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Novel Anti-Cancer Therapies and Cardiac Outcomes :Systematic Reviews

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Abstract

Background

Noval oncological therapies as chemotherapeutic drugs, immunotherapeutic, olecular target therapy and radiotherapies have improve cancer survivorship by potentially life-saving. These noval anti-neoplastic therapies have a significant adverse outcomes, particularly cardiotoxicity which prevent patients from complete receiving cancer treatment and so increase morbidity and mortality rate. Cardiovascular disease is the leading cause of noncancer deaths. Cardiovascular disease and cancer consider as the first and second most common cause of the burden of disease and death. Nowadays they are highly recognized and its drawback prevention remains challenging in cancer survivorship . Development of cadiovascular affection is associated with multiple modifiable risk factors including obesity, hypertension , diabetes, alcohol consumption, smoking, age, chronic kidney disease. Pre-assessment of those patients most likely to be given the cardioprotective therapy to improve cardiac outcomes in patients with preexisting heart disease .

Objective

to thorough the light on the importance of assessment of cardiac status before beginning in anti-cancer therapies to avoid cardiotoxicity .

Methods

a systematic literature review depends on collecting data from an evidence-based studies.Searches were made of forty electronic databases: the Cochrane Oral Health Group's Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, Scopus and Web of science, MEDLINE(PubMed).

Results

Systematic reviews have demonstrated correlation between anti cancer therapies and cardiovascular diseases (cardiotoxicity) especially with patients have a pre-existing risk factors .

Conclusions

Close collaboration among oncologists, hematologist , cardiologists, and primary care physicians to work together in a multi-disciplinary setting for effective management of patients.

Keywords: Chemotherapy, Radiotherapy, Molecular-target-therapy, Immunotherapy, Cardio-oncology, Cardiotoxicity, ,Pericarditis,Chestpain , Myocardial infarction, Myocarditis, Chemotherapy-induced toxicity, Heart failure, Heart disease, Hypertension ,malignancy.

Introduction

Noval anti-neoplastic therapies consider as a cornerstone of treatment for many cancers. These therapy-related cardiac dysfunction (CTRD) is a major source of morbidity and mortality in long-term cancer survivors. Cardiotoxicity is a potential complication of anticancer therapy which covers a broad range of clinical signs and symptoms like :chest pain , pericarditis , atrial fibrillation , cardiac arrhythmias ,and congestive heart failure . Scientist classified this sign into five categories according to its severity: mild, moderate, severe, life threatening and fatal. The last three categories described above correspond to high-grade cardiovascular adverse events (CVAE) [1].

Chest pain consider a common symptoms of Pericarditis. Acute pericarditis is caused by the inflammation of the pericardium. The most common cause of acute pericarditis is viral, but there are other systemic causes of pericarditis including malignancy, autoimmune disease, and uremia. External causes such as medications (e.g., hydralazine, isoniazid), bacterial infection, and radiation It is possible [2, 3].

Patient may survive cancer only until develop heart failure (cardiomyopathy), which has a higher mortality rate than cancer .Treatment-induced cardiotoxicity (particularly cardiomyopathy), defined as the direct effects of cancer treatment on heart function and structure. The relationship between cancer and CVD is bidirectional [4].

During cancer treatment, hypertension patients have a signifcantly higher risk of developing cardiovascular complications. There are more evidence base studies about , the internal relationships between hypertension-related genes and diferent types of cancer.. Poorly controlled hypertension influences cancer management, leading to temporary or complete cessation of life-saving therapies. Depending on the type and dose of treatment, systemic hypertension of new-onset is a common side effect of many anticancer agents . The hypertension-related genes are shown to play important roles in cancer progression and may be promising therapeutic targets for cancer treatment and side effect management. So the importance of adequate monitoring , diagnosis and management of hypertension in patients with underlying malignancy is highly recommended during cancer treatment [5, 6].

Pathogenesis of Cancer cell growth and proliferation mostly depends on a blood supply, which is provided through angiogenesis .Angiogenesis is controlled by many growth factors through their specific receptor tyrosine kinases and activation of multiple tyrosine kinase pathways. VEGF and its receptors (VEGFR) are one of the most important growth factor pathways and play major role in endothelial cell function . Patients with solid tumors receiving targeted therapy (VEGFR/ EGFR tyrosine kinase inhibitors) have the highest risk of hypertension events .On the other hand, hypertension is related to an increased risk of cancer [7].

