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Cardio-Oncology
Cardiovascular toxicity and antineoplastics

Cardio-Oncología
Toxicidad cardiovascular y antineoplásicos

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ABSTRACT

The last century has witnessed record-high life expectancy, mainly related to decreasing infectious disease as the cause of mortality, paralleled with this tendency there has been a shift in mortality towards non-infectious causes, mainly cardiovascular disease and cancer. With new antineoplastic therapies there is now a large number of long term cancer survival population. It is now known that specific cancer therapies increase the risk of cardiovascular disease, and in the last 20 or 30 years, we have observed an increased prevalence of heart failure, ischemic heart disease, arrhythmias, and hypertension in cancer patients survivors. In this article, we review general aspects related to antineoplastic therapy, including action mechanism of most common used anti-cancer agents, also, issues over tyrosine-kinase inhibitors nomenclature, and classification of cardiotoxicity. The variety of anti-cancer agents is increasing every day, and we will briefly summarize the description of different antineoplastic drugs, including traditional and new targeted and immune-oncological therapeutic agents and how they relate to cardiovascular toxicity. Classic clinical cardiovascular risk factors are known predictors of potential cardiotoxicity, and together with cardiac biomarkers and imaging techniques facilitate the early diagnosis of cardiotoxicity in the subclinical/asymptomatic stage that permits implement preventive measures. There have also been therapeutic advances in the symptomatic stage that will be disclosed. This area is in continuous evolution, and it is convenient to involve the general cardiologist mind in this relatively new topic, understanding that in not all the world there are specialized cardio-oncology units, but equally, as cardiologist, we have to collaborate with the oncologist in the treatment of patients with cancer.

RESUMEN

El último siglo ha sido testigo de un incremento sin precedentes en la expectativa de vida, principalmente por la disminución en las enfermedades infecciosas como causa de mortalidad. En forma paralela, se ha observado un cambio en la mortalidad hacia causas no-infecciosas, como enfermedad cardiovascular y cáncer. Con las nuevas terapias antineoplásicas se ha incrementado la población de sobrevivientes de cáncer a largo plazo; ahora se sabe que algunas de estas terapias incrementan el riesgo de enfermedad cardiovascular, ya que en los últimos 20 a 30 años se ha observado una mayor prevalencia de insuficiencia cardiaca, cardiopatía isquémica, arritmias e hipertensión arterial en sobrevivientes de cáncer. En este artículo revisamos aspectos generales relacionados a terapia antineoplásica, incluyendo mecanismos de acción de los agentes anticancerosos de uso más común, además de aspectos sobre la nomenclatura de inhibidores de tirosina quinasa y clasificación de cardiotoxicidad. La variedad de agentes anticáncer se incrementa día a día y de manera breve hacemos una descripción de diferentes drogas antineoplásicas, incluyendo agentes terapéuticos tradicionales y los nuevos que afectan blancos terapéuticos específicos, agentes inmunooncológicos y su relación con toxicidad cardiovascular. Los factores de riesgo cardiovascular clínicos clásicamente conocidos son predictores de potencial cardiotoxicidad, y junto con biomarcadores y técnicas de imagen han facilitado el diagnóstico temprano de cardiotoxicidad en estadios subclínicos/asintomáticos, lo cual permite implementar medidas preventivas. Ha habido también avances terapéuticos en la fase sintomática que serán discutidos. Esta es un área en evolución continua y es conveniente involucrar la mente del cardiólogo general en este, relativamente nuevo, tópico, en el entendido de que no en todas partes existen unidades especializadas de cardio-oncología; sin embargo, como cardiólogos debemos colaborar con oncólogos en el tratamiento de pacientes con cáncer.

