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Characteristics and Clinical Outcomes of Patients Referred to a Cardio-Oncology Clinic:The First Lebanese Experience

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Abstract

Introduction: Survival rates in cancer patients have improved dramatically in the past ten years, especially with the discovery of novel cancer therapy which was found to be associated with multiple cardiovascular complications. The development of cardio oncology clinics has evolved in order to address this issue.

Objectives: This study is aimed to report the characteristics and clinical outcomes of patients presenting to our cardio oncology clinic in order to improve the care for this patient population.

Material and Methods: Hematologic and solid malignancy patients referred to the cardio oncology clinic at the American University of Beirut Medical Center will be included in this study.

Results: Of the 119 patients, the median age was 59, and 57% were women. The most common reason for referral was pre-therapy assessment. After a follow up period of 12 months, 55% of the patients who had a drop in their LVEF achieved full recovery, 22.5% experienced partial improvement. 55% of the patients completed their chemotherapy regimen where 8% had discontinued the treatment at some point. 83% of patients were alive at the end of follow up, 17% died with septic shock being the most common cause.

Conclusion: Despite challenges, the COC demonstrated significant success in managing patients at risk or with known cardiovascular comorbidities who are being treated for cancer, emphasizing the importance of multidisciplinary care. These findings underscore the importance of specialized cardiac care within the realm of oncology and emphasize the need for early risk stratification, early preventive measures, and continued research to optimize the management of cardiovascular health in cancer patients.

Keywords: Cardio-oncology; Cardiotoxicity; Left ventricular dysfunction; Left ventricular ejection fraction; Global longitudinal strain

Introduction

Over the past twenty years, cancer-related mortality has dropped by around 33%, translating into approximately 3.8 million fewer deaths than expected. The cancer death rate declined from 2019 to 2020 by 1.5%. This tremendous improvement in survival rates was attributed to early cancer detection and the development of improved treatment protocols, including targeted therapy and immunotherapy [1]. However, these effective therapies can lead to short- and long-term adverse effects, particularly cardiovascular complications that can

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profoundly impact cancer patients' quality of life and survival [2]. Cardiotoxicity related to cancer therapy can occur early or late during the course of the disease and even years post-treatment completion or remission [3]. Its manifestation varies and can present as cardiac dysfunction, heart failure, hypertension, arterial and venous thrombosis, arrhythmias, pleural and pericardial effusion, pulmonary hypertension, QTc prolongation, and metabolic side effects that may indirectly affect the cardiovascular system [4]. Given these potential cardiotoxic effects of traditional, targeted, immunotherapy and newly developed cancer therapies, the involvement of cardiologists has become more recommended to manage cardiac complications of cancer therapy and to assist in the overall care of cancer patients from the initial assessment to survivorship. The process of cardiovascular risk stratification and monitoring is recommended in all patients who are expected to receive a potentially cardiotoxic anticancer therapy. Hence, the development of "cardio-oncology" clinics has evolved to recognize cardiovascular complications related to cancer therapies early and address them in a multidisciplinary approach. A close collaboration between the oncologist/hematologist and cardiologist is essential for proper care. In 2020, The American University of Beirut Medical Center (AUBMC) launched the Cardio-Oncology program, which is a joint initiative between the division of Cardiology and Hematology-Oncology, aiming to provide an integrated multidisciplinary standardized care to patients with cancer who are at an increased risk of cardiotoxicity related to chemotherapy throughout their journey to improve their overall care and track possible changes in survivorship to improve patient outcomes. It entails a pro-active screening process of high alert criteria related to patient co-morbidities and the proposed chemotherapy plan, according to which patients are labeled as high risk for cardiotoxicity. In this study, we will report the first Lebanese experience of cancer patients presenting to our cardio-oncology clinic.