In our risk factor analysis, CVD risk factors of age, hypertension, and diabetes mellitus type II were not found to be significantly associated with cardiac events or mortality. we found obesity to be associated with lower mortality. We also found smoking to be associated with increased cardiac events but without association to mortality . Cardiovascular disease in general, and HF in particular, appear strongly related to cancer .They share classical risk factors, including smoking, sedentary lifestyle, and obesity. Immunologic responses are critically important in cardiac remodeling and may have strong implications for the physiology of tumors. The sex and racial differences in immune response signaling pathways could explain the increase in adverse events, as the mechanisms for immune-related adverse events during anti-cancer treatment which considered related to changes in patterns of T and B cell expression [8].

Another patients lacking these high-risk features and develop cardiomyopathy. Earlier detection of subclinical myocardial dysfunction may identify these individuals, allowing for closer clinical monitoring during and after therapy and prior to initiation of potentially cardioprotective interventions. Two-dimensional speckle tracking echocardiography (STE) with global longitudinal strain (GLS) has become a well-established and important tool to predict subsequentcancer therapy-relatedcardiac dysfunction (CTRD) [9].

Exercise may be a potential and an effective strategy to counteract these toxicities. Exercice is a regular regimen of structured physical activity performed with the goal of improving health or physical fitness as to counter the adverse effects of cancer therapy. The cardiovascular benefit of exercise in the non-cancer setting has been extensively studied, with regular moderate to vigorous-intensity exercise currently recommended by the American Heart .Association to reduce cardiovascular risk including lowering of cholesterol and blood pressure . Physical activity and weight gain are known risk of cardiovascular outcomes in non-cancer populations [10].

Cancer Treatment varies depending on multiple tumor-specific factors including size, lymph node involvement, presence or absence of distant metastasis, hormone receptor status. Taking into consideration these factors, treatment generally utilizes a multimodality approach of surgery, systemic therapy (e.g. chemotherapy, targeted therapy, or endocrine therapy), and radiotherapy. Patient-specific factors and other comorbidities are then taken into consideration in determining the optimal treatment regimen [11].

Noval anti-cancer treatment ,raise the burden of acute and chronic side effects. A major outcomes of newly adjuvant cancer therapy is cardiotoxicity, which can lead to dose-reduction in potentially life-saving cancer therapy. High risk cancer patients may be exposed to several cardiotoxic problems [12].

Radiotherapy remains a cornerstone of treatment for many cancers. Lung, esophageal, breast, and proximal gastric cancers still receive incidental radiation to the heart as part of curative intent or palliative care .Contemporary and more sophisticated adminis-

tration of thoracic radiotherapy and systemic immunotherapy have been effective in reducing cancer-related mortality and limiting exposure to the heart. However, radiotherapy to the chest increases the risk for cancer-unrelated morbidity and mortality, especially cardiovascular mortality, in a dose-dependent manner .Furthermore, recent studies have shown that major adverse cardiovascular events, like acute myocardial infarction and stroke, are likely occurring earlier post-treatment than previouslythought [13].

Preclinical studies have shown that there is an acute series of events following radiotherapy characterized by inflammation resulting in impaired contractile reserve, followed by cell death leading to a reparative fibrotic response in the pericardium, myocardium and valvular structures Activation of pro-inflammatory pathways likely play an important role in the early changes seen following radiotherapy. CRP, a systemic inflammatory biomarker and surrogate for IL-1 activity, could identify patients with radiotherapyinduced impairment in cardiac function or reserve [14].

Radiation-induced pericarditis. Proton Beam Therapy is a new form of radiation used to treat cancers. .Conventional radiation therapy utilized photon rays, which induced irreversible damage in the DNA of tumor cells, resulting in tumor cell death. However, there is associated normal tissue death with radiation. Newer targeted forms of photon radiation have been developed, but the risk of normal cell death and the occurrence of a second malignancy due to DNA damage are risks to be considered. Proton Beam Therapy is a relatively new form of radiation used to treat cancers .This Newer radiation techniques involve charged particle radiotherapy, which involves charged protons (H+) instead of photons .Because charged protons have a very rapid energy loss in the last few millimeters of penetration, it allows for very precise localization of the radiation while minimizing the radiation-induced adverse effects on normal tissue [15].