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INTRODUCTION

Since the past century, several chemical compounds known as chemotherapy agents together with radiotherapy have been a mainstay for treatment of cancer, as a result of these therapies, there is an increasing population of childhood cancer survivors. After ten years, the risk of progression/recurrence of the original cancer is very small. Unfortunately, the long term follows up of cancer survivors have disclosed that the cumulative mortality after 30 years since a cancer diagnosis is still 30 or 40 percent higher than non-cancer patients, and this mortality is not cancer related. After cancer diagnosis and treatment, there is a gradual and progressive increase in cardiovascular morbidity and mortality.[1] In the '70s of past century, observations where done related to cardiac toxicity of anthracycline compounds[2,3] since then, as knowledge of extracellular and intracellular signalling pathways in cancer has increased, also treatment modalities have expanded. Unfortunately, cardiotoxicity has been associated with several different groups of these anti-cancer agents *(Figure 1)*.

The different group of anti-cancer therapies associated with cardiotoxicity include: 1. Classical chemotherapeutic agents, 2. Specific target humanized antibodies, 3. Small molecule tyrosine-kinase inhibitors (TKI), 4. Immune checkpoint inhibitors (ICI), 5. CAR T cell therapy, 6. Radiotherapy and others.

In this review, we will discuss anthracyclines as one of the first chemotherapeutic agents associated with cardiotoxicity. We will also describe other chemical compounds involved in cardiac damage, including new antineoplastics that target specific signalling tyrosine-kinase pathways such as monoclonal antibodies and TKI. There are new oncology agents such as ICI that together with CAR T cell therapy are involved as immune-oncological agents for specific neoplastic disease, also with well described cardiovascular toxicity. Radiotherapy associated cardiac toxicity has also been documented. In the diagnostic section, we will describe clinical aspects, electrocardiography, biomarkers and imaging techniques such as echocardiography, magnetic resonance and computed tomography and others, all very useful for early diagnosis of cardiotoxicity in the subclinical/asymptomatic stage and decision making concerning the implementation of preventive and therapeutic measures.[4]

How do antineoplastic drugs act? Basics

Cancer molecular aspects and antineoplastics action mechanisms are complex and difficult to cover by a non-biologist or oncologist. Briefly, in this review we will describe some of the most common anti-cancer drugs, and how they affect cardiovascular function.

Anthracyclines

Topoisomerase 2B (TOP2B) alters the tension of DNA during replication and transcription by breaking, twisting and resealing DNA sustaining in this way its integrity. Anthracyclines intercalate between DNA strands inhibiting its synthesis, also forms a complex with TOP2B inhibiting its activity, leading to p53 activation, decreasing mitochondrial biogenesis and function, resulting in the death of cardiomyocytes, mitochondrial DNA injury is an essential mechanism of cardiotoxicity and has been related to the long term risk of anthracycline myocardial damage *(Figure 2)*. There is also the generation of reactive oxygen species (ROS) that damage DNA, part of ROS generation induced by doxorubicin is iron mediated[5] and this results in lipid peroxidation and protein carbonylation that causes cellular dysfunction and death.[1,6,7]

Targeted anti-cancer therapies

Targeted therapies have been a breakthrough in cancer treatment. Knowing the specific target mutation involved in neoplastic cellular replication has been followed by therapies directed at such mutation. Several malignant neoplasms have mutations that overexpress growth factors regulated by tyrosin kinases of the human «Kinoma».

The «Kinoma» of an organism is the set of protein-kinases in our body. Human genome has 518 protein kinases, and kinases are enzymes that catalyze the transfer of a phosphate

group from ATP to aminoacids/proteins, and by this phosphorylation it modifies its action, subcellular location, and stability. There are three groups of kinases: a) kinases that phosphorylate the aminoacids serine and threonine (serine-threonine kinases), b) kinases that phosphorylate tyrosin (tyrosin kinase), and c) some kinases that phosphorylate both. About 90 of the 518 humane kinase are tyrosin kinase.