Methods

This observational study was conducted at the American University of Beirut Medical Center, a leading tertiary academic medical center in Lebanon and the Middle East. We included patients aged 18 and above with a history of hematologic or solid malignancy referred to the Cardio-Oncology Clinic (COC) during a period that extended from June 2020 to June 2021 after obtaining institutional review board approval. Data included patient demographics, cancer type, stage at diagnosis, cancer therapy used, and reason for referral. Cardiovascular risk factors and data were also collected and included body mass index, history of smoking, dyslipidemia, hypertension, history of coronary artery disease, history of heart failure, family history of early cardiovascular events in addition to cardiac biomarkers such as NT-Pro BNP, and troponin. Electronic charts in the electronic medical record system were used for data collection. Results of left ventricular systolic function and global longitudinal strain (GLS) of the left ventricle before, during, and after cancer therapy as well as newly prescribed cardiac medications and interventions, were also reported. Clinical outcomes were measured by the completion of prescribed cancer therapy, improvement in left ventricular systolic function. Cancer therapy-related cardiac dysfunction (CTRCD) was defined, according to the 2022 European Society of Cardiology (ESC) guidelines as a new left ventricular ejection fraction (LVEF) reduction by ≥ 10 points to a LVEF 40–49% or a new relative decline in GLS by > 15% from baseline and/or a new rise in cardiac biomarkers [5]. Data was analyzed using SPSS IBM version 27.0. Descriptive analysis summarized numerical variables, median, mean, and range, whereas categorical variables were described by counts and relative frequencies. Crosstabs in the form of 2x2 tables were plotted to identify correlations between changes in LVEF and the therapy used, patients' comorbidities, cancer type, cardiac medications used, and lifestyle-related variables. The chi-square test was referred to for correlations between categorical variables. Alternatively, Fischer exact test was used when tables had cells with low counts. Analysis was performed using SPSS software IBM v.25, a p-value < 0.05 was considered statistically significant in all analyses.

Results

Patient demographics and Baseline Data

One hundred nineteen patients were referred to the COC at AUBMC between June 2020 and June 2021. Patients' demographics and the reasons for referral are presented in Table 1. The median age of the patients presenting to the clinic was 59 years (range: 22–93), and 57% were female. The most common cancer types among the patients were hematological malignancies (n = 67, 56%), followed by breast cancer (n = 28, 24%). Metastases were present in 28.6% of the patients (n = 34). At the initial assessment, the patients' median LVEF was 55%.

Table 1: Patient demographics and reason for referral to the cardio-oncology clinic

Patients (n)	119
Age (years)	
Median	59
Range	22–93
Sex [n (%)]	
Women	68 (57)
Men	51(43)
Primary tumor type [n (%)]	
Breast	28 (24)
Lung	5(4)
Other solid tumors*	19(16)
Hematologic	67 (56)
Risk factor types [n (%)]	

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Smoking	53(45)
Hypertension	47(40)
Obesity (BMI > 30)	27(23)
Dyslipidemia	33(28)
Diabetes mellitus	23(19)
Coronary artery disease	18(15)
Reason for referral [n (%)]	
Decreased LVEF or GLS	27(23)
Pre-therapy assessment	37(31)
Arrhythmia	24(20)
Congestive heart failure	13(10)
Other**	18(15)
*Colo-rectal cancers, prostate cancer, ovarian cancer, sarcoma, bladder cancer, pancreatic cancer	
**Valvular heart disease, hypertension, dyspnea, pericardial disease, orthostatic hypotension	

The most common reasons for referral were pre-therapy assessment, either pre-chemotherapy cardiac risk assessment or before starting targeted therapy (n = 37, 31%), decreased LVEF or GLS (n = 27, 23%), arrhythmias (n = 24, 20%) and HF 10%.

Systematic Therapy and Rates of Therapy Completion

Regarding treatment, 64% received combined therapy of chemo- and targeted therapy at the same time (n= 76), whereas 24% received chemotherapy alone (n = 28) and 8% received targeted therapy alone (n = 10), either monoclonal antibodies or tyrosine kinase inhibitors (Table 2).

Fifty-eight patients (49%) had exposure to anthracyclines, and the median dose was 240 mg/m2. 24% of the patients (n = 28) had a history of chest radiation therapy with a median dose of 36 mGy. 55% of the patients (n = 66) completed their chemotherapy regimen; in contrast, 8% (n = 9) had discontinued the treatment whereas the remaining where continuing their therapy.

Outcomes

During the follow-up period, various interventions were implemented as part of the multidisciplinary care provided by the clinic. These interventions included optimizing cardiovascular risk factors, adjusting cancer treatment regimens, and initiating cardioprotective medications. After a follow-up period of 12 months, the overall outcomes showed that 55% of the patients who had a drop in their LVEF achieved full recovery, with their LVEF returning to the normal range. No significant changes in LVEF were observed in 20% of the patients. These patients maintained a stable ejection fraction throughout the follow-up period. Additionally, 22.5% of the patients experienced partial recovery of LVEF, showing improved left ventricular function but not reaching the normal range. Furthermore, all patients who had a drop in their LVEF were started on cardiac medications during their referral to the COC: 25% on beta-blockers alone, 13% on angiotensin-converting enzyme inhibitors (ACEi) alone or an angiotensin receptor blocker (ARB) alone, and 62% on combination therapy of multiple medications (ACEi and beta-blockers, Angiotensin Receptor Blocker and Beta-blockers or others) (Table 3).