Androgen deprivation therapy (ADT) and radiotherapy (RT) are the mainstay treatment for localized prostate cancer and recurrence after surgery. ADT also causes a wide range of metabolic side effects including obesity, insulin resistance, and lipid alterations that contribute to cardiovascular (CV) risks. Cardiovascular (CV) toxicity of ADT is increasingly recognized. Cardiovascular disease has become the leading cause of death in men with prostate cancer in the United States [16].

The advent of humanized anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody (pembrolizumab) have higher incidence of cardiac events. The list of malignancies that can be treated with these antibodies continues to grow and includes bladder cancer, melanoma, lung cancer, renal cell cancer, head and neck cancers, hepatocellular carcinoma, and more . Common side effects of these medications include: colitis, dermatitis, endocrinopathies, hepatitis, and pneumonitis. Since the early 2000s, cardiotoxic effects have been reported [17].

Gilteritinib, a novel chemotherapeutic drugs which tyrosine kinase inhibitor of FLT3, was rapidly approved by the United States Food and Drug Administration (FDA) in 2018 after the multicenter, randomized phase III ADMIRAL trial which demonstrated significantly higher overall survival and response rates in chemotherapy in AML(acute amyloid leukemia). There is increasing evidence that FLT3 tyrosine kinase inhibitors are associated with cardiac adverse events that is lead to cardiovascular toxicities, such as cardiomyopathies and QT prolongation in cancer clinical trials [18].

Modern therapies in oncology have increased cancer survivorship, as well as the incidence of cardiovascular adverse events. While immune checkpoint inhibitors have shown significant clinical impact in several cancer types, the incidence of immune-related cardiovascular (CV) adverse events poses an additional health concern. Antibodies targeting programmed cell death protein (PD-1), programmed deathligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) work to re-fresh the immune system to recognize and lyse tumors.Immune checkpoint inhibitors (ICIs) had a profound effect in the treatment of cancer by inhibiting down-regulation of T-cell response to malignancy.It has revolutionized the management of a diverse spectrum of solid and hematological malignancies previously associated with poor prognosis. Immune checkpoint blockade removes inhibitory signals of T-cell activation enabling tumorreactive T cells to mount an effective antitumor response by overcoming regulatory mechanisms. Currently, FDA-approved ICIs are inhibitors of either the cytotoxic T-cell lymphocyte-associated protein-4 (CTLA-4) or the programmed cell death receptor 1 (PD-1) or its ligand (PD-L1). ICIs have been reported to cause an immunerelated adverse events (irAE), mostly involving the skin, endocrine system, liver, lungs, and gastrointestinal tract. These targeted therapies affect specific signaling pathways that can also induce cardiotoxicity .a high incidence of newly diagnosedCVD after the initiation of ICI therapy. To better address this important knowledge gap, baseline cardiac assessment may be helpful for certain high-risk individuals (e.g., receiving combination ICI therapy, rapid decline in global longitudinal strains or a history of cardiac disease) [19, 20].

Incidence of increase rate of myocarditis in patients receiving immunotherapy compared to chemotherapy . As increased numbers of new targeted and immune-based therapies enter the market, the management of cancer patients continues to become more complicated with an increased need for predictive biomarkers. we still do not fully understand which risk factors that may predispose a patient to lethal cardiac adverse events. Immune checkpoint inhibitors (ICIs) have increased cancer survivorship and are now standard of care for numerous cancer types. T cell receptor recognition in the heart thus results in a cytotoxic effect on cardiac tissue. Johnson et al. reported the presence of infiltrating lymphocytes and macrophages in the cardiac muscle. Lymphocyte receptor sequencing showed a significant overlap of TCR sequences among cardiac, skeletal, and tumor infiltrates, suggesting that the antigens in the myocardium and skeletal muscle were recognized by infiltrating lymphocytes [21, 22].

Breast cancer is the most common female cancer worldwide. Effective therapies including doxorubicin and trastuzumab have

improved survival, but are associated with a substantial risk of cardiovascular disease. Mechanisms underlying cancer treatment-induced cardiotoxicity (CTC) Progress made in early cancer diagnosis and therapy has translated into increased longevity for patients with breast cancer. As survival has increased, the potential cardiotoxicity of cancer chemotherapy regimens has become an important issue for survivorship. Highly effective therapies, including anthracyclines, trastuzumab (TRZ), and radiotherapy have resulted in improved cancer survival rates. However, these therapies are associated with a substantial risk of cardiovascular (CV) disease. Cardiotoxicity is a significant issue in the short-term, as cardiomyopathy and heart failure can result in treatment interruptions ,and in the longterm,as CV mortality exceeds that of cancer in survivors [23].

TRZ is a a recombinant humanized monoclonal antibody that disrupts signaling, it can result in clinically significant cardiotoxicity. Endothelial cell (ECs) are one of the most abundant cell types in the heart and their dysfunction been shown to contribute to CV disease . TRZ treatment affects proteins forming the junctional complexes that are necessary for a tight endothelial barrier and that TRZ may alters its permeability . Trastuzumab which is overexpressed in 20–30% of breast cancers and associated with aggressive tumour activity . Trastuzumab induces cell death through antibody-dependent cellular cytotoxicity in cells overexpressing HER2, and has revolutionized the care of breast cancer patients by demonstrated marked survival benefit in adjuvant and metastatic settings. While trastuzumab improves breast cancer outcomes, it is also associated with a risk of trastuzumab-induced cardiotoxicity (TIC) [24, 25].

the treatment of hematologic malignancies and solid tumors, anthracyclines can lead to cancer therapy-related cardiac dysfunction (CTRD) in approximately 9% of patients and is mostly diagnosed within the first year of treatment in patients who are monitored prospectively. The American Society of Clinical Oncology (ASCO) recommends heightened monitoring for patients at higher risk of CTRD, and these risk factors include higher dose, or chest radiation, age, traditional cardiac risk factors, and prior myocardial infarction [26].

Multiple myeloma (MM) is a clonal plasma cell pathology that represents approximately 10% of the malignant hematological disorders The phases of cancer treatment include initial therapy with immunomodulators, protease inhibitors, and dexamethasone. Subsequently, if the patient is eligible, autologous stem cell transplant (ASCT) is performed. A maintenance phase follows, and its duration varies according to the identified cytogenetic profile and individual risk factors. Finally, the last phase consists of treating patients with refractoriness or relapse despite established management. In the latter case, triple therapy with immunomodulators, dexamethasone, and proteasome inhibitors (PI) such as carfilzomib is indicated .One of the adverse events of carfilzomib is its cardiotoxicity, which covers a broad range of clinical signs and symptoms classified into five categories according to its severity: 1: mild, 2: moderate, 3: severe, 4: life threatening or disabling, and 5: fatal [27, 28]

Anthracyclines are commonly used anti-neoplastic agents in the treatment of a variety of malignancies, including lymphoma; and cardiotoxicity remains an irreversible complication of anthracycline-based chemotherapy. Most current guidelines and clinical trials describe cardiotoxicity as changes in resting cardiac systolic function ,defined by the current European Society of Medical Oncology Anthracycline cardiotoxicity (ACT) leads to cardiomyocyte damage, ventricular wall thinning and ultimately manifests as a dilated cardiomyopathy The onset of ACT can be either acute or chronic, and can be clinically appreciable, or subclinical in its presentation. Acute ACT occurs within a week of commencing treatment and occurs in less than 1% of patients .Conversely, chronic ACT is more frequent and develops over an extended period of time in the months to years following treatment .Symptomatic ACT is usually defined as congestive cardiac failure, whereas patients with subclinical cardiotoxicity remain asymptomatic. Symptoms and signs of congestive cardiac failure include pulmonary or peripheral oedema, dyspnoea and exercise intolerance [29].

Fortunately, it is better initial monitoring and intervention during cancer treatment, and continued surveillance after treatment, cardiotoxicity can be prevented or ameliorated. It is clear that a good linkages between oncology and cardiology, are essential to ensure best practice in this area [30].

Results

New guidelines recognise the need for a ‘dynamic partnership’ between oncologists and cardiologists; along with the development of risk management plans which are a product of explicit and organised collaboration between specialists from the two fields [31].

Table 1: Risk of cardiac events associated with CVD risk factors:

Covariate	Incidence RateRatio (95%CI)	Adjusted *P* Valuea
Age	1.012 [0.970, 1.056]	-
Gender	3.340 [1.421, 7.849]	0.0057
Raceb (Caucasian reference)	3.388 [1.141, 10.055]	0.0279
BMI	1.026 [0.957, 1.010]	-
Hypertension	1.029 [0.402, 2.637]	-
Diabetes Mellitus Type II	0.327 [0.075, 1.435]	-
Smoker	4.212 [1.289, 13.763]	0.0173
Adjusted for age, race and gender b Only assessed African Americans and Caucasians		

Table 2: Risk of mortality associated with CVD risk factors:

Covariate	Odds Ratio (95%CI)	Adjusted P Valuea
Age	0.997 (0.981,1.015)	-
Gender (Female reference)	1.10 [0.769,1.595]	-
Raceb (African American reference)	1.149 [0.647,2.040]	-
BMI	0.937 [0.910,0.965]	< .0001
Hypertension	1.244 [0.852,1.818]	-
Diabetes Mellitus Type II	1.369 [0.835,2.244]	-
Smoker	1.285 [0.883,1.871]	-
a Adjusted for age, race and gender b Only assessed African Americans and Caucasians		

Table 3: FDA Adverse Event Reporting System analysis case demographics:

Characteristics	n (%)
Total	90,740
Age	63 (53–70
Sex	
Male	41,162 (45.4%)
Female	49,578 (54.6%)
Weight (kg)	73.5 (59.8–84.0)
Cardiac Adverse Events	8300 (9.1%)
Myocarditis	345 (0.4%)
Pericarditis	143 (0.2%)
Heart Failure	1706 (1.9%)
Myocardial Infarction	1594 (1.8%)
Arrhythmias	3858 (4.3%)
Coronary Artery Disease	654 (0.7%)
Anti-inflammatory medication use	18,797 (20.7%)
Cardioprotective medication use	23,372 (25.8%)
Treatment groups	
anti-PD-(L)1	18,536 (20.4%)
anti-CTLA4	1855 (2%)
combination immunotherapy	4442 (4.9%)
Chemotherapy	65,907 (72.6%)
PD-(L)1 = Programmed cell death protein -1 and Programmed death ligand-1 therapies; CTLA = cytotoxic T-lymphocyte-associated protein 4	

Table 4: Baseline characteristic by cardiotoxicity (defined as drop EF>10% from baseline and EF< 50% at each time measurement):

	Total	Cardiotoxicity		P- value
	N = 188	N = 165	YES N = 23	
Age (years)	53.89 ±	14.40 52.92 ±	14.59 60.87 ±	10.89 0.013
Male	62 (32.98	50 (30.3)	12 (52.17)	0.056
BMI (kg/m_2)	28.40 ± 6.08	28.40 ± 6.20	28.44 ± 5.19	0.98
Race	0.40			
Asian	5 (2.66)	5 (3.03)	0	(0.001)
Black	24 (12.77)	21 (12.73)	3 (13.04)	
Caucasian	99 (52.66)	84 (50.91)	15 (65.22)	
Hispanic	50 (26.60)	47 (28.48)	3 (13.04)	
Other	10 (5.32)	8 (4.85)	2 (8.70)	
Systolic	129.42 ± 17.68	128.22 ± 16.35	137.74 ± 23.86	0.015
Diastolic	70.97 ± 10.66	70.67 ± 10.62	73.09 ± 10.93	0.31
Heart Rate	76.38 ± 13.31	76.23 ± 13.28	77.53 ± 13.85	0.69
Family history of Heart Disease	19 (10.11)	15 (9.09)	4 (17.39)	0.26
Diabetes	35 (18.62)	29 (17.58)	6 (26.09)	0.39
Hypertension	80 (42.55)	64 (38.79)	16 (69.57)	0.007
Hyperlipidemia	52 (27.66)	44 (26.67)	8 (34.78)	0.46

Coronary Artery Disease	9 (4.79)	8 (4.85)	1 (4.35)	1.00
Hypothyroidism	21 (11.17)	20 (12.12)	1 (4.35)	0.48
Smoking	48 (25.53)	33 (20.00)	15 (65.22)	< 0.001
Ejection Fraction	64.09 ± 3.94	64.43 ± 3.73	61.70 ± 4.60	0.002
Baseline GLS	-19.13 ± 2.91	-19.36 ± 2.86	-17.51 ± 2.77	0.004
Cancer type				0.018
Breast	80 (42.55)	76 (46.06)	4 (17.39)	
Hematologic	99 (52.66)	81 (49.09)	18 (78.26)	
Other	9 (4.79)	8 (4.85)	1 (4.35)	
Chemotherapy dose	168.70 ± 102.91	175.62 ± 102.49	118.02 ± 93.32	0.013
Data were presented as mean ± SD for continuous variables and number (%) for categorical variables. Chi-square or Fisher's exact test (categorical variables) and ttest or Mann-Whitney test (continuous variables) were used to compare patients between cardiotoxicity status				

Table 5: Participant demographics, baseline clinical characteristics and pre-existing cardiovascular risk factors (Medical Record Review cohort only)

Demographics	**N = 46 n (%)**
Female	23 (50)
Married/de facto	28 (61)
Country of birth (Australia)	32 (70)
Private health insurance	15 (33)
Mean age of cardiotoxicity diagnosis (years)	58.5
Baseline clinical characteristics (pre-existing risk factors)	
≥ 1 risk factor	41 (90)
≥ 4 risk factors	11 (24)
Diabetes (type 1 or 2)	12 (26)
Hypertension	22 (48)
Hypercholesterolemia	14 (30)
Stroke	1 (2)
Angina	5 (11)
Arrhythmia (atrial fibrillation)	6 (13)
Valvular disease	1 (2)
Current−/ex-smoker	19 (41)
Social drinker	11 (24)
Overweight/obese	18 (39)
Family history of cardiovascular disease	11 (24)
Participants with four or more risk factors	11 (24)

Table 6: Cardiotoxicity treatment: pre-and-post 2012 ESMO Guidelines Date of cardiotoxicity diagnosis 1994–2011

	(n = 14)a	2012–2015	(n = 31)a	Change P value
-Referred to cardiologist (pre-chemotherapy)	0 (0%)	7 (37%) ↑	37%	0.060
-Referred to cardiologist (any)	8 (57%)	19 (61%) ↑	4%	0.793
-Baseline ECHO undertaken	8 (57%)	23 (72%) ↑	5%	0.253
-Died during study period	6 (43%)	10 (32%) ↓	11%	0.492
a Values and Percentages based on 45 of the 46 cases reviewed due data unavailability				

Table 7: Cardiotoxicity events by clinical risk score:

	Low (0–3)	Moderate (4–5)	High (≥ 6)
Patients (n)	90 (70)	25 (19)	12 (9)
Cardiotoxicity [n (%)	6 (4)	5 (4)	2 (1)
Permanent reduced EF [n (%)]	5 (4)	2 (1)	1 (0.1)

Table 8: Sensitivity analyses of the clinical risk score:

Clinical Risk Score

	Moderate + Value 95%	High Risk (≥ 4) CI Value 95%	High Risk (≥ 6) CI
Sensitivity	0.19 0.09	–0.36 0.17 0.03	–0.49
Specificity	0.92 0.84	- 0.97 0.89 0.82	–0.94
Positive predictive value	0.50 0.24	–0.76 0.14 0.03	–0.44
Negative predictive value	0.74 0.64	–0.81 0.91 0.84	–0.95

Discussion

Cardiovascular disease accounts for between 30 and 40% of global mortality in the general population. Heart failure, the final stage of many cardiovascular conditions, is one of the most common causes of morbidity and mortality, representing about 62% of the global cardiovascular deaths, and is growing daily. In the oncological population, ventricular dysfunction and heart failure cause significant limitations in treatment strategies and therefore have a considerable impact on prognosis [32].

Cardiotoxicity mechanism, the cardiac endothelium seems to be a primary target of the toxic chemotherapeutic effects. The more than 50% loss of cardiac endothelial cells and the significant lower number of small diameter coronary blood vessels support this conclusion. The loss of endothelial cells can alter vessel permeability and increased permeability can result in increased inflammatory infiltration and alter contractility of the myocardium [33].

Radiotherapy is an integral treatment modality for many cancers. The relationship between ionizing radiation, inflammation and cardiotoxicity is complex and incompletely understood .A number of acute effects including endothelial damage followed by inflammatory cell infiltration with subsequent fibrotic changes have been described. Systemic inflammation following radiotherapy has been associated with transient cardiac dysfunction including HF and elevated pre-treatment serum CRP levels have been associated with poorer prognosis in esophageal cancer patients .Moreover, cross-sectional studies in breast cancer survivors have shown a correlation between elevation in the proinflammatory markers CRP and IL-1 receptor antagonist and persistent post-treatment fatigue [34].

Unfortunately, cancer diagnosis and treatment type are not always regulated in studies and it can be difficult to make conclusions about cardiovascular toxicity with regards to specific populations and therapies. Healthcare Process Mapping is a new and important form of clinical audit that examines how we manage the patient journey, using the patient's perspective to identify problems and suggest improvements. Process Mapping allows us to "see" and understand the patient's experience by separating the management of a specific condition or treatment into a series of consecutive events or steps (e.g. activities, interventions, staff interactions). Process Mapping has shown clinical benefit across a variety of specialties, multidisciplinary teams, and healthcare systems. Our Process Mapping included medical recorded review augmented with in-depth, semi-structured, one-to-one interviews. There were 3 important timeframes described in this study 1) Cancer diagnoses (1979–2015); Cardiotoxicity diagnoses (1994–2015); and the timeframe in which the study was conducted 2010–2015 [35, 36].

It has been widely accepted that the risk of cardiovascular diseases is lower in women than in men .Nevertheless, women may suffer poorer outcome after the occurrence of an adverse cardiovascular event [37].

Based on the growing evidence on the safety and efficacy of exercise training during and after cancer therapy, the American College of Sports Medicine (ACSM) convened an expert panel to formulate exercise guidelines for cancer survivors .These guidelines are consistent with the Physical Activity Guidelines published by the US Department of Health and Human Services and recommend 150 min of moderate-intensity exercise or 75 min of vigorous-intensity exercise per week. For patients diagnosed with cancer, it should be acknowledged that reaching this level of exercise is a long-term goal that will require progressive and step-wise increments in frequency, intensity, time, and type of exercise [38].

There is growing interest in how to deliver CVD risk management programs that address risk reduction strategies. Targeted CVD programs help patients make lifestyle changes, monitor symptoms, and promote treatment adherence in order to prevent disease progression and reduce health complications. In addition, risk management programs facilitate patient empowerment and activation whereby people have the capacity and confidence to manage their health and health care [39].

The hypertension-related genes are shown to play important roles in cancer progression and may be promising therapeutic targets for cancer treatment and side efect management .That were identifed using the gene set enrichment analysis (GSEA) pre-ranked tool [40].

Conclusions

Cardio-oncology is a broad, active, and new field of medicine. Growing cooperation between oncologists and cardiologists can foster development of consensus-based guidelines for surveillance, prevention, and care of individuals. pre-evaluation of general systemic health, heart condition and hypertension is helpful in prognosis of patient treatment map .Close monitoring and appropriate management for hypertension are strongly recommended during cancer treatment. New studies highly encourage hematology-oncologists to work together with cardiooncologists in a multi-disciplinary setting for effective management of the patients.

Recommendation

Clinicians are advised to obtain a baseline and ongoing cardiovascular assessment in patients on targeted therapies for early recognition of potentially serious . The creation of the interdisciplinary team has facilitated the implementation of prevention strategies and development of clinical pathways of therapy designed to standardize clinical care among multiple subspecialists caring for these patients.

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