There are two major types of tyrosine-kinase: a) RTKs (receptor tyrosine-kinase), anchored in the cell membrane with an extracellular domain that attaches the soluble extracellular ligand and an intracellular domain with kinase activity responsible for the signalling process, and b) NRTKs (non-receptor tyrosine-kinase): localized inside the cell *(Figure 3)*.[8] There is a growing number of anti-cancer agents based on inhibition of these tyrosine-kinase, and several of them are involved in cardiotoxicity that we will describe in next sections.

Immune checkpoint inhibitor

During normal immune system development, T cells in our body acquire the capacity to react and eliminate foreign elements through the interaction of antigen presenting cells (APC)/Major Histocompatibility Complex (MHC), with T cell receptor (TCR) and other co-stimulatory signals such as CD80/B27 in the APC and CD28 in the T cell. APC and T cells have inhibitory signals that induce immune tolerance, balancing this immune stimulation, with less reactivity against host cells, so they act as co-inhibitory signals and by this mechanism downgrades immune response, including T cell response against cancer cells. Cytotoxic Lymphocyte Antigen-4 (CTLA-4) from T cell interacting with CD80/B7 on APC, and Programmed Death-1 of T cells are two of those T cell immune response inhibitors *(Figure 4)*. It is known in cancer biology that several

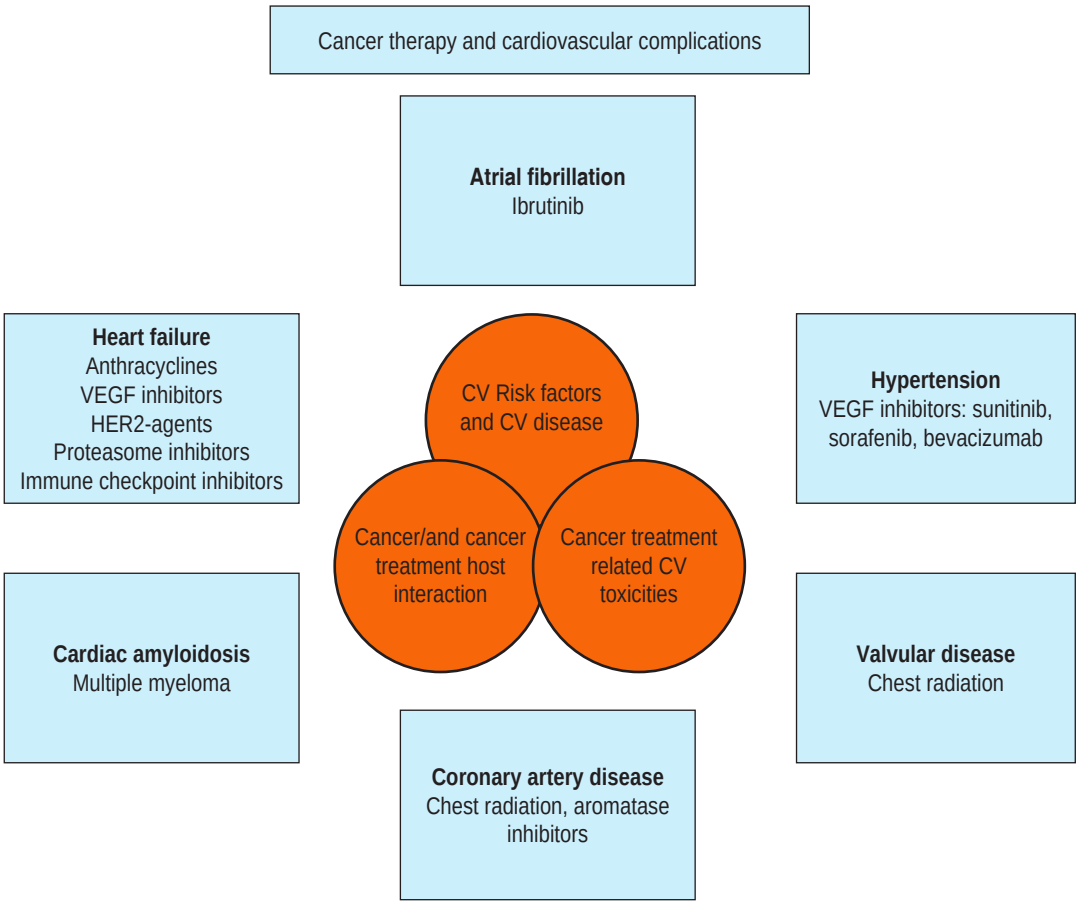


Figure 1:

Interaction between several host factors, different antineoplastic agents administration modes and expressions of cardiotoxicity. CV= Cardiovascular, VEGF = vascular endothelium growth factor, HER2 = human epidermal growth factor receptor-2.

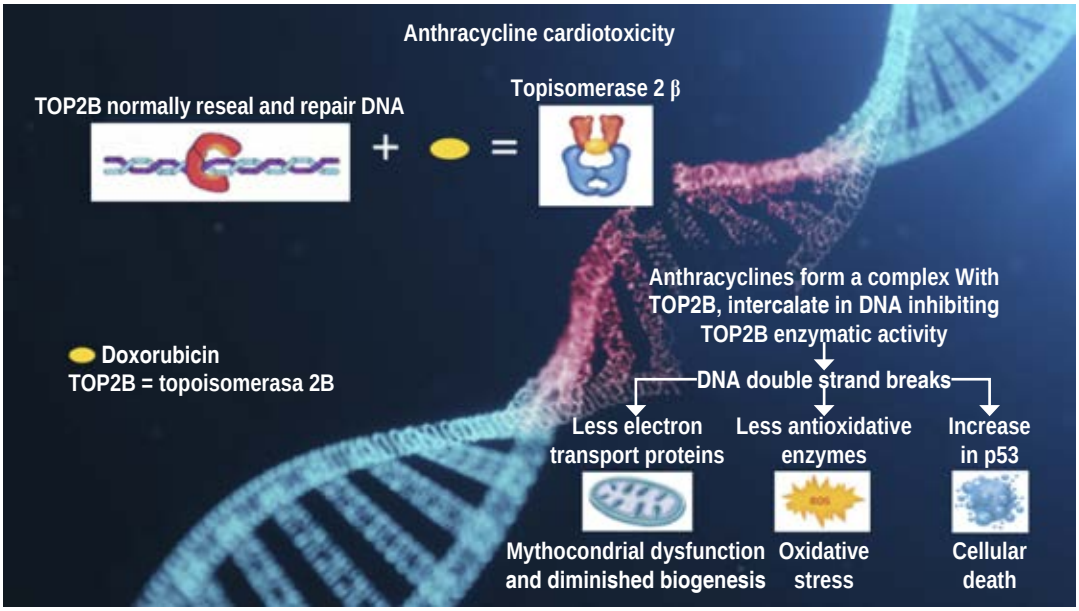


Figure 2:

Anthracycline interacts with topoisomerase 2B and intercalates in DNA altering its repairing properties. The consequences are increased p53 and oxidative stress and diminished mitochondrial bioenergetics and biogenesis that results in cell death.

tumours express different molecules that may act as an antigen, and if we inhibit T cell repression by CTLA-4 and PD-1 and mount a strong immune/active response against tumour antigens, it may have a favorable antineoplastic effect. Several studies have corroborated this, and immune checkpoint inhibitors (ICI) are current anti-cancer therapies in common use these days.[9] In September 2017, there were 940 immune based anti-cancer therapies in clinical development,[10] at the same, time there are more than 3,000 clinical trials evaluating efficacy in almost 600,000 patients. As much as 46.6% of patients with cancer in 2018 were considered eligible for ICI. More than 50% of the research & development of pharmaceutical companies is in the area of immuno-oncology.[11]

Chimeric antigen receptor T

The Chimeric antigen receptor T (CAR T) is an *in-vitro* engineered therapy where autologous T cells are obtained/drew from the patient, and usually with a lentivirus vector, genetic material is introduced into the patient T cell, this genetic material codifies for a receptor directed against a specif antigen or protein of tumoral cells. The in-vitro engineered T cells are re-injected into the patient causing tumoral lysis. Recently anti-CD19 CAR T cell therapy has shown efficacy in patients with B cell neoplasms; also, promising results have been observed in patients with melanoma.

Knowing new antineoplastic drugs nomenclature

We will witness the development of a large number of new therapies in cancer, most of them targeted TKI, it may be useful to disclose some aspects related to its «nomenclature». As previously stated, we have larger molecule monoclonal antibodies acting over extracellular receptor tyrosine-kinases (RTKs) or its ligand, and small molecule non-receptor tyrosine-kinase (NRTKs) that act mainly over intracellular tyrosine-kinases (TK). The therapeutic monoclonal antibodies may be murine, humanized, or mixed. The more humanized and less murine antibodies are associated with less antigenicity. The antibodies that act on RTK all end with de suffix «mab», and depending on if it is completely murine, partially, or completely humanized we complete suffix as:

1. Murine (0% human) = omab,
2. Chimeric (65% human) = ximab,
3. Humanized (> 90% human) = zumab,
4. Completely human (100% human) = umab.

For small NTRKs whose main action is intracellular, the suffix is «nib».[12]

How to classify different aspects of cardio-oncology and cardiotoxicity?

Cancer is a very complex disease with several diverse aspects such as mechanism of malignant cell proliferation, mutations/genetics, external chemical or viral etiological issues, host aspects, including the immune system that may predispose to perpetuate cancer or maybe eliminate neoplastic cells. Treatment of cancer is also a very complex issue with a variety of host cells and patient response to antineoplastic therapies, this, together with the many diverse action mechanism of antineoplastic therapies affecting the tumour, and that cardiac injury is usually related to more than one single mechanism of damage makes the classification of cardiotoxicity difficult.

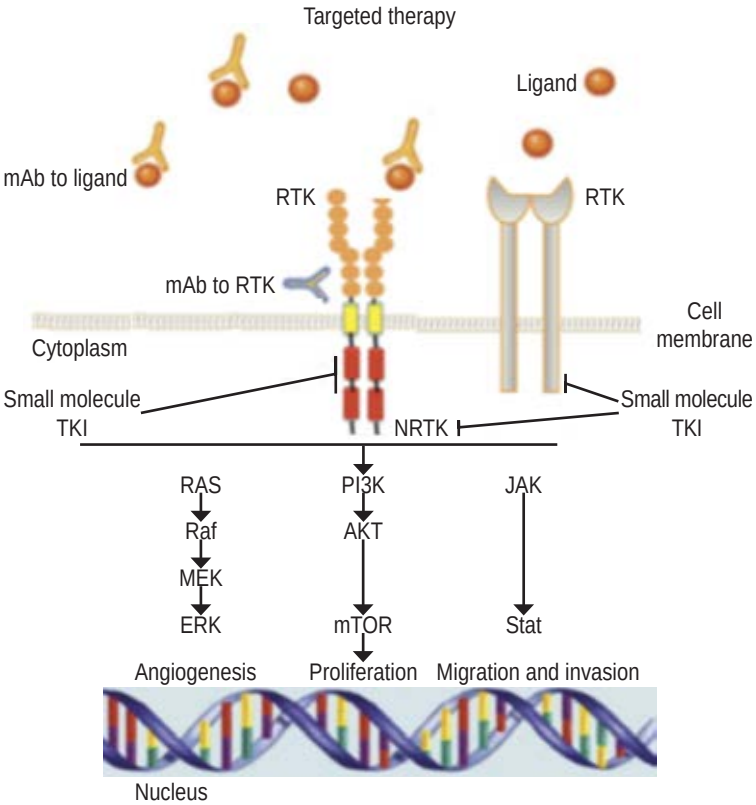


Figure 3: Monoclonal antibodies and non-receptor tyrosin-kinase inhibitors. mAb = Monoclonal antibodies, TKI = Tyrosin-kinase inhibitors, RTK = Receptor tyrosin-kinase, NRTK = non-receptor tyrosin-kinase.

Initially, cardiotoxicity was classified as type I: non-reversible damage associated with cell loss (necrosis/apoptosis) and progressive cardiovascular disease (doxorubicin) and, type II: reversible, associated with cellular dysfunction (mitochondrial/protein), with normalization of cardiovascular function after discontinuation of the antineoplastic drug (trastuzumab).[13,14] Recently, in a review article from Mayo Clinic, they classified cardiotoxicity in three subtypes based on pathophysiology and mechanism of tissue injury:

- Type I: direct cardiomyocyte toxic lesion (anthracycline drugs),
- Type II: non-direct toxic effect over cardiomyocyte, with cardiac damage mediated by a different mechanism (vasospasm, ischemia), and,
- Type III: inflammatory damage with the expression as myocarditis (Immune checkpoint inhibitors, ciclophosfamide).[7]

ANTINEOPLASTICS

Conventional chemotherapy *(Table 1)*

Anthracycline induced cardiac dysfunction

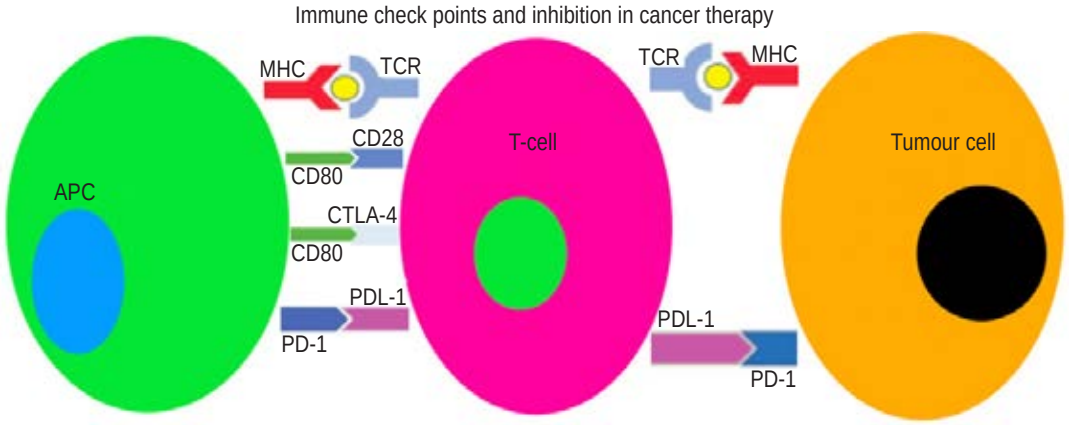
- Doxorubicin, epirubicin, liposomal doxorubicin

Non anthracycline chemotherapy and Cardiac dysfunction *(Table 1)*:

- Alkylating agents: cyclophosphamide, isosfamide, busulfan, melphalan.
- Antimetabolites: 5-Fluouracil, capecitabine, gemcitabine, cytarabine.
- Microtubule agents: docetaxel, paclitaxel, vinblastine, vincristine.
- Platinum agents: cisplatin, oxaliplatin.
- Antibiotics: bleomycin.
- Immunomodulatory drugs: thalidomide, lenalidomide.

Targeted anti-cancer therapies *(Table 2)*

- Monoclonal antibodies: trastuzumab, pertuzumab, rituximab, bevacizumab and several others.



Approved immune check point inhibitors

Anti-CTLA4: ipilimumab
Anti-PD1: novolumab, pembrolizumab, cemiplimab
Anti-PDL1: atezolizumab, durvalumab, avelumