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BACKGROUND

Pericardial Diseases (PD) are frequent complications in the cancer patient and may be related to some neoplasms (lymphomas, lung and esophagus), chemotherapy, radiotherapy and opportunistic infections. However, Constrictive Pericarditis (CP) is present in only 4% of these cases. We present a case of Hodgkin's Diasease (HD) involving the pericardium.

CASE

Female, 26 years-old, without comorbidities, diagnosed with HD on chemotherapy programming, triggered progressive dyspnea associated with orthopnea. Cardiac tamponade by Transthoracic Echocardiography (ECOTT) with signs of restriction to ventricular filling was evidenced, and the patient underwent emergency relief pericardiocentesis. Serous fluid and biopsy compatible with nonspecific granulomatous inflammatory tissue, initiating the ABVD regimen (Dacarbazine, Doxorubicin and Vimblastine). ECOTT performed showed no pericardial effusion. After the final cycle of ABVD, she started with daily afternoon fever and dyspnea with detection of moderate pericardial effusion without restriction, moderate pleural effusion and febrile neutropenia.

PET-CT ruled out recurrence of pericardial lymphoproliferative disease and suggest acute pericarditis (AP). Cardiac Magnetic Resonance (CMR) was performed and confirmed AP. Colchicine and prednisone was prescribed. In outpatient return, she related fever and dyspnea. ECOTT showed right atrial thrombus and long-term catheter, and a new CMRI revealed 3 moving images in the right atrium, close to the central venous catheter, in tricuspid supravalvular topography and demonstrated significant thickening/fibrosis of pericardial leaflets, especially parietal, measuring up to 0.6 cm, suggestive of CP. Hypotheses Thrombus are raised and anticoagulation treatment was started. New PET-CT ruled out hematologic recurrence and right pleural uptake. Pleural biopsy revealed a tuberculoid-type chronic granulomatous inflammatory process and added COXCIP regimen.

DISCUSSION

This case demonstrates that different etiologies of PD may be present in the same patient. Although HD is a frequent cause of PD and CP, other diagnoses should always be ruled out in these patients.

Acute ventricular dysfunction in an immunotherapy patient: Diagnostic challenge

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BACKGROUND

Checkpoint inhibitors (CPI) are monoclonal antibodies used in various types of cancer which have shown promising results, such as increased survival and cure. However, severe side effects are described in the literature, especially myocarditis.

CASE

Female patient, 70 years old, with a history of hypothyroidism and metastatic cutaneous melanoma in the central nervous system, liver and lungs. CPI treatment started with ipilimumab and nivolumab. After 7 days, the patient was hospitalized with pulmonary and systemic congestion and an acute heart failure (HF) was also diagnosed. Transthoracic echocardiogram (TTE) showed 23% left ventricular ejection fraction (LVEF). A cardiac magnetic resonance imaging (MRI) was performed for diagnostic completion and a significant ventricular dysfunction (LVEF 30%) involving diffuse hypokinesis was identified, which was more intense in the anterior and septal wall, T2-weighted sequence hypersignal, compatible with myocardial edema, and absence of late enhancement. Healing treatment with carvedilol and enalapril was started and pulse therapy with methylprednisolone was chosen. On the second day of pulse therapy, a repeated TTE showed partial LVEF recovery to 40%. Patient refused endomyocardial biopsy (EMB). Negative viral panel. MRI was repeated 30 days after the event, with recovery of LVEF, which showed 50% LVEF involving mid-apical anteroseptal hypokinesia, absence of edema and myocardial fibrosis.

DISCUSSION

Myocarditis is a rare but potentially fatal side effect in patients with CPI (1). The gold-standard diagnosis is made with EMB, but because it is an invasive method, it is not always possible to be performed, as in the case above. Cardiac MRI is a noninvasive method that helps in the diagnosis, and it suggests myocarditis when myocardial edema and late non-ischemic pattern enhancement are identified (2). Late enhancement is present in most cases and has prognostic value. Takotsubo Syndrome is a differential diagnosis of myocarditis in this scenario, which appears showing a decrease in LVEF, myocardial edema, absence of late enhancement and recovery of ventricular function within 21 days (3).

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Postoperative acute coronary syndrome complicated by urological bleeding: Case report

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BACKGROUND

The presence of common risk factors between cancer and acute coronary syndrome (ACS) turns perioperative infarction into an important morbidity among cancer patients. Perioperative management of ACS is a major challenge, given the difficult balance between pro and antithrombotic factors and the high presence of comorbidities in these patients.

CASE

H.B.S, male, 66 years old, hypertensive, diabetic, with Gleason 7 Prostate adenocarcinoma, was submitted to videolaparoscopic radical prostatectomy. The surgery was performed without intraoperative complications. Although asymptomatic, in the immediate postoperative period, electrocardiogram showed V3-V6 ST-segment depression, followed by T inversion throughout the anterior wall and anterior plus-minus pattern (Figure 1). There was a significant increase in troponin t, with a peak of 1,22 ng/mL (normal range < 0,014 ng/mL). Diagnosis of non-ST-Segment Elevation Acute Myocardial Infarction (NSTEMI) was established. Treatment according to current guidelines was performed and coronary catheterization was indicated, which showed subocclusion of proximal anterior descending artery (ADA). An attempt of

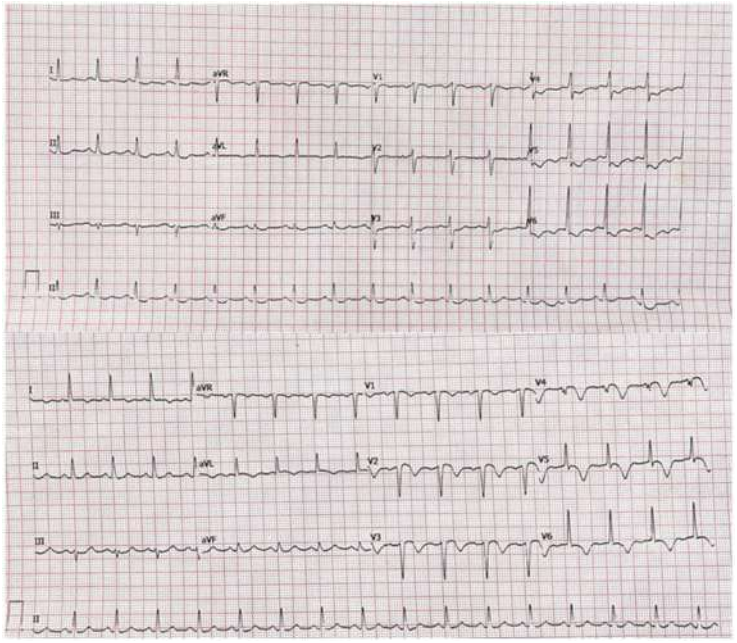

FIGURE 1: Electrocardiogram showed V3-V6 ST-segment depression, followed by T inversion throughout the anterior wall and anterior plus-minus pattern.

angioplasty was performed, however, there was a great technical difficulty due to the high amount of calcium in the lesion. Balloon angioplasty was then performed. On a second attempt, pharmacological stent angioplasty was performed, with the aid of Rotational Atherectomy System (RAS), this time with success. After the procedure, patient developed macroscopic hematuria, which improved with bladder irrigation. Post-event transthoracic echocardiogram showed anterior hypokinesia, with left ventricular ejection fraction of 40%. The patient had a good recovery and was discharged using acetylsalicylic acid, clopidogrel, atorvastatin, enalapril, and carvedilol.

DISCUSSION

Approaching ACS in the postoperative period of cancer surgery is often difficult, especially in asymptomatic patients and after urological surgeries,

where postoperative bleeding is expected and sometimes complicated to manage. This case illustrates how ACS management should be individualized, pondering thrombotic risk vs. bleeding risk.

Carfilzomib treatment and cardiotoxicity

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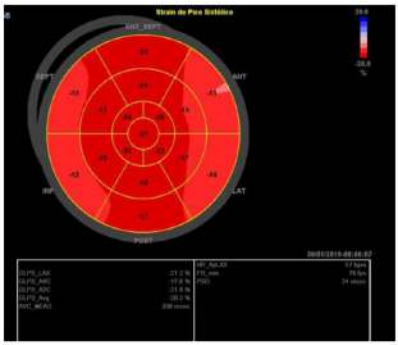
INTRODUCTION

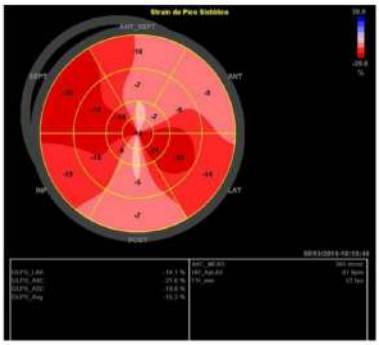
Carfilzomib (CFZ) is a second-generation proteasome inhibitor (PI) that is approved for patients with relapsed or refractory multiple myeloma (MM). In the literature estimated incidence of cardiotoxicity is 8.68%. The main reports are palpitations, dyspnea, ischemic heart disease, hypertension, and heart failure. Prior risk factors such as age (children and the elderly), women, previous comorbidities, prior mediastinal irradiation, and exposure to cardiotoxic chemotherapies such as anthracyclines may increase the chance of cardiotoxicity. The identification and early management of these complications becomes increasingly necessary for the maintenance of patient treatment.

CASE REPORT

Male, 56 years old, no comorbidities, with refractory MM, started CFZ treatment. On the first day of treatment, the patient had elevated blood pressure controlled with low doses of enalapril. After the 15th day, the patient developed arterial fibrillation with high ventricular. As the disease progressed, chemotherapy with doxorubicin, cyclophosphamide and etoposide were started. After the first cycle, the biomarkers were elevated and Global Longitudinal Strain by Echocardiography (ECHO) revealed global longitudinal strain (GLS) of –16% (baseline of –22) (Figure 1) and metoprolol was started. Only 15 days later ECHO strain and biomarkers were reevaluated and no abnormality was found. The patient was released for a new cycle of chemotherapy. Successfully evolved and maintained the antineoplastic with good treatment response.



Basal Global Longitudinal Strain by Echocardiografy



Post-chemotherapy Global Longitudinal Strain by Echocardiografy

DISCUSSION

As CFZ is being increasingly used in real-world settings and in clinical trials in combination with other agents, it is important for oncologists and cardiologist to be aware of the risk of cardiotoxicity associated with CFZ to monitor and treat it appropriately. Although it is recommended that patients receiving CFZ should be closely monitored for cardiac complications, proper monitoring strategy is still a subject of debate and needs further research. In the case report, the search for cardiotoxicity and tests such as electrocardiogram, Global Longitudinal Strain by Echocardiography and cardiac biomarkers resulted in the early identification of toxicity and the beginning of cardio protection. Treatment resulted in myocardial recovery and maintenance of treatment for disease control.

Coronary computed tomography angiography in combination with coronary artery calcium scoring for the preoperative cardiac evaluation in cancer surgery

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BACKGROUND

Cardiovascular complications are among the leading causes of morbidity and mortality in patients undergoing non-cardiac surgery. Clinical scores and functional tests are the strategy of choice for evaluating these patients, however over one-third of perioperative MACCE occur in patients with a negative study. The computed tomographic coronary angiography (CTCA) and coronary calcium score (CAC) are emerging in this context as important predictor of clinical outcomes.

METHODS

Patients older than 45 years and presenting two or more cardiovascular risk factors with indication for oncologic surgical treatment were consecutively included. All patients underwent CTCA before surgery. Patients with contraindications to CTCA or previous heart disease were excluded. Clinical and laboratory information, including troponins levels, were collected in postoperative evaluation. Multivariable models were constructed using linear regression.

RESULTS

84 patients were included, 57% male, mean age 68 (+/-8). 83.3%, 45.2% and 34.5% had hypertension, dyslipidemia and diabetes, respectively. Obstructive coronary arterial disease (CAD) was identified in 12.2% of patients and CAC > 100 was present in 36.9%. The incidence of myocardial injury (MI) was 38 (45%) and MACE (death, infarction, complex arrhythmias and stroke) was 6 (7.1%). The prevalence of CAC> 100 were high in patients with MI than patients without MI (55.2% vs. 21.7%, p 0.005). Similarly, there were more obstructive CAD than non-obstructive CAD in patients who development MI (31.4% vs. 8.7%, p 0.022). Multivariable models showed multivariate analysis showed preoperative blood glucose and anesthesia duration as significant factors.

CONCLUSION

Predictive value of CCTA and CAC is high for perioperative MI in patients with cancer undergoing surgical treatment. It may be considered as a valuable tool for preoperative risk assessment in these patients, as an alternative to other noninvasive methods.

An atypical case of a young patient with Lymphoblastic Lymphoma T Cell who developed acute heart failure

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BACKGROUND

Cardiotoxicity is more frequent in patients with risk factors such as age extremes, previous heart disease, high blood pressure, diabetes, combined use of chemotherapy agents and mediastinal radiotherapy. The use of anthracycline at doses above 400 mg/m^2 may lead to ventricular dysfunction or heart failure in 5 to 35% of the cases. Case report of a young patient diagnosed with T lymphoblastic lymphoma who developed severe heart failure after the use of anthracycline at a dose of less than 400 mg/m^2.

CASE

A 17-year-old female NSH patient admitted for adenomegaly and pancytopenia. In cervical mass biopsy, T-lymphoblastic lymphoma was diagnosed. Proceeded with chemotherapy induction GRAAL 2003 protocol with combined drug regimen: vincristine 2 mg/day D1, D8, D15, D22. prednisone 60 mg/m^2/day D1 to D14, daunorubicin 50 mg/m^2 day D1, D2, D3 and 30 mg/m^2 D15 and D16, L-asparaginase 6000 IU/m^2/day D8, D10, D12, D20, D22, D24, D26 and D38, and cyclophosphamide 750 mg/m^2 on D1 and 500 mg/m^2 on D15 and D16. Previous echocardiography with left ventricular ejection fraction (LVEF) showed: 75%. After induction therapy, the patient developed febrile neutropenia, which was reversed. No response to treatment was observed in reassessment exams, and rescue therapy with idarubicin 12 mg/m^2 D1, D2 and D3 combined with cytarabine 2000 mg/m^2 D1 to D4 was chosen. As the patient did not respond, even after rescue therapy, it was decided to change the chemotherapy protocol to Hyper-CVAD, being administered on an even cycle with methotrexate 1 g/m^2 in 24 hours followed by cytarabine 3 g/m^2, total of 4 doses. Ten days later, the patient developed heart failure.

Echocardiography showed LVEF: 28%. Administration of dobutamine by cardiogenic shock was necessary, with little response. Due to associated sepsis, she died three months after chemotherapy was initiated.

CONCLUSION

It is important to consider that even young patients without cardiac risk factors can have anthracycline cardiac toxicity, even at doses below 400 mg/m^2.

Profile of patients with heart failure by cardiotoxicity and analysis of predictors of recovery of ventricular function

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BACKGROUND

The prognosis of cancer improved with the advancement of treatment. Cardiotoxicity is a relatively common, due to common risk factors and chemotherapy. Heart failure (HF) is one of the worst scenarios and it has been related mostly with the use of Anthracycline and Trastuzumab.

METHODS

Retrospective study, performed at a cancer institutite. We included patients with HF caused by cardiotoxicity during 2 years. Cardiotoxicity was defined as decrease of at least 10% of left ventricular ejection fraction (LVEF) to values below 50% during follow-up. Demographic, clinical and echocardiographic characteristics were analyzed, and patients were divided into two groups: recover LVEF (> 50%) and not recover.

RESULTS

We included 110 patients: 88.2% were female, 52.7% had hypertension (HT), 16.4% had diabetes, 17.3% were dyslipidemic and 36.4% had previous smoking history. The mean age was 57.6 (+/-12.7) years. The most prevalent tumors were breast cancer (74%) and lymphoma (22%). Regarding chemotherapy, 89% received Anthracycline, 85% cyclophosphamide and 45% Trastuzumab. Dyspnea was present in 65% (majority in NYHA I-II). At diagnosis, mean LVEF

Table 1: Characteristic of the sample divided by recovery of the ventricular ejection fraction

	Did Not Recover LVEF (N = 57)	Recovered LVEF (N = 53)	P value
	N (%)	N (%)	
Comorbidities			
Female	52 (91.2)	45 (84.9)	0.381
Hypertension	39 (68.4)	19 (35.8)	0.001
Diabetes	12 (21.0)	6 (11.3)	0.206
Dyslipidemia	10 (17.5)	9 (17.0)	1.000
Smoking	4 (7.0)	5 (9.4)	0.734
Ex-smoking	19 (33.3)	12 (22.6)	0.289
Primary Tumor			
Breast Cancer	43 (75.4)	38 (71.7)	0.672
Lymphoma	10 (17.5)	14 (26.4)	0.356
Sarcoma	1 (1.7)	1 (1.9)	1.000
Chemotherapy			
Cyclophosphamide	51 (89.4)	42 (79.2)	0.188
Anthracyclines	54 (94.7)	44 (83.0)	0.067
Trastuzumab	18 (31.5)	31 (58.5)	0.007
Medications			
Furosemide	32 (56.1)	19 (35.8)	0.037
Spironolactone	22 (38.6)	16 (30.1)	0.424
Enalapril	45 (78.9)	39 (73.6)	0.654
Losartan	10 (17.5)	13 (24.5)	0.482
Carvedilol	51 (89.5)	44 (83.0)	0.408
Ivabradine	2 (3.5)	1 (1.9)	1.000
Nitrate with Hydralazine	0 (0)	1 (1.9)	0.482
Digoxin	1 (1.7)	1 (1.9)	1.000
Deaths	8 (14.0)	5 (9.4)	0.560
	Mean (SD)	**Mean (SD)**	
Age (years)	60.35 (11.54)	54.66 (13.52)	0.472
Echocardiogram (LVEF %)			
First	61.24 (7.36)	63.82 (5.65)	0.473
Worst	32.72 (8.77)	40.57 (6.72)	0.072
Last	37.46 (9.12)	58.20 (5.36)	0.001

Left ventricular ejection fraction (LVEF), absolute number (N), percentage (%), standard deviation (SD).

was 36.5% (+/- 8.7). From all patients, 48% recovered LVEF after treatment (LVEF 47.4% (+/- 12.8)) and 12% died (Table 1). Carvedilol (86%), Enalapril (76%), Losartan (21%) and Spironolactone (35%) were prescribed. Analyzing the groups, we found that HT increased the chance of non-recovery (OR 3.877, CI 1.756-8.559; p=0.001). On the other hand, exposure to Trastuzumab increased the chance of cardiac function reversibility (OR 0.328, CI 0.150-0.715; p=0.007).

CONCLUSION

This study describes the profile of patients who had the diagnosis of cardiotoxicity in a cardio-oncology service. The presence of hypertension increased the risk of heart failure. Adequate control of hypertension must be a goal of prevention of cardiotoxicity in these patients.

10 years of Brazilian cardio-oncology: The experience of Instituto do Câncer do Estado de São Paulo (ICESP)

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BACKGROUND

Cardio-oncology is a relatively new area of activity in Brazil and in the world. The importance has grown due the high prevalence of cancer patients and survivors with cardiovascular risk factors and cardiovascular disease during treatment and follow up, and the particular management in this population. We describe our experience in 10 years of cardio-oncology program, highlighting the performance in assistance, but also in education and research.

METHODS

A retrospective analisys of ICESP Cardiology Group from 2009 to 2019. Clinical characteristics were extracted from our data of patients treated in our service. The results are expressed as the means with standard deviations or as the medians with interquartile ranges. A p value < 0.05 was considered statistically significant.

RESULTS

There were 20991 outpatient care and 5444 inpatient care. 4525 patients have been evaluated since 2013. Clinical characteristics of these patients were separated by type of care, as shown in Table 1.

Table 1: Comparison of clinical characteristics according to the type of outpatient care

Follow up Reason:	Pre Chemotherapy	Cardiotoxicity	General	Pre-operative	p
	n=132	n=448	n=2675	n=1270	
Cancer Type:					<0.001
Gastrointestinal	51 (38.6%)	39 (8.7%)	628 (23.5%)	321 (25.3%)	
Breast Cancer	20 (15.2%)	237 (52.9%)	490 (18.3%)	109 (8.6%)	
Hematological	25 (18.9%)	118 (26.3%)	549 (20.5%)	21 (1.7%)	
Gynecological and urinary tract	19 (14.4%)	20 (4.5%)	486 (18.2%)	422 (33.2%)	
Others	17 (12.9%)	34 (7.5%)	522 (19.5%)	397 (31.2%)	
Risk Factors/CVD					
Diabetes	39 (29.5%)	67 (15%)	596 (22.3%)	379 (29.8%)	<0.001
Hypertension	87 (65.9%)	196 (43.8%)	1562 (58.4%)	890 (70.1%)	<0.001
Dyslipidemia	48 (36.4%)	87 (19.7%)	687 (25.7%)	459 (36.2%)	<0.001
Smoker	39 (29.5%)	107 (24.2%)	907 (33.9%)	457 (36%)	<0.001
Coronary arterial disease	30 (22.7%)	22 (4.9%)	358 (13.5%)	236 (18.6%)	<0.001
Age (medians with inter-quartile ranges)	67 (57–73)	59 (48–66)	66 (58–74)	69 (62–76)	<0.001
Echo Analysis					
Diastolic Diameters (medians with interquartile ranges)	47 (44–52)	49 (45–53)	47 (43–51)	49 (44–53)	<0.001
LVEF (medians with inter-quartile ranges)	61 (50–66)	55 (41–63)	62 (55–66)	62 (55–66)	<0.001

CONCLUSION

The prevalence of cardiovascular risk factors and heart disease is very high in cancer patients. A specialized service allows a better quality of care, once these patients have different management than general patients.

Extracorporeal membrane oxygentation in severe heart failure secondary to doxorubicin cardiotoxicity as bridge to heart transplantation in an osteosarcoma survivor patient

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Doxorubicin is one of the most important anticancer drugs, but it can cause potentially dose-related and irreversible cardiac toxicity, which can progress to heart failure (HF). In some situations it may evolve to cardiogenic shock, requiring the use of assist devices and cardiac transplantation.

A 29-year-old female patient with a history of right femoral osteosarcoma in adolescence treated with local surgery and chemotherapy with Doxorubicin (320 mg/m^2), Cisplatin (480 mg/m^2) and Ifophosphamide (54 mg/m^2) from October 2004 to May 2005. With no evidence of neoplastic disease, she developed late heart failure secondary to anthracycline, treated with Enalapril, Spironolactone and Carvedilol. She was hospitalized in August of 2018 with decompensated HF, after treatment of pneumonia. One month later, with no evidence of clinical improvement, the patient was referred to our service. At admission, she was receiving Dobutamine 5 mcg/kg/min, with poor perfusion and with echocardiography showing severe left ventricular (LV) dysfunction with ejection fraction (EF) of 20% and diffuse hypokinesia. Patient evolved with refractory cardiogenic shock requiring circulatory support with the use of intra-aortic balloon (IAB). She remained unstable despite the use of Dobutamine 20 mcg/kg/min and IAB 1:1. Extracorporeal membrane oxygentation (ECMO) was inserted with two drainage lines: venous, through the right femoral vein (cannulation to the right atrium) and arterial by the tip of the LV. With progressive clinical improvement in the postoperative period, the patient

was extubated, the IAB was removed and there was progressive weaning of vasoactive drugs. She remained for 15 days with ECMO awaiting cardiac transplantation in INTERMACHS 2 profile. On October 31, a bicaval orthotopic cardiac transplant was performed with ECMO decanulation without complications. Patient was discharged wihtout organ failure, with preserved EF, receiving cyclosporine, mycophenolate and corticosteroid.

Cardiac transplantation related to cardiotoxicity by chemotherapy in a cancer survivor patient was first reported in 1987. This is another case of severe heart failure associated with cardiotoxicity secondary to doxorubicin. Circulatory support through the use of ECMO allowed organ failure recovery and the well sucessful heart transplantation. The follow-up of these patients is important to prevent, and to perform early diagnosis and appropriate treatment.

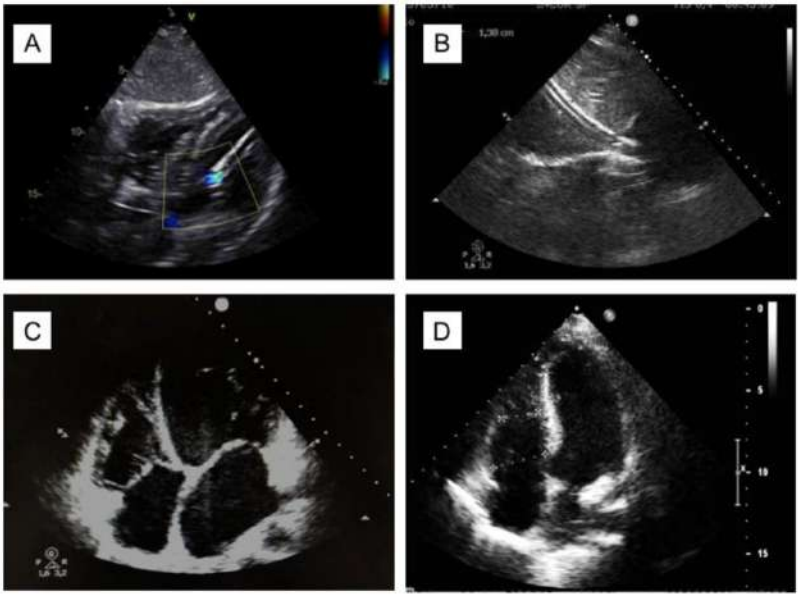

FIGURE 1: (**A**) Transesophageal echocardiogram performed after passage of ECMO demonstrating cannula in the right atrium. (**B**) Transthoracic echocardiogram visualizing cannula in the right atrium. (**C**) Transtoracic echocardiogram in a four chamber window identifying dilated cardiomyopathy with diffuse hypokinesia at patient admission. (**D**) Transthoracic echocardiogram in a four-chambered window, after cardiac transplantation, with preserved ventricular function.

Cardiovascular complications of antineoplastic therapy in patients attending in the cardio oncology clinic

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INTRODUCTION

The cancer and the cardiovascular diseases are both still the main cause of mortality in the world population. The progress of oncology therapy is responsible for big changes in the survival ratio and mainly responsible for a better quality of the oncology patient's life. However, this antineoplastic drugs are associated with a higher incidence of cardiovascular disease and significant repercussions on morbidity and Mortality.

METHODS

A retrospective study was carried out with all the clinic outpatients attended by the cardiology team at Instituto do Câncer de São Paulo in 2017. All of them had the hypothesis of cardiotoxicity during the oncology treatment. Clinical and demographic variants, type of antineoplastic drug, laboratory exams (including biochemistry) and Doppler echocardiography were collected, which are presented as percentages and/or mean (Standard deviation). Pearson Chi-square, T-student, Mann-Whitney test was performed, as indicated for statistical analysis. $P < 0.05$ was considered significant.

RESULTS

A hundred and ten patients were attended with this profile, being 82% female, mean age 58 (±11) years old. The main risk factors were hypertension (53.3%), dyslipidemia 23.4%, smoking 43% and diabetes 14.9%. The most frequent oncology diagnosis were: breast cancer, 59.8%; Non-Hodgkin lymphoma 19.6%, Hodgkin's lymphoma 5.6%. From these 57.9% received previous radiotherapy and 45.8% underwent oncologic surgery. The most used antineoplastic drugs were Anthracycline, 78 (70.9%), cyclophosphamide 74 (67.3%), paclitaxel 50 (45.5%), and cisplatin 13 (11.8%). The main cardiovascular complications were heart failure in 46 patients (41.8%), tachyarrythmias 5.7%, bradyarrhythmias 4.7%, hypertensive urgency 8.4%,tromboembolism 14% and death (in one year) 23.4%. From the patients who presented heart failure, 26% died in the first year after the diagnosis.

CONCLUSION

In this study was evidenced the profile of outpatients clinic attended by the Instituto do Cancer de São Paulo cardiology team in the year of 2017 with cardio toxicity hypothesis. A hundred and ten patients were analyzed evidencing the breast cancer as the main oncology disease involved and the ventricular dysfunction as the main complication in 41.8% of the cases (considered fall below 50%) and with a high mortality ratio in one year (26%)

Protracted LV recovery with dual HER2-targeted therapy-related cardiotoxicity

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BACKGROUND

Trastuzumab (T) has been associated with reversible and dose-independent cardiac dysfunction. It has been suggested that the addition of pertuzumab (P) to T does not have additive risk of cardiotoxicity.

METHODS

Eighteen patients with *HER2/neu*-positive breast cancer were identified with cardiac dysfunction after treatment with T and P. All patients underwent left ventricular ejection fraction (LVEF) measurement before T and P and at least 6 weeks after treatment discontinuation. Reversible dysfunction was defined as LVEF recovery within 5% of baseline; partially reversible LVEF: at least 10% improvement but still more than 5% below baseline; irreversible LVEF: less than 10% improvement and more than 5% below baseline for at least 6 weeks. All patients with significant LV dysfunction were treated with heart failure therapy. Those with a recovered or stable LVEF were re-treated with T alone.

RESULTS

Mean baseline ($\pm$ standard deviation) LVEF was 62.1% $\pm$ 6.1%, and decreased to 42% $\pm$ 10.7% after treatment with T and P (Figure 1). Of the 18 patients, 9 (50%) experienced LVEF recovery and 3 (17%) partial LVEF recovery, while 6 (33%) appeared to have irreversible LV dysfunction. Half (50%) with irreversible LV dysfunction had prior anthracycline-based chemotherapy, while the majority without previous exposure had some LVEF reversibility. The mean

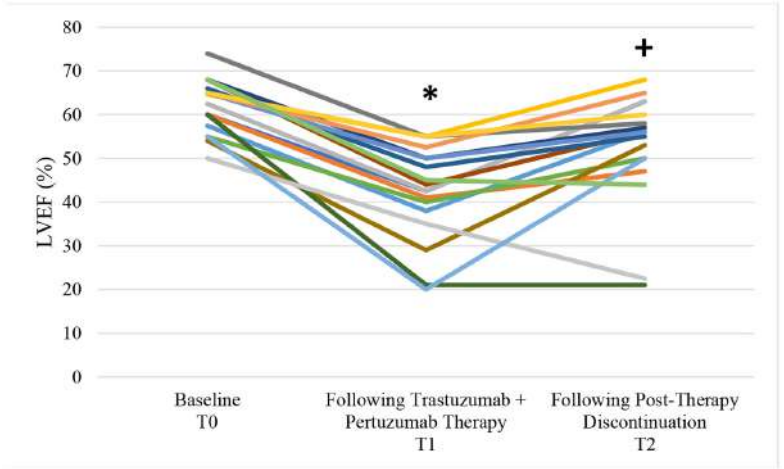

FIGURE 1: Changes in LVEF from baseline (T0) to LV dysfunction (T1) to post-treatment discontinuation and recovery (T2). The mean time from T0 to T1 was 13.4 months (± 13.8 months) and time to recovery of LVEF from T1 to T2 was 5 months (± 3 months).
*T0 LVEF is significantly higher than T1 LVEF ($p<0.001$ by Wilcoxon signed-rank test)
+T2 LVEF is significantly higher than T1 LVEF ($p<0.0001$).

time to LV recovery (either complete or partial) was 5 months, which is longer than observed with T alone.

CONCLUSION

Preliminary data demonstrates a significant improvement in LVEF after discontinuation of T and P. It appears that patients with prior exposure to anthracyclines have a higher risk of irreversible LV dysfunction. Compared to LVEF recovery observed in patients treated with T alone, those treated with T and P experience a longer recovery time.

A patient with chronic myeloid leukemia and asymmetric septal cardiomyopathy obstructive-case report

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BACKGROUND

Hypertrophic obstructive cardiomyopathy (HOCM) is a relatively common disorder. It can be genetically transmitted or can occur in individuals without family history secondary to de novo mutations. HOCM is a significant cause of sudden cardiac death in young people, affecting men and women equally.

HOCM is classified as obstructive or non-obstructive, once the asymmetric septal hypertrophy causes outflow obstruction of the left ventricle (LV). The majority of patients are asymptomatic. Patients may complain of syncope, angina, dyspnea and dizziness. Symptoms can be exacerbated by exertion.

Chronic myeloid leukemia (CML) is a malignant clonal disorder of pluripotent hematopoietic stem cells and accounts for 15% of all adult leukemia. Treatment with tyrosine kinase inhibitors (TKIs) have revolutionized its treatment. 1st TKI generation Imatinib as first-line therapy for CML patients is associated with a 10-y survival rate of 85–90%.

Some TKIs have been implicated in higher CV risk. To our knowledge, there is no description of TKI use and development of HOCM.

CASE

A 70y male CML patient, in use of Imatinib since 1996 was referred to the department of Cardio-Oncology on June, 2018, for thoracic pain. Previous history includes coronary artery disease with stent placing in 2006, hypothyroidism, hypertension, and hyperlipidemia.

Cardiac evaluation was performed. Echocardiography showed normal left ventricular ejection fraction without segmentar dysfunction. Coronariography showed intra-stent restenosis of anterior descending artery, which was treated with angioplasty. Two years later, patient complained of exercise-induced thoracic pain. Coronariography showed no obstructive coronary lesions. Echocardiography showed asymmetrical hypertrophy with outflow obstruction of the LV (maximum gradient VSVE 124 mmHg) and increased aortic valve gradient (medium gradient 32 mmHg and valve area 1.5 cm). Findings were confirmed by cardiac MRI. Considering refractory angina, the team decided to perform septal alcoolization.

DISCUSSION

To our knowledge, this is the first case of HOCM development in a patient with CML in chronic use of imatinib.

ST-segment elevation acute coronary syndrome in a patient with acute lymphoid leukemia: Case report

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INTRODUCTION

Coronary disease in cancer patients has special characteristics that should always be considered, as these patients are prone to develop thrombocytopenia. Acute coronary syndrome (ACS) occurs in 30% of cancer patients with thrombocytopenia and treating these patients has become a challenge.

CASE DESCRIPTION

A 61-year-old male patient, hospitalized for typical angina, was diagnosed with acute ST-elevation myocardial infarction and a circumflex artery drug-eluting stent was indicated. On admission laboratory examination, leukocytosis with blastocytosis was verified and acute lymphoblastic leukemia was diagnosed. It was decided to start induction chemotherapy treatment on the sixth day after acute myocardial infarction (AMI) with prednisone, methotrexate, daunorubicin, vincristine, asparaginase and cyclophosphamide, followed by rescue treatment with idarrubicin and cytarabine. The patient evolved with pancytopenia and presented 12,000 platelets using double antiplatelet therapy (DAPT), with acetylsalicylic acid (ASA) and clopidogrel. Platelet transfusion was performed and DAPT was maintained. However, the patient developed intestinal bleeding one month after the event and decided to discontinue clopidogrel.

DISCUSSION

Approaching acute coronary syndrome in cancer patients is a challenge, especially in thrombocytopenia patients. Current recommendations suggest that ASA may be used in a patient undergoing chemotherapy when the platelet count is > 10,000. DAPT can be safely maintained when the platelet count is above 50,000. Below 30,000 or if there is active bleeding, suspension is recommended. However, in the context of recent ST-elevation myocardial infarction, the risk of stent thrombosis is high and discontinuation of DAPT should be avoided, thus platelet transfusion can be considered. In the case above, DAPT was maintained and platelet transfusion was performed; however, the patient developed bleeding, requiring the suspension of DAPT, maintaining only the ASA.

Pulmonary hypertension associated with dasatinib for chronic myeloid leukemia: Case report

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BACKGROUND

Pulmonary hypertension (PH) is a rare, severe and progressive disease. PH is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). Different drugs have been identified to be causative of PH, which represents only 10.5% of cases. Dasatinib is a multi tyrosine kinase inhibitor approved for therapy of chronic myeloic leukemia (CML). Since it was approved, several papers relate this drug to the development of PH.

CASE

A 58 years old female patient, with a past medical history of arterial hypertension and polycythemia vera, was diagnosed in 2009 with CML. She was treated with Imatinib until 2011, when gastrointestinal toxicity appeared and medication was changed to Dasatinib. On March 2018, she complained of intermittent New York Heart Association functional class III dyspnea during the past 6 months. Chest radiography revealed an increase in cardiac area and pleural effusion. NT pro BNP levels were elevated. The diagnosis of pulmonary thromboembolism was excluded by pulmonary angiography. Transthoracic echocardiogram showed right atrium and right ventricle dilation with pulmonary artery systolic pressure of 63 mmHg. After clinical compensation, the patient was discharged without Dasatinib. Reintroduction of the drug

was performed by Hematology Clinic, with recurrence of dyspnea. Other PH causes were excluded. RHC was performed, PAPm = 39 mmHg was observed, with no response to vasodilation with nitric oxide. dasatinibe was considered the cause of PH and was suspended again. Patient has been asymptomatic after chemotherapy withdrawal.

DISCUSSION

Long-term treatment with Dasatinib may be causative of PH, the true incidence remains elusive and potential mechanism is currently unclear. Potentially though, immune mechanisms are involved because dasatinib-induced PH is often associated with exudative pleural effusions (and even pericardial effusion). Clinical improvement is usually observed after discontinuation of the dasatinib, but pulmonary pressures may never fully normalize. Routine cardiopulmonary evaluation before and during treatment with dasatinib will be needed in patients with clinical manifestations.

Fatal cardiotoxicity associated with immune checkpoint inhibitors

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BACKGROUND

Therapy with immune checkpoint inhibitors (ICI) has been one of the great advances in medicine in the last years, with great outcomes particularly in patients with metastatic melanoma. The increasing use of this therapy has been associated with reports of cardiotoxicity, rare but often severe.[1] Arrhythmias, vasculitis, pericardial disease and myocarditis have been described.[1,2] Myocarditis associated with CTLA-4 and PD-1 inhibitors is more severe and unpredictable than other types of myocarditis, and appears to be more common when there is combination of two agents of ICI therapy.[2,3]

CASE

We report a case of a 61 year old female patient with a history of metastatic melanoma treated with combined therapy of nivolumab and ipilimumab, followed by nivolumab, that presented during treatment with vitiligo and mild colitis and was admitted later due to chest pain. She had mild diabetes and dyslipidemia and no history of previous known cardiac disease. Troponin dosage was elevated at admission, and she was submitted to coronary angiogram that excluded coronary artery disease and coronary abnormalities. She had a prior echocardiogram 3 months before admission with normal global systolic function, with strain GLS 21,7% and MAPSE 1,9. At admission her echocardiogram showed GLS 12,4%, with MAPSE 1,4. She presented multiples episodes of ventricular tachycardia, treated with electric cardioversion, amiodarone, lidocaine, supplementation of magnesium. Investigation showed no signs of acidosis, metabolic disease, thyroid disease or other possible causes of arrhythmias. Cardiac magnetic resonance at the initial

24 h showed no evidence of ischemia or myocarditis. She was treated with high doses of corticoids to induce immune suppression with initial control of arrhythmias and symptoms, but further echocardiograms showed worsening of LV function. After a few days, new episodes of ventricular tachycardia occurred, unresponsive to all measures, leading to cardiac arrest and death.

DISCUSSION

Immune checkpoint inhibition with ipilimumab and nivolumab produces anti tumor responses in patients with metastatic melanoma, but rare ICI cardiac side effects have been reported as more cases of patients using this kind of treatment have emerged.[3,4] Although the full spectrum of cardiovascular disease associated with ICI still needs to be understood, cases similar to the one we report have been described and a better definition for theses complications have been proposed.[4] Patients that use ICI should be evaluated prior and during treatment to assess cardiovascular risk and in case of possible cardiovascular symptoms, troponin and electrocardiogram are easy and cheap tools for initial evaluation and identification of these complications.[3,4] The mechanism is not completely understood and further research and investigation are needed to understand the consequences at short and long time as well as molecular understanding of the action of these medications.

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Vascular toxicity by cisplatin

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INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is a common cause of acute coronary syndrome. It is more common in young patients and women, and may affect patients without traditional risk factors for coronary artery disease. The tendency for greater involvement in women may be associated with high estrogen rates. The increased thrombotic state may also predispose the occurrence.

The presentation, outcomes and management of SCAD have been extensively described in the literature. Nevertheless, long-term angiographic outcomes are still scarce. Few cases of SCAD associated with chemotherapy have been reported so far. We report a case of acute SCAD after cisplatin infusion in one patient with cervical cancer.

CASE PRESENTATION

A 77-year-old woman with malignant cervical cancer who underwent chemotherapy with cisplatin (last infusion 19 days after admission) was admitted to the emergency department with dyspnea on minor exertion 3 days ago. The patient underwent angiography of the pulmonary vessels, which showed acute pulmonary thromboembolism (APT). She was hospitalized for enoxaparin parenteral anticoagulation. One day after hospital admission, the patient developed severe nonspecific abdominal pain. The electrocardiogram performed showed ST-segment elevation of 2 mm in the anterior wall, and was referred for urgent coronary angiography. An 80% lesion was identified in the proximal segment of the anterior descending artery (ADA) and image suggestive of spontaneous dissection in the mid-distal segment of the same coronary artery. Due to the angiographic finding, she underwent angioplasty

of the proximal lesion and mid-distal segment dissection was maintained under clinical treatment.

Transthoracic echocardiography performed after the acute event showed moderate left ventricular systolic dysfunction with an estimated 37% ejection fraction by the Simpson method due to apical aneurysm. After 3 days, the patient presented cardiogenic shock refractory to all therapeutic measures and died.

DISCUSSION

Cisplatin as already known increases the risk of thrombotic events during and a few days after infusion. Some cases associating the occurrence of SCAD with cisplatin have been reported in the literature in patients with testicular cancer. The above patient was admitted with APT, evolving with spontaneous dissection of the ADA. With the elevated thrombotic status caused by cisplatin, the likelihood that APT and acute SCAD were triggered by chemotherapy is increased.

Correlation between patient reported exercise levels and objective assessment of cardio-pulmonary fitness in breast cancer survivors

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INTRODUCTION

Patients receiving cancer therapy are encouraged to exercise during their cancer treatment in order to prevent a decline in functional capacity (VO_{2peak}) often associated with receiving cancer therapies. The Goodin Leisure Exercise -Time questionnaire is an objective way to assess patient reported exercise levels. However, whether this patient reported information translates to objective assessment of VO_{2peak} is unknown.

METHODS

Consecutive women with HER2+ breast cancer who completed treatment with anthracyclines followed by trastuzumab were prospectively asked to complete the Goodin Leisure-Time Exercise Questionnaire within 1 month of trastuzumab completion. This was followed by Cardiopulmonary exercise testing (CPET) on a supine bicycle to determine VO_{2peak}. Associations between the weekly leisure time activity score and VO_{2peak} were determined.

RESULTS

We enrolled a total of 68 women with a mean age of 52.6 $\pm$ 9.8 years. Amongst these patients cardiac risk factors included hypertension (n=6), diabetes (n=1), and prior smoking history (n=16). The mean (SD) Goodin Leisure Exercise Score for the included patients was 31.1 $\pm$ 25.1. When patient reported exercise was compared to their VO_{2peak}, no correlation was identified (Figure 1, r =0.041). The patients were then divided into two groups based on the median VO_{2peak} in the cohort of 18.8mL.kg^{-1}min^{-1}. Patients with VO_{2peak} less than 18.8 mL.kg^{-1}min^{-1} (n=33) had a weekly leisure time activity

score of 30.5 ± 27.4 (VO_{2peak} mean 15.4 ± 2.4mL.kg^{-1}min^{-1}). Whereas, patients with VO_{2peak} above median (n= 35, mean VO_{2peak} 23.5 ± 4.5 mL.kg^{-1}min^{-1}) had an activity score of 31.8 ± 23.1 (p=0.46) (Figure 1).

CONCLUSION

Our data suggests that a significant proportion of women have low cardiopulmonary fitness based on VO_{2peak} at the completion of cancer therapy. However, this objective measure was not associated with patient reported exercise levels. Given the prognostic importance of cardiopulmonary fitness in cancer survivors, patient reported exercise levels alone may be insufficient to determine the need for cardiac rehabilitation. Objective assessment of cardiopulmonary fitness should be sought whenever possible.

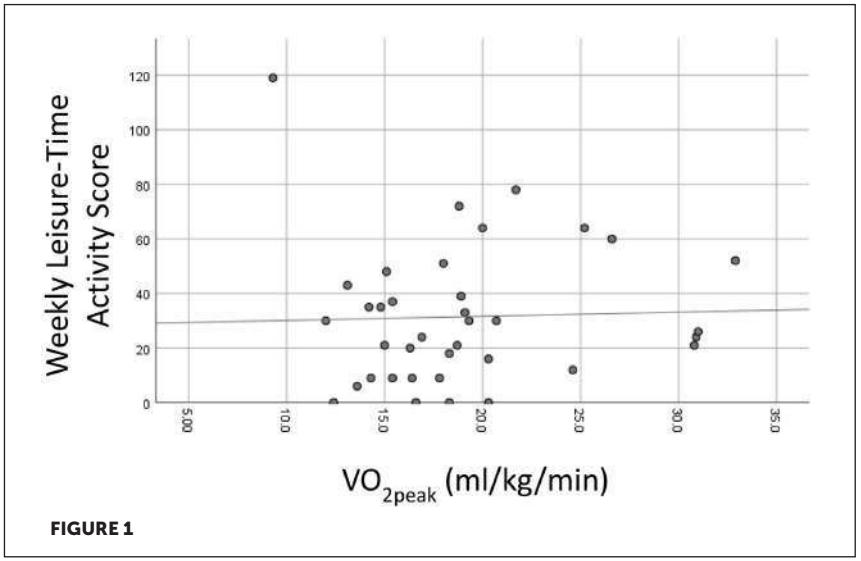

FIGURE 1

Case report

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BACKGROUND

Immune checkpoint inhibitors (ICI) encompass a new class of anti-cancer therapy that has the potential to cause cardiotoxicity. This side effect has been related to myocardial PD-1 inhibition, leading to T cell-mediated inflammatory infiltrate, causing ventricular dilatation and systolic dysfunction. Although rare, ICI-related cardiotoxicity can be fatal. Herein we report a case of an anti-PD-1-related myocarditis.

CASE

An 83 year-old female patient with previous history of hypertension, dyslipidemia, hypothyroidism and subclinical coronary artery disease, was admitted to our hospital with acute onset symptoms of heart failure. Symptoms have appeared ten days after completing seven cycles of pembrolizumab for metastatic breast cancer. Upon admission, BNP level was 1310 pg/mL and an echocardiogram showed mild left ventricular dysfunction and severe restrictive diastolic dysfunction, which were absent in her previous exam from nine months earlier. Although institution of optimized heart failure treatment, the patient remained oxygen dependent and at NYHA functional class III; drug related cardiotoxicity was suspected. A cardiac magnetic resonance was performed which showed signs of myocarditis, later confirmed by endomyocardial biopsy (giant cell myocarditis). Immunosuppressive treatment with prednisone and cyclosporine was instituted, leading to excellent clinical response. However, less than three months after hospital discharge, the patient presented progression of the neoplastic disease resulting in death.

DISCUSSION

Although ICI-related cardiotoxicity is considered rare, the present case exemplifies the severity of myocardial aggression seen in some patients. Among the immune-mediated side effects, myocarditis presents the highest fatality rate.

Cancer sensitizes cardiovascular tissue to chemotherapy-related toxicities

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Due to advances in diagnosis and design of new cancer drugs, it is expected by the year 2024, about a 20 million population of cancer survivors in the United States alone. This is a remarkable milestone, but that success comes with serious adverse side effects, mainly in the cardiovascular system. Therefore, relevant translational models are needed to develop new therapies to prevent the onset of chronic cardiovascular diseases in patients. Our data shows that mice bearing breast cancer tumors have exacerbated cardiac dysfunction when compared to non-tumor bearing mice after Doxorubicin (DOX) treatment. We observed an average decline in ejection fraction of tumor-bearing mice treated with DOX of 28.7% (SD=7.8) and was which was statistically different from no decline ($p=0.02$) this compared to a decline of only 15.7% (SD=11.3) that was not significantly different from ($p=0.14$). Moreover, in wild type non-tumor bearing mice treated with DOX fractional shortening, cardiac output and stroke volume did not change from baseline after 4 weeks post DOX treatment. On the other hand, in tumor bearing mice these parameters were significantly reduced when compared to baseline, suggesting that the presence of the tumor potentially sensitizes the heart damage by chemotherapy. In vitro studies in cardiac myoblasts shows that cells are more to sensitive to death by DOX treatment when incubated with conditioned media from cancer cells compared to regular media. These, results were observed with other chemotherapies including, platinum compounds, pemetrexed and taxol, suggesting that the observed effects are not limited to anthracyclines. Overall, our data shows that, the presence of the tumor may exacerbate the cytotoxic effects of cancer therapies in the heart, indicating that this should be considered in the design of therapeutic regimens of cancer patients as well as the design of preclinical models to study mechanisms of chemotherapy related cardiotoxicity.

Changes in health-related quality of life in women receiving breast cancer therapy followed in a cardio-oncology program

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INTRODUCTION

Women receiving breast cancer treatment followed in Cardio-oncology clinics often report changes to health-related quality of life (QOL). However, the timing of these changes and its relation to development of cardiotoxicity are undefined. We sought to use common measures of health-related QOL such as EQ5D questionnaire and Minnesota Living with Heart Failure Questionnaire [MLHFQ] to define the temporal changes in women receiving breast cancer therapy.

METHODS

We prospectively enrolled 69 women with early stage HER2+ breast cancer followed within the Cardio-oncology program at the Peter Munk Cardiac Center. All patients completed both the EQ5D and the MLHFQ before treatment initiation, pre-herceptin and every 3 months thereafter. All patients were followed for the development of cardiotoxicity based on CREC criteria. ANOVA and post-hoc analyses were used to determine changes over time.

RESULTS

Women were on average 51.7 $\pm$ 9.8 years of age. Compared to baseline (16.2 $\pm$ 17.5) there was a significant increase in MLHFQ scores (worsening QOL)

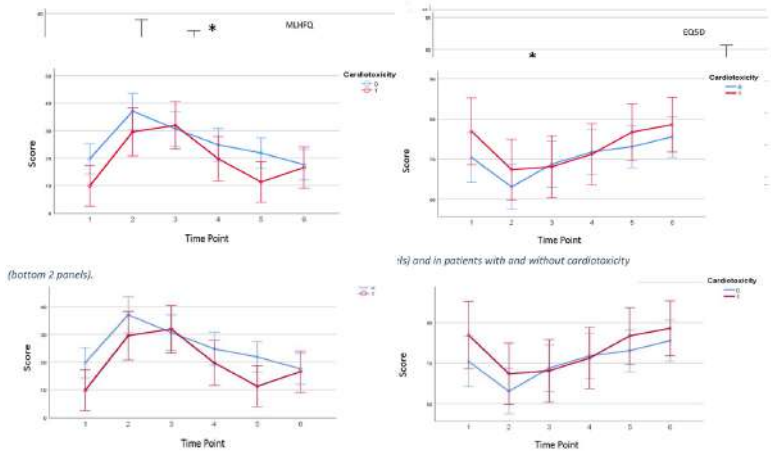

FIGURE 1: Longitudinal EQ5D and MLHFQ scores in the overall population (top 2 panels) and in patients with and without cardiotoxicity (bottom 2 panels).

post anthracycline (34.4 $\pm$ 20.2) that remain reduced until 6 months into trastuzumab therapy ($p<0.0125$, Figure 1). Both emotional and physical subdimensions were equally affected (Table 1). Similarly, EQ5D scores decreased immediately post anthracycline (Figure 1) and returned to baseline at 6 months into trastuzumab therapy. All dimensions of the EQ5D score followed similar trend except for anxiety, which was the highest pre-initiation of cancer therapy (Table 1). There was no difference in the changes in MLHFQ or EQ5D in patients with and without cardiotoxicity.

CONCLUSION

Women with breast cancer receiving treatment experience deterioration in QOL early during cancer therapy. Interventions to mitigate these deteriorations are likely to be most relevant early during treatment. The fact that MLHFQ and EQ5D scores were not different in those with and without cardiotoxicity reinforces the challenges in using patient reported measures alone to monitor for cardiotoxicity.

Table 1

	MLHFQ (n=59)			EQ5D (n=59)					
	Total Score	Emotion Sub-scale	Physical Sub-scale	EQ5D Total Score	Mobility	Self-care	Pain	Anxiety	Daily Activities
Baseline	16.2 ± 17.5	6.4 ± 6.4	4.7 ±7 .2	72.7 ± 19.1	1.1 ± 0.3	1.0 ± 0.2	1.4 ± .53	1.6 ± 0.6	1.3 ± 0.6
Pre-Herceptin	34.4 ± 20.2	8.3 ± 5.4	15.6 ± 6.9	64.6 ± 17.2	1.3 ± 0.5	1.1 ± 0.3	1.4 ± .50	1.5 ± 0.5	1.5 ± 0.5
3 months	31.1 ± 19.5	6.7 ± 5.0	15.4 ± 9.7	68.5± 17.5	1.2 ± 0.4	1.1 ± 0.3	1.6 ± .50	1.5 ± 0.5	1.6 ± 0.6
6 months	23 ± 18.5	6.0 ± 5.6	10.0 ± 8.8	71.6 ± 17.2	1.2 ± 0.4	1.1 ± 0.2	1.5 ± .50	1.4 ± 0.5	1.4 ± 0.5
9 months	18.1 ± 17.4	4.5 ± 5.0	8.1 ± 8.1	74.4 ± 16	1.1 ± .0.3	1.0 ± 0.0	1.4 ± .50	1.3 ± 0.5	1.3 ± 0.5
Post-Herceptin	17.2 ± 17.0	4.3 ± 4.8	9.2 ± 9.4	76.6 ± 15.5	1.2 ± 0.4	1.0 ± 0.1	1.4 ± .50	1.3 ± 0.5	1.3 ± 0.5
ANOVA p	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

Baseline Cardiovascular (CV) and metabolic risk in treatment-naive Patients (Pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) starting Tyrosine Kinase Inhibitor (TKI) therapy in a real-world setting

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BACKGROUND

TKIs have significantly improved long-term outcomes in pts with CML-CP. However, TKI exposure may enhance development or worsen underlying comorbidities such as CV/metabolic complications. A comprehensive assessment of baseline comorbidities may inform physicians of pts' clinical status, risk, and facilitate treatment decisions.

METHODS

CA180-653 is an ongoing, non-interventional, prospective US study characterizing the impact of first-line dasatinib (DAS), imatinib (IM), and nilotinib (NIL) on CV and metabolic risk factors in pts with CML-CP. CV/metabolic assessments were reported every 3 mo. Descriptive analysis was performed.

RESULTS

Of 68 pts enrolled at data cutoff (June 2019), 30, 27, and 11 pts were treated with DAS, IM, and NIL, respectively. Mean age was 56 yrs and 84% had an ECOG PS of 0–1. At baseline, 35 (51%) pts were noted to have pre-study CV/metabolic conditions, most commonly hypertension (24/35; 69%) and hyperlipidemia (19/35; 54%). Coronary artery calcification was present in 31% of pts (Table 1), but did not affect left ventricular ejection fraction.

Table 1: Baseline CV/metabolic characteristics[a]

	DAS (n = 30)	IM (n = 27)	NIL (n = 11)	All (N = 68)
Cardiac CT scan performed	26 (87)	24 (89)	11 (100)	61 (90)
Coronary artery calcification present	5 (19)	8 (33)	6 (55)	19 (31)
Pericardial effusion[b]				
Normal	17 (65)	15 (63)	6 (55)	38 (62)
Abnormal, NCS	6 (23)	6 (25)	1 (9)	13 (21)
EKG performed[b]	24 (80)	24 (89)	6 (55)	54 (79)
Normal	17 (71)	15 (63)	4 (67)	36 (67)
Abnormal, NCS	7 (29)	9 (38)	2 (33)	18 (33)
HbA_{1c} evaluated	11 (37)	11 (41)	3 (27)	25 (37)
Mean (SD) HbA_{1c}	6.4 (0.9)	6.5 (1.5)	5.9 (0.2)	6.4 (1.9)

[a]Data are n (%) unless otherwise noted.
[b]No abnormal, CS results reported.

The majority of pts (36/54; 67%) had a normal electrocardiogram (EKG), 18 (33%) pts had an abnormal but non-clinically significant (NCS) finding. Follow-up analyses are ongoing.

CONCLUSIONS

Preliminary findings suggest that pts with CML-CP in a real-world setting carry significant CV risk at baseline and highlight the need to consider baseline CV risk factors when selecting appropriate TKIs.

Suboptimal use of cardioprotective drugs in patients with a history of cancer

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INTRODUCTION

Success of modern cancer therapy leads to a decline in death rates for cancer patients. Cardiovascular disease (CVD) is now a leading cause of long-term morbidity and mortality among cancer survivors. There is increasing need to be more vigilant in the use of cardioprotective therapies for primary and secondary prevention of cardiovascular diseases in patients living with cancer. This study aims to examine the use of cardioprotective therapies in patients with or without previous history of cancer admitted to cardiology.

METHODS AND RESULTS

Patients (n=333, mean age: 65$\pm$13 yrs) who were admitted to cardiology unit at John Hunter Hospital for either acute or chronic CVD from July to November 2018. N=76 (23%) of patients had a history of cancer (Hx Ca) as documented in case notes at the time of admission. There was no difference in the prevalence of cardiac ischemia, hypertension, dyslipidemia, diabetes, or heart failure, but significantly higher atrial fibrillation in patients with Hx Ca (26%) vs. those without (16%). There was under-use of cardiovascular medications in patients with Hx Ca vs those without: antiplatelets (53% vs. 73%, $p<0.01$); β-blockers (61% vs 70%, $p=0.17$), ACEi/ARB (50% vs 61%, $p=0.1$), and statins (59% vs 78%, $p<0.01$). On multivariate analysis, patients with Hx of Ca had significantly lower usage of statins adjusted for age, BMI, gender, and cardiovascular risk factors.

CONCLUSIONS

Cardioprotective therapies appear to be under-utilised in patients with previous history of cancer with comparable CV risk factors. Strategies are required to increase cardioprotective pharmacotherapies in these patients.

T1 mapping and myocardium strain evaluated through tissue tracking in patients with lymphoma treated with anthracyclines

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BACKGROUND

Lymphoma treated with anthracyclines have survival rates of 86% at 5 years. However, cardiac toxicity of these drugs is common and usually leads to advanced heart failure. Current strategies for early detection of cardiotoxicity during chemotherapy are not yet fully established.

METHODS

From June 2017 to March 2019, patients with lymphoma planned to start chemotherapy with anthracyclines were evaluated by a cardiologist to check the eligibility criteria. At baseline (Time 1), at the end of 3° cycle (Time 2) and 30 days after the final cycle (Time 3), patients were evaluated through cardiac biomarkers, electrocardiogram and cardiac magnetic resonance (CMR). Strain, MapT1 and extracellular volume (ECV) were evaluated in all patients. Cardiotoxicity was defined as drop of the left ventricular fraction (LVEF) > 10% or LVEF decrease below 50%. A p value < 0.05 was considered statistically significant. We report here the MR parameters.

RESULTS

We included 48 patients, mean age was 45.32 (± 17.84) years-old and 25 (52.1%) were female. The prevalence of hypertension, diabetes and dyslipidemia was 18.8%, 10.4% and 10.4%, respectively. Cardiotoxicity was diagnosed in 13 patients (27%). At baseline, there was no difference between cardiotoxicity group (CT) and no cardiotoxicity group (nCT) in CMR diastolic volume, systolic volume, nativeT1 mapping and global longitudinal strain (GLS), respectively (116 [103.6 – 138.1] ml vs 136.3 [115.7-173.8], p= 0.069), (46 [38.0 – 58.5] ml vs 63.0 [44.5 – 74.2,p=0.069), (1540.6 [1478.3 – 1591.1] ms vs 1514.8 [1487.5 – 1786.3] ms, p= 0.568) and (-15.94 ± 2.91% vs -14.84 ± 2.65 %, p= 0.243). Regarding the others CMR parameters, we showed that comparing CT patients with nCT patients at Time 3, diastolic volumes were similar (127 [114.8 – 144.6] ml vs 152.0 [115.9 – 196.4]ml, p=0.256), systolic volumes were higher (54.8 [45.0 – 67.0] ml vs 78.51 [53.9 – 96.3] ml, p=0.007), right ejection fraction was lower (53.41 ± 9.73% vs 46.29 ± 3.93%, p=0.002), left ejection fraction was lower (58.7 ± 5.69% vs 46.67 ± 8.12%, p < 0.001) and GLS and radial strain were also reduced (-13.92 ± 1.76% vs -12.44 ± 2.7%, p=0.043) and (22.9 [21.18 – 27.43]% vs 19.84 [17.12 – 21.73], p=0.017), respectively. The global circumferential strain at Time 3 was similar between the two groups (-15.1 ± 1.98% vs -13.64 ± 3.36%; p=0.097). We did not observe any difference between groups in the native T1 mapping did between groups at Time 2 and 3 1537.75 (1493.76 – 1589.72) ms vs 1601.99 (1501.12 – 1673.44) ms (p 0.383) and 1538.43 (1479.03 – 1633.6) ms and 1612.85 (1522.74 – 1638.34) ms (p=0.289). Similarly, when we analyzed the ECV values there was no difference between groups at Time 2 and 3 (25.17 [23.62 – 32.83]% vs 24.42 [22.75 – 27.47], p=0.281 and 27.5 [23.59 - 31,9]% vs 27.2 [23.84 – 28.47]%, p=0.529, respectively).

CONCLUSIONS

Cardiotoxicity is a frequent complication in anthracycline treated patients, usually diagnosed after 1 year of therapy. CMR evaluation, through analysis of volumes, ejection fraction and strain might early identify these patients, aiming to initiate preventive strategies to prevent heart failure.

Adjuvant treatment with 5-FU and oxaliplatin does not affect neurovascular control, cardiac function and physical capacity in patients with colon cancer

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BACKGROUND

Adjuvant chemotherapy with fluorouracil (5-FU) and oxaliplatin increases recurrence-free and overall survival in patients with stage II-III colon adenocarcinoma, but these agents have been associated with neuro- and cardio-toxicity. We investigated the effects of adjuvant treatment with 5-FU +/- oxaliplatin on neurovascular control, cardiac function and physical capacity in patients with colon cancer.

METHODS

Twenty-nine patients with prior colectomy for stage II-III adenocarcinoma and with clinical indication for adjuvant chemotherapy were accrued: 5-FU alone (5-FU 370 mg/m^2 + leucovorin 50 mg/m^2 weekly for 30 consecutive weeks; n= 12) or 5-FU+oxaliplatin (5-FU 500 mg/m^2 + leucovorin 20 mg/m^2 weeks 1-6 and oxaliplatin 85 mg/m^2 on weeks 1, 3 and 5 every 8 weeks for 3 cycles; n= 17). Muscle sympathetic nerve activity (MSNA) was directly recorded by microneurography, muscle blood flow (FBF) by venous occlusion plethysmography and endothelial function by flow-mediated dilation (FMD). Cardiac function was assessed by echocardiography and speckle-tracking, cardiac autonomic control by heart rate variability (HRV) and physical

capacity by cardiopulmonary exercise test. These evaluations were performed before the beginning and after the chemotherapy period.

RESULTS

MSNA was not changed by 5-FU and 5-FU+oxaliplatin (34 ± 3 vs. 31 ± 2 bursts/min and 33 ± 2 vs. 32 ± 2 bursts/min, respectively, P interaction = 0.55). FBF and FMD were unchanged in both groups. 5-FU and 5-FU+oxaliplatin did not cause no changes in left ventricular ejection fraction (57 ± 2 vs. 53 ± 3% and 58 ± 1 vs. 57 ± 2%, respectively, P interaction = 0.49) and longitudinal strain (-19 ± 1 vs. -18 ± 1% and -18 ± 1 vs. -19 ± 1%, respectively, P interaction = 0.28). HRV was unchanged between groups. In addition, no changes were observed in peak oxygen uptake after 5-FU and 5-FU+oxaliplatin (19 ± 1 vs. 20 ± 1 mL/kg/min and 21 ± 1 vs. 19 ± 1 mL/kg/min, respectively, P interaction = 0.16).

CONCLUSION

This study provides for the first time evidence that the adjuvant treatment with 5-FU and 5-FU+oxaliplatin does not alter the neurovascular control, cardiac function and functional capacity in patients with colon adenocarcinoma.

Circulating progenitor cells and cardiovascular outcomes in breast cancer patients treated with antrhacyclines

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INTRODUCTION

Doxorubicin (DOX) is an antineoplastic agents with significant cardiotoxic potential. Detection of cardiotoxicity based on left ventricular ejection fraction (LVEF) reflects a late adaptation to cardiac damage. Changes in the frequency of circulating progenitor cells (CPCs) have been reported to be associated with acute myocardial damages. Thus, it may also predict or early detect cardiac toxicity induced by chemotherapy regimens.

OBJECTIVE

To investigate the association between changes is CPCs frequency and incidence of cardiovascular outcomes in breast cancer patients treated with DOX and/or TZB.

METHODS

Prospective cohort. Women diagnosed with breast cancer, which received indication of DOX-based chemotherapy regimens. Patients underwent cardiologic evaluation by echocardiography and serum cardiac troponin T measurements. They were also tested for individual DNA repair capacity by comet assay and quantification of CPCs by flow cytometry. Time points for assessments were as follows: baseline and immediately after the first and fourth cycle of DOX (pre-C2 and post-C4, respectively).

RESULTS

So far, 14 patients were included (43% luminal B subtype; mean age: 52 $\pm$ 11 years; BMI 28.85 $\pm$ 8.5 kg/m^2). Baseline mean troponin T levels were 7.10 $\pm$ 4.7 pg/mL and it increased to 36.9 $\pm$ 14.1 pg/mL after 4 cycles of DOX ($p<0.05$). LVEF was preserved throughout DOX cycles (Baseline: 66.6 $\pm$ 6.3%; Pre-C2: 65.1 $\pm$ 7.4%; Post-C4: 62 $\pm$ 8.5%). The same was found for global longitudinal strain (GLS) after the first cycle of DOX (baseline: -21.4%; Pre-C2: -25.7; $p=0.19$). Only two patients were assessed for CPCs quantification at baseline (mesenchymal progenitor cells: 57 $\pm$ 16 cells/million; endothelial progenitor cells: 47 $\pm$ 45 cells/million; hematopoietic stem cells: 729 $\pm$ 474 cells/million). DNA repair capacity showed impairment along accumulation of DOX treatment. No cardiovascular event was reported during observation period.

CONCLUSION

Despite of LVEF preservation in both assessed timepoints, GLS was slightly reduced after 1 cycle of DOX and Troponin T levels were increases after the fourth cycle of DOX. Moreover, DNA repair capacity decreased over cycles. Thus, these preliminary results may indicate that LVEF does not translate early DOX impairment of cardiac function. However, it may be indicated by alterations in Troponin T, GLS and DNA repair capacity collectively.

Keywords: cardiotoxicity, breast cancer, circulating progenitor cells, DNA repair capacity

Effect of renin-angiotensin system modulation and DNA repair on doxorrubicin toxicity in murine cardiomioblasts

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INTRODUCTION

Doxorubicin (DOX) is one of the most commonly used antineoplastic agents, and the induction of double DNA breaks is one of the main mechanisms implicated in its cytotoxicity. However, use of DOX is limited by the risk of cardiotoxicity. DOX also induces DNA damage to cardiomyocytes, thus activating the enzyme poly (ADP-ribose) polymerase-1 (PARP1). Overactivation results in depletion of cell energy stores, leading to cell death. Currently, the main cardioprotective strategies involve pharmacological modulation of the Renin-Angiotensin System (RAS), but still unable to prevent cardiotoxicity. Thus, pharmacological inhibition of PARP1 may be an alternative in this context.

OBJECTIVE

To compare the protective potential of a Mas receptor (MasR) agonist (Ang-(1–7)), an AT1 receptor antagonist (AT1R) (Losartan) and a PARP1 inhibitor (DPQ) on the induction of DNA damage and DOX-mediated cytotoxicity in rat cardiomioblasts.

METHODS

Rat cardiomioblasts (H9c2) were treated with DOX (0.1 and 1 μM) in the presence or absence of 100nM Ang-(1-7), 100 μM Losartan and/or 10μM

DPQ for 24h. Cell viability (Sulforodamine B), induction of DNA breaks (Comet Assay) and apoptosis induction (Annexin V-PE/7AAD and Flow Cytometry) were evaluated. At least three independent experiments were performed and compared by analysis of variance ANOVA. Differences with p values <0.05 were considered significant.

RESULTS

Viability assay showed that inhibition of AT1R protects cardiomyoblasts from DOX toxicity at concentrations up to 0.25 μM. Inhibition of PARP1 led to a decrease in DOX-induced DNA breaks at a concentration of 0.1 μM. The 24-hours co-treatments with 0.1 μM DOX in the presence of Ang-(1-7) as well as the combined incubation with Ang-(1-7) and Losartan led to a reduction in apoptotic cell frequency. However, this effect was not achieved with treatment at 1 μM DOX concentration. Co-treatment with DPQ also showed a protective effect on the lower DOX concentration, while on the higher concentration an increased necrotic cell frequency was detected.

CONCLUSIONS

Our results suggest the cardioprotective effect of the three suggested approaches. However, these effects are observed only in combinations with the therapeutic concentrations of DOX, reinforcing the importance of the cumulative dose of DOX in the induction of cardiotoxicity.

Keywords: cardiotoxicity, doxorubicin, renin-angiotensin system

Influence of aerobic exercise on DNA repair capacity in rats with doxorubicin-induced cardiotoxicity

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INTRODUCTION

Anthracyclines, such as Doxorubicin (DOX), are the core treatment of several chemotherapy regimens for solid and hematological malignances. However, its application is limited by the risk of cardiotoxicity. Severity of DOX-mediated cytotoxicity in both neoplastic cells and cardiomyocytes depends on DNA repair capacity to process base oxidation and DNA strand breaks. The practice of aerobic exercise is associated with increase of DNA repair capacity and antioxidant responses, which may counteract the deleterious effects of DOX in cardiomyocytes.

OBJECTIVE

To evaluate the effect of preventive aerobic exercise on DNA damage repair capacity in peripheral blood mononuclear cells in rats with DOX-induced cardiomyopathy.

METHODS

Experimental study. 64 male Wistar Kyoto rats were divided into four groups (C= sedentary control; D= sedentary DOX; CT= trained control; DT= trained DOX).

D and DT received 4mg/kg of DOX weekly during 4 weeks. CT and DT performed effort exercise testing and treadmill aerobic training (4 days/week for 4 weeks) before treatment with DOX or saline. Cardiac function was assessed by echocardiography. DNA repair capacity was evaluated by Comet Assay in peripheral mononuclear blood cells treated in vitro with tert-butyl hydroperoxide and allowed to recover for 1 or 2 hours in the absence of the oxidizing agent. Blood count and myelogram were performed for toxicity evaluation. Results were analyzed by two-way ANOVA and differences with $p<0.05$ were considered significant.

RESULTS

DOX-induced cardiomyopathy was achieved after a cumulative dose of 16 mg/km of DOX, verified by the reduction of the left ventricular ejection fraction (C: XX%; D: XX%. P=xxx). DOX group presented regenerative anemia, leukopenia and toxic granulation in neutrophils. Myelogram also showed toxicity, which was characterized by vacuolization, cytoplasmic basophilia and changes in cell morphology. In vitro treatment of mononuclear blood cells with the oxidizing agent led to the formation of DNA breaks. During the first two hours of repair, reduction of damaged DNA was greater in both CT and DT groups.

CONCLUSION

Preventive aerobic exercise increased DNA repair capacity regardless of DOX treatment, which may result in a long-term cardio protective effect.

Keywords: cardiotoxicity, aerobic exercise, DNA repair capacity

Modulatory effects of mas receptor/ angiotensin-(1-7) axis in an in vitro model of doxorubicin-induced cardiotoxicity

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INTRODUCTION

Pharmacological blockage of Angiotensin II (Ang II) actions is the main approach to the management of doxorubicin (DOX)-induced cardiotoxicity. However, cardioprotective effects of this intervention are also mediated by the activation of the counter-regulatory axis, which includes Ang-(1-7), and Alamandine (Ala) peptides and their receptors, MasR and MrgD. Thus, activation of MasR/Ang-(1-7) axis may be a potential strategy in the context of cardiotoxicity.

OBJECTIVE

To evaluate the effect of pharmacological modulation of MasR and MrgD on DOX-induced cardiotoxicity *in vitro*.

METHODS

Murine cardiomyoblasts (H9c2) were exposed (30') to a MasR antagonist (A779, 10 μM) followed by their agonist (Ang-(1-7), 100 nM) or the MrgD agonist (Ala (100 nM) prior to 24h treatment with DOX (0.1 μM and IC_{50}: 0.35 μM). Cell viability (Neutral Red and Trypan Blue), cell death profile (Annexin/7AAD),

DNA damage induction (Comet Assay) and mitochondrial membrane integrity (Rhodamine 123) were evaluated. The experiments were performed in triplicate, and data were analyzed by ANOVA, considering $p < 0.05$.

RESULTS

Both isolated agonism and antagonism of MasR, increased cell proliferation in comparison to controls (A779: 116.8 ± 9.8%; Ang-(1-7): 117.0 ± 8.5%, $p<0.05$; Ala: 110 ± 10%). However, prior MasR modulation to DOX treatment did not prevent DOX-induced deleterious effects in cell viability and cell death profile. DNA strand breaks were induced by DOX in both concentrations (C: 27.5 ± 13.4; DOX 0.1 μM: 53.5 ± 9.1; DOX IC_{50}: 109.5 ± 17.6 U.A.). Pre-treatment with Ang-(1-7) or A779 attenuated the generation of DNA strand breaks induced by DOX (DOX 0.1 μM + Ang-(1-7): 36.5 ± 6.3; DOX 0.1 μM +A779: 36.5 ± 0.7 U.A.). DOX-induced loss of mitochondrial membrane integrity was prevented by previous treatment with all peptides if alone, but not in combination.

CONCLUSION

Selective modulation of MasR or MrgD (agonism or antagonism) attenuated DNA damage and loss of mitochondrial membrane integrity induced by lower concentration of DOX. These effects seem to be independent on MasR activation by Ang-(1-7), suggesting a possible crosstalk among other renin-angiotensin receptors, including MrgD.

Keywords: cardiotoxicity, doxorubicin, angiotensin-(1-7)

Effect of aerobic exercise on cardiac and sympathovagal functions in rats with doxorubicin-induced acute cardiotoxicity

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INTRODUCTION

The efficacy of doxorubicin (DOX) cancer treatment may be compromised by its potential cardiac toxicity. Sympathovagal alterations, which may occur prior to functional cardiac impairments, are influenced by cardioprotective strategies, such as exercise. However, it was not explored in the context of DOX-induced cardiotoxicity.

OBJECTIVE

To evaluate the effect of preventive exercise on cardiac and sympathovagal function in rats with DOX-induced acute heart failure.

METHODS

Experimental study with male Wistar Kyoto rats. The animals were divided into four groups (C=sedentary control; D=sedentary DOX; CT=trained control; DT=trained DOX). DT and CT groups performed treadmill aerobic training 4 days/week for 4 weeks before receiving 4 mg/kg DOX or saline for 4 weeks;

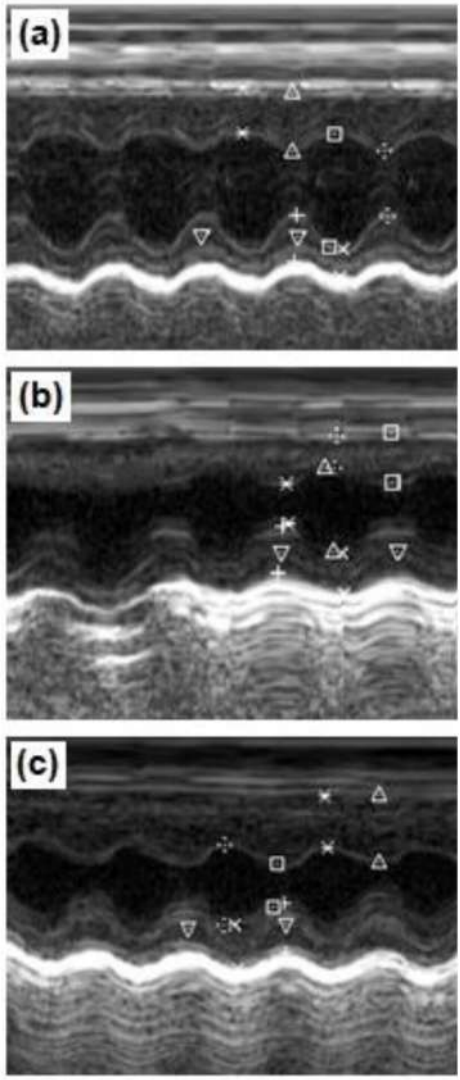

FIGURE 1: (**A**) Final electrocardiograms (M-mode) of Control, (**B**) Doxorubicin and (**C**) Trained Doxorubicin groups.

groups D and C were sedentary until receiving DOX or saline. At the end, we evaluated: cardiac function by echocardiography; blood pressure and sympathovagal modulation by artery-femoral registration. Results were analyzed by one-way ANOVA and differences with $p<0.05$ considered significant.

RESULTS

DOX induced reduction in left ventricular ejection fraction (D: 63 $\pm$ 4 vs. C: 73 $\pm$ 4 %, p=0.04), cardiac output (D: 32 $\pm$ 9 vs. C: 56 $\pm$ 14 mL/min, p=0.001) and systolic (D: 96 $\pm$ 5 vs. C: 128 $\pm$ 6 mmHg, p=0.02) and diastolic (D: 68 $\pm$ 5 vs. C: 85 $\pm$ 2 mmHg, p=0.02) blood pressures; increased heart rate (C: 370 $\pm$ 32 vs. D: 553 $\pm$ 0.5 bpm, p=0.03) and exacerbated parasympathetic predominance (LF/HF, C: 0.30 $\pm$ 0.006 vs. D: 0,11 $\pm$ 0.010, p=0.0006). Physical exercise preserved diastolic blood pressure (D vs. DT: 92 $\pm$ 8 mmHg, p=0.003), diastolic area (D: 0.25 $\pm$ 0.04 vs. DT: 0.31 $\pm$ 0.04 cm^2, p=0.007) and diastolic diameter (D: 0.49 $\pm$ 0.05 vs. DT: 0.55 $\pm$ 0.06 cm, p=0.04) in DOX treated animals.

CONCLUSION

The cumulative dose of 16 mg/kg DOX at the end of 4 weeks induced systolic heart failure and sympathovagal alteration. However, except for acute diastolic functions, preventive aerobic exercise was not able to prevent DOX-induced cardiotoxicity.

Keywords: doxorubicin, physical exercise, heart failure

Effect of preventive cell therapy on doxorubicin-induced cardiomyopathy

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INTRODUCTION

Mesenchymal Stromal Cells (MSC) therapy for doxorubicin (DOX)-induced cardiomyopathy is still on debate. Since myocardial regeneration does not involve differentiation of MSC into cardiomyocytes but its paracrine effects, whether preventive administration of MSC have clinical application for DOX cardiomyopathy remain to be elucidated.

OBJECTIVE

To evaluate the effect of preventive MSC therapy on DOX-induced cardiomyopathy and DOX toxicity on the hematological and stromal compartment.

METHODS

Experimental arm: 60 Wistar-Kyoto male rats were allocated into four groups: C (saline solution), DOX, DOX+MSC and DOX+V (4 mg/kg of DOX weekly for 4 weeks). DOX+MSC and DOX+V received intramyocardial adipose-derived MSC ($2x10^5$ cells) and saline, respectively, after second dose of DOX. MSC was isolated from adipose tissue of Lewis eGFP for cell therapy. Cardiac function (Echocardiogram). In vitro arm: After euthanasia of C and DOX groups, MSC

were isolated from heart and assessed for DNA repair capacity (Comet Assay), adhesion capacity, clonogenic survival and growth kinetics.

RESULTS

MSC therapy did not impede DOX impairment on left ventricular ejection fraction (LVEF) (DOX: 61 ± 8%, n=10; DOX+MSC: 73 ± 4.4%, n=7) and cardiac output (CO) (DOX: 38 ± 8 mL/min; DOX+MSC: 62 ± 8 mL/min; $p<0.05$). Adhesion capacity of heart-derived MSC was not affected by systemic DOX treatment, but it did impair clonogenic potential (DOX: 22.5 ± 0.7 % of control; $p<0.02$). Oxidizing agent-induced DNA damage in C and DOX heart-derived MSC equally decreased after longer periods of recovery (C 1 hour: 258.5 ± 6.4 *vs.* C 6 hours: 153 ± 22.6; DOX 1 hour: 244.5 ± 17.7 *vs.* DOX 6 hours: 166.5 ± 16.26).

CONCLUSION

DOX-induced heart failure was not prevented nor attenuated by preventive MSC therapy. Clonogenic survival of heart-derived MSC from systemic treated-DOX animals was decreased, but adhesion and DNA repair capacities were preserved. It suggests that mechanisms of DOX-induced cardiomyopathy may include impairment of resident MSC pool and settlement newly injected MSC.

Keywords: cardiotoxicity, doxorubicin, cell therapy

Antineoplastic and cardioprotective effects of renin-angiotensin receptors in breast cancer

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INTRODUCTION

Oncological effectiveness of doxorubicin (DOX) in breast cancer (BC) treatment is limited by the risk of cardiotoxicity. Clinical management of DOX-induced cardiomyopathy includes pharmacological modulation of Renin Angiotensin System (RAS). However, Pleiotropic effects of RAS are mediated by its receptors, AT_1R, AT_2R, MasR and Mrgd and occur beyond cardiovascular system, including neoplastic cells. Alterations in these receptors are associated with phenotypes of aggressiveness and response to chemotherapy, and may be influenced by systemic RAS pharmacological modulation of DOX-induced cardiomyopathy.

OBJECTIVES

To evaluate the influence of RAS receptors in DOX-induced cytotoxicity and cardiotoxicity *in vitro* and in clinical outcomes of patients with breast cancer.

METHODS

BC cell lines (MCF-7 and MDA-MB-231) and murine cardiomyoblasts (H9c2) were treated with DOX and an agonist (Angiotensin-(1-7)) and/or antagonist (A779) of MasR for 24h or 48h. Cell viability (MTT or SRB), cell death profile (Anexin V/7AAD – flow cytometry) and DNA damage induction were accessed. Additionally, gene expression of RAS receptors in invasive breast cancer

tumors was obtained from GDC TCGA BRCA dataset and its prognostic value was evaluated.

RESULTS

Selective stimulation of MasR reduced cell viability of luminal A BC (MCF-7) without, however change cell viability of triple negative BC (MDA-MB-231) cell type. Both Angiotensin 1-7 and A779 isolated induced DNA damage in luminal A BC cells, which was not repaired after the recovery period. Nevertheless, MasR modulation did not change toxicity and cell death parameters induced by DOX in cardiomyoblasts. 1217 cases of invasive breast carcinoma were included for survival analysis. After adjustments for age and staging, Cox Regression demonstrated that overexpression of *MAS1* (HR: 1.492; IC95%:1.096 - 2.031; p=0.011) and *MRGPDR* were associated with poor overall survival (HR: 1.373; IC95%:1.026 - 1.839, p=0.033). Patients whose tumours presented concomitant overexpression of all four SRA evaluated genes also presented poor prognosis in comparison to those with none of SRA genes overexpressed (HR: 2.963; IC95%: 1.549 - 5.666, p=0.001).

CONCLUSION

Overexpression of *MAS1* and *MRGPD* are independent prognostic factors in invasive breast carcinoma. These findings suggest that RAS modulation, in Mas and MrgD receptors, could be a novel therapeutic target in positive hormone receptors breast tumors treated with DOX. Despite this strategy potentially offers antineoplastic effects, cardioprotection may not occur simultaneously.

Cardiovascular events among patients with treated acute myeloid leukemia – risk factors and the impact of clonal hematopoiesis associated mutations

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BACKGROUND

Cancer survivors are at an elevated risk of cardiovascular events (CVEs). This is driven by shared risk factors and the impact of cancer treatment on the cardiovascular system. However, few studies have described CVEs in patients with acute myeloid leukemia (AML) and potential risk factors. The aim of this study is to identify common clinical and hematological characteristics, including clonal hematopoiesis (CH) associated mutations related to CVEs in patients with AML.

METHODS

This is a retrospective cohort study of 204 AML patients at Princess Margaret Cancer Centre, Toronto, diagnosed between 2015 and 2019. Through electronic patient records we assessed all patients for baseline cardiac risk factors, AML subtypes, treatment, mutations associated with CH and the occurrence of CVEs after the diagnosis. CVEs included heart failure (HF), stroke, acute coronary events (ACEs) and cardiac-related death. CH associated mutations were determined based on the most common recurrent somatic mutations found among individuals without hematological malignancies associated with CVEs including *DNMT3A, TET2, ASXL1* and *TP53*. Follow-up ended on June 30th, 2019.

		CVE (n=47)	*No CVE (N=118)*	*P-value*
Demographics				
Age		66 ± 13	62 ± 15	**0.04**
Gender	Male	25 (53%)	54 (46%)	0.40
Ethnicity	Caucasian	25 (71%)	56 (60%)	0.65
Baseline Risk Factors and Comorbidities				
Diabetes		9 (19%)	22 (19%)	1.00
Dyslipidemia		17 (36%)	23 (19%)	**0.03**
Obesity		20 (43%)	24 (20%)	**0.006**
Hypertension		23 (49%)	43 (36%)	0.16
Chronic Kidney Disease		1 (2%)	1 (1%)	0.50
Smoking (currently or previously)		22 (47%)	52 (44%)	0.86
Prior Cardiovascular Disease		13 (28%)	11 (9%)	**0.006**
Prior Myocardial Infarction		3 (6%)	6 (5%)	0.72
Prior Revascularization		5 (11%)	8 (7%)	0.52
Atrial Fibrillation		6 (13%)	7 (6%)	0.20
Heart Failure		5 (11%)	2 (2%)	**0.02**
Valve Heart Disease		0 (0%)	4 (3%)	0.58
Baseline Medications				
Aspirin		8 (17%)	13 (11%)	0.31
Statin		15 (32%)	25 (21%)	0.16
ACE/ARB		15 (32%)	26 (22%)	0.23
Beta Blocker		19 (40%)	26 (22%)	**0.02**
MRA		1 (2%)	0 (0%)	0.29
AML Diagnosis and Treatment				
AML Type (WHO)				
Recurrent Cytogenetic Abnormalities		2 (5%)	17 (16%)	0.10
Not Otherwise Specified		21 (54%)	59 (55%)	1.00
MDS-Related Changes		12 (31%)	29 (27%)	0.68
Therapy-Related		4 (10%)	2 (2%)	**0.04**
AML Karyotype				
Abnormal		10 (36%)	41 (43%)	

(*Continued*)

Complex	9 (32%)	18(19%)	
Monosomal	0 (0%)	2 (2%)	
Other Abnormal	1 (4%)	21 (22%)	
Normal	18 (64%)	55 (57%)	0.66
Treatment			
Induction	33 (70%)	96 (81%)	0.14
Consolidation	24 (51%)	84 (71%)	**0.02**
Allogenic HCT	18 (38%)	40 (34%)	0.60
Other	14 (30%)	50 (42%)	**0.002**
No Treatment	8 (17%)	7 (6%)	**0.04**
Anthracycline dose (Doxorubicin Equivalent mg/m^2)			
0	17 (37%)	48 (45%)	
<250	11 (24%)	29 (25%)	
>250	18 (39%)	56 (48%)	0.44
AML Outcome			
Remission	18 (49%)	48 (45%)	0.85
Relapse/Refractory	19 (51%)	58 (55%)	
Clonal Hematopoiesis-Related Mutations at Diagnosis			
TP53	10 (22%)	11 (10%)	0.07
TET2	8 (17%)	28 (24%)	0.41
DNMT3A	10 (22%)	33 (28%)	0.55
ASXL1	12 (26%)	29 (25%)	1.00
BCORL1	4 (9%)	21 (18%)	0.16

RESULTS

Thirty-nine patients were excluded due to incomplete clinical data. Of the 165 patients included, 47 (28%) experienced at least one CVE during follow-up: 37 HFs, 10 strokes, 5 ACEs, and 8 cardiac deaths. The clinical characteristics of patients with and without CVEs are summarized in the Table. Patients with CVEs were older, had more cardiac risk factors (dyslipidemia, obesity), prior CVEs and were more likely to have therapy-related AML. Amongst CH related mutations there was a trend towards TP53 mutation being more common in those with CVEs, however no differences were seen with the othermutations.

CONCLUSION

Denovo CVEs were common in patients with AML diagnosis. This was associated with the presence of traditional cardiovascular risk factors, prior CVEs and certain AML subtypes. CH related mutations were present in our patients, with a trend in TP53 mutations being more common in patients with CVE. Understanding risk factors for CVEs can promote apt intervention and monitoring in AML survivors.

Serum hepatocyte growth factor has diagnostic and prognostic utility in cardiac amyloidosis

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BACKGROUND

Delays in diagnosis of up to 36 months are common for cardiac amyloidosis, with longer delays in diagnosis associated with more advanced disease at presentation. We sought to evaluate the usefulness of hepatocyte growth factor (HGF) in the diagnosis and prognosis of cardiac amyloidosis.

METHODS

We prospectively enrolled patients referred to the Vanderbilt Amyloidosis Multidisciplinary Program (VAMP) to evaluate for cardiac amyloidosis. Additionally, we enrolled patients with left ventricular hypertrophy or systolic heart failure without evidence of amyloid to serve as a control group. Patients underwent baseline assessment including HGF measurement and were followed at regular intervals.

RESULTS

There were 102 consecutive patients enrolled with AL or TTR amyloidosis of which 72 had cardiac involvement. Additionally, there were 44 control patients with LVH and 42 control patients with systolic heart failure. HGF values were significantly elevated in cardiac amyloidosis (455 pg/mL, Interquartile Range (IQR) 322-735) compared to both patients with LVH (105 pg/mL IQR

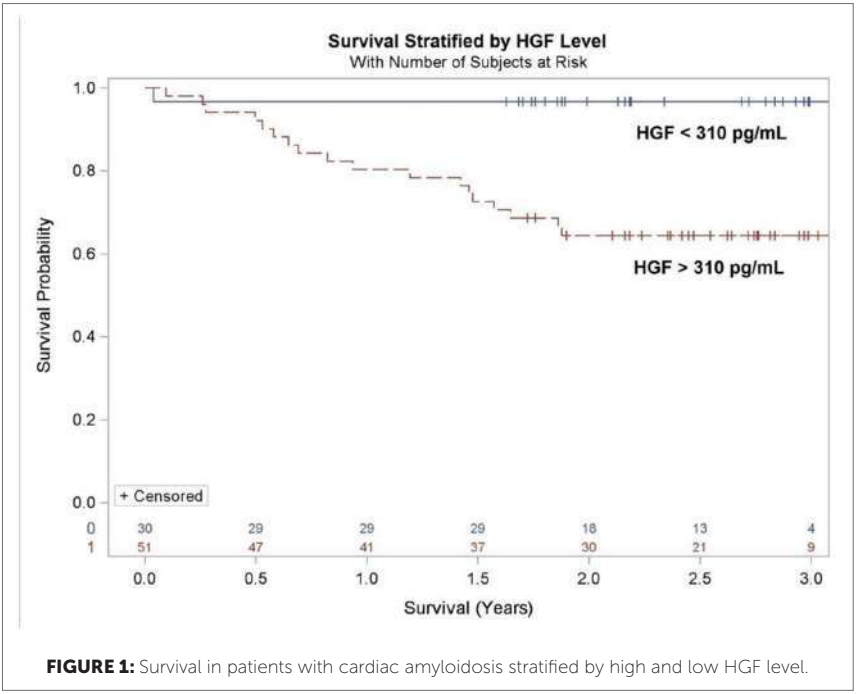

FIGURE 1: Survival in patients with cardiac amyloidosis stratified by high and low HGF level.

66-151) and systolic heart failure (131 pg/mL IQR 89-225), p <0.01 for both. Additionally, in patients with amyloid, an HGF cutoff of 310 pg/mL had a sensitivity and specificity of 69% for cardiac involvement. Of patients with cardiac amyloidosis, an HGF cutoff of 310 pg/mL was associated with increased hazard of death over a median 2.2 years of follow-up (p=0.0006) (Figure 1). Only one patient with a HGF value less than 310 pg/mL died.

CONCLUSION

In our pilot study, hepatocyte growth factor has both diagnostic and prognostic utility for cardiac amyloidosis and may prove to be a useful biomarker for the disease after further validation.

Western and mediterranean dietary patterns modulate chemotherapy responsiveness in triple-negative breast cancer and regulate the development of cardiac toxicities

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BACKGROUND

As women with a breast cancer diagnosis are living longer, it is becoming more prevalent that previous breast cancer treatment results in long-term consequences for a woman's risk of dying from cardiovascular disease, making the unique long-term health concerns of this growing population a public health priority. Standard-of-care chemotherapy regimens are administered to women for treatment of breast cancer because they result in improved outcomes compared to other treatments. However, high cumulative doses of chemotherapies (such as anthracyclines) can increase the risk of congestive heart failure by up to 26%. This leads to excess morbidity and mortality, reduced quality of life, and increased medical expenditures for breast cancer survivors. Consuming a Mediterranean diet has been reported to lower risk of death from cancer, heart disease and respiratory disease due to the robust anti-inflammatory and antioxidant activity of Mediterranean dietary components. Moreover, Mediterranean dietary patterns have been reported to, inhibit coagulation, improve glucose homeostasis, and reduce oxidative damage and inflammation. Taken together, these data suggest that Mediterranean diet consumption may ameliorate cardiac damage induced by standard of care chemotherapeutic treatments administered to breast cancer patients.

METHODS

To determine whether dietary patterns effect the development of chemotherapy-mediated cardiac toxicities and modulates the development of breast cancer metastases, we used a triple negative breast cancer resection murine

model in mice fed a standard rodent chow, a Western diet (high in saturated fat and sugar), or a Mediterranean diet (high in monounsaturated fat and polyunsaturated fat). Primary 4T1-luciferase breast tumors were allowed to grow for 21 days in the mammary fat pad before tumor was resected. Once a week 3.3 mg/kg doxorubicin was administered IV for 3 weeks. Tumor lung metastases were monitored by IVIS. Cardiac function was measured using a Vevo ultrasound in M and B mode at 8 weeks of age (diet only effects), 11 weeks old (diet+ primary breast tumor effects), and 15 weeks old (1 week post final DOX treatment).

RESULTS

Consumption of a high fat diet (Western or Mediterranean diet) increased primary breast tumor growth when compared with low fat control diet. However, only Western diet consumption decreased the time to lung metastatic lesion formation, increased lung metastases formation, and decreased anti-cancer doxorubicin efficacy. Consumption of a Western diet also resulted in poor cardiac function; Western diet-fed mice treated with doxorubicin had decreased cardiac output, ejection fraction, and fractional shortening. Staining cardiac tissue with picrosirius red also indicated that consumption of a Western diet significantly increased cardiac fibrosis that was prevented by consumption of a Mediterranean diet.

CONCLUSION

Dietary patterns affect primary tumor growth, metastatic lesions formation, tumor response to chemotherapy, and the development of chemotherapy-mediated cardiac toxicities. Consumption of a Mediterranean diet may reduce metastatic breast cancer and prevent chemotherapy-induced cardiac dysfunction overall improving patient survival.

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