Table 2: Treatment details for 119 patients receiving systemic therapy.

Therapy [n (%)]	
Chemotherapy alone	28(24)
Targeted therapy alone	10(8)
Chemotherapy and targeted therapy	76(64)
Exposure to Anthracyclines [n (%)]	58(49)
Median Anthracycline dose (mg/m2)	240
Exposure to chest radiation therapy [n (%)]	28(24)
Median dose of chest radiation (mGy)	36
Chemotherapy completion rate [n (%)]	
Completed	66(55)
Ongoing	27(23)
Discontinued	9(8)

Table 3: Cardiac Outcomes

Median baseline LVEF (%)	55
Change in LVEF (%)	
Stable	60 (58)
Drop by < 10%	15 (14)
Drop by ≥ 10%	25 (24)
Increase by < 10%	0 (0)
Increase by ≥ 10%	4 (4)
LVEF outcome n (%)]	40
Full recovery	22(55)
Partial recovery	9(23)
Stable	8(20)
Declining	1(2)
Cardiac medications initiated [n (%)]	40
ACE inhibitor	5(13)
Beta-blocker	10(25)
Combination of drugs*	25(62)
* Patients were started on multiple drugs at the same time (ACEi + Beta-blockers, ARB + Beta-blockers)	

In June 2021, most patients (n = 99; 83%) were still alive, and 20 died (17%). Most deaths were attributable to septic shocks due to immunosuppression. Only one death was attributed to heart failure and cardiogenic shock (Table 4).

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Table 4: Cardiac Outcome.

Living	99(83)
Deceased	
From disease progression	1(0.8)
From cardiac causes	2(1.6)
From other causes	17(14)

Discussion

The definition of "cardiotoxicity" is not universally agreed upon. Due to the multidisciplinary aspect of cardio-oncology, many definitions originate from different specialties. The National Cancer Institute defines it as "the toxicity that affects the heart"[6]. This toxicity is not limited to the myocardium but also affects the pericardium, the endocardium, and coronary vasculature [7]. Recently, the term cardiotoxicity has been used interchangeably with "Cancer Therapy Related Cardio-Vascular Toxicity" (CTR-CVT). This term includes CTRCD, which can be symptomatic HF or only asymptomatic drop in LVEF or GLS or biomarkers abnormalities; immuno-checkpoint inhibitors myocarditis, vascular toxicities (coronary artery disease, peripheral artery disease, thromboses, stroke or transient ischemic accidents), arterial hypertension or cardiac arrhythmias (QT prolongation, atrial fibrillation, supraventricular tachycardia). This definition is adopted by the ESC guidelines 2022 and was initially created by the International Cardio-Oncology Society (IC-OS) [8]. Cardioprotective approaches to prevent CTR-CVT include concomitant strategies of cardiovascular disease and/or others specific to cancer and its therapy. Taking the multiple-hit model of HF as observation and extrapolating it to the CTRCD, patients with previous or subclinical cardiovascular risk factors will not tolerate additional injury due to less cardiac functional reserve [7]. Thus, COC aims to reduce this risk associated with modifiable risk factors by providing strategies related to pharmacological and non-pharmacological approaches and ensuring the most cardio-protection and quality of life for these patients. It is crucial to sustain the collaboration between medical oncology/ hematology, cardiology, and other healthcare professions charged with the care for cancer patients who have or are at risk of CTR-CVT to limit cancer treatment's short- and long-term effects. The present study provides valuable insights into the characteristics and clinical outcomes of patients referred to a multidisciplinary COC in Lebanon. In this cohort, we focused on CTRCD.

The findings highlight the effectiveness of the clinic in managing impaired LVEF in cancer patients, with a significant proportion of patients achieving either full or partial recovery of LVEF. In contrast, most of the patients completed the desired therapy. Thirty-one patients (77.5%) out of 40 who had a decrease in LVEF initially have recovered from this drop, whether having complete or partial recovery. This finding is particularly noteworthy, as it demonstrates that restoration of cardiac function is possible in a significant proportion of patients despite all the risk factors, especially with good risk stratification, protective measures, and close follow-ups. This recovery is associated with better clinical outcomes. The interventions done during COC visits are based on evidence-based approaches and depend on patients' tolerance. It was statistically significant that the drop in LVEF was worse in patients who were not started on the combination of ACEi and beta-blockers, with a p-value of 0.022. Recently, interim analysis results of a 4-arm, randomized trial (SAFE [Cardiotoxicity Prevention in Breast Cancer Patients Treated with Anthracyclines and/or Trastuzumab]) evaluating the effect of bisoprolol, ramipril, or their combination to reduce anthracycline-associated subclinical cardiac injury were published.

These results included a 12-month follow-up period showing a statistically significant difference in LVEF reduction in patients in the placebo group compared to the ramipril, bisoprolol, and combination arms [9]. Other predictors that might be helpful from risk stratification are troponin level and N-terminal-pro-B type Natriuretic Peptide. Elevated levels of these markers at baseline were associated with worse outcomes, reflecting a worse cardiac reverse. Here comes the role of neurohormonal inhibition that modulates the response to injury rather than the cardiotoxic process. More data is required to stratify patients into risk categories and decide how aggressive the cardioprotective treatment should be [10]. The multidisciplinary care provided in the COC likely contributed to the observed improvements in LVEF. Optimization of cardiovascular risk factors, adjustment of cancer treatment regimens, and the use of cardioprotective medications are all essential components of the comprehensive care delivered by the clinic [11, 12]. These interventions likely played an indispensable role in managing cardiovascular complications and promoting LVEF recovery [5]. Furthermore, an adequate initial risk stratification and close follow-up lead to a better therapy completion rate and a low rate of discontinuation or interruption. In our study, treatment was discontinued only in 9 patients (8%). This shows that strict cardiac monitoring and appropriate cardiovascular therapy initiation or optimization warrant the majority of patients to maintain and complete their prescribed cancer therapy [13-15]. Patients are typically referred to cardiac-oncology clinics for various reasons, often associated with potential cardiotoxicities from cancer treatments. In our study, most referrals were pre-therapy assessments (31%), either before a bone marrow transplant or before starting a drug known to have cardiac toxicity. This approach reflects the preventive assessment needed for cancer patients and the need for risk stratification. The second most common reason for referral was a drop in the cardiac function. Monitoring for early cardiovascular symptoms detection is essential in oncologic treatment. Moreover, baseline risk stratification is crucial to identify patients at higher risk of developing

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cardiotoxicities. The process involves evaluating baseline cardiac function, cardiovascular risk factors, and cancer type and treatment that could be potentially cardiotoxic [5].

One of the challenges in Lebanon and the MENA region is lack of awareness among oncologists and cardiologists regarding the importance of cardio-oncology. This can lead to delayed referrals and inadequate monitoring. Facing these challenges should include access to specialized care clinics, continuous training and awareness for healthcare professionals, and spreading awareness on different levels to prevent missed opportunities for early intervention. Educational programs at all levels must be implemented. Patients should be educated about cancer treatment's potential cardiovascular side effects and encouraged to communicate any symptoms or concerns with their healthcare providers. Interdisciplinary collaboration is necessary between oncologists and cardiologists to enhance cancer patients' overall quality of care. The findings of this study align with existing literature on the importance of cardio-oncology programs in managing cardiovascular health in cancer patients [16, 17]. However, it is essential to consider the limitations of this study, including its retrospective design and the absence of a control group. A control group is necessary to assess the comparative effectiveness of the interventions provided in the cardiac- oncology clinic. Future research should aim to address these limitations and explore the optimal strategies for managing impaired LVEF in cancer patients. Data on patient satisfaction and quality of life are essential and should be quality metrics for any intervention in the care of these patients. Prospective studies with larger sample sizes and control groups are needed to validate the effectiveness of multidisciplinary COC in diverse patient populations. Long-term follow-up studies can provide valuable insights into the durability of LVEF recovery and its impact on long-term outcomes, including overall survival and quality of life.

Conclusion

In conclusion, this initiative in one of the MENA region's referral centers highlights the multidisciplinary COC's success in managing patients at risk of or with known cardiovascular comorbidities being treated for cancer. The significant proportions of patients achieving either full or partial recovery of LVEF demonstrate the potential for improving cardiac function in this population. This improvement highlights the importance of specialized cardiac care in this vulnerable population. The multidisciplinary approach adopted by the clinic, involving collaboration between cardiologists and oncologists, appears to be effective in addressing the complex cardiovascular needs of cancer patients. These findings underscore the importance of specialized cardiac care within the realm of oncology and emphasize the need for early risk stratification, early preventive measures, and continued research to optimize the management of cardiovascular health in cancer patients.

Declaration

Ethical approval

IRB approval was required prior to data collection (IRB. ID: BIO-2021- 0279). The records of the study were kept confidential. Only the investigator and co-investigators had access to the data.

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Availability of data and materials

The records of this study were kept confidential and anonymous. Only the investigators and co- investigators had access to the data which is all electronic and was kept on the principal investigator's work computer that contains a password.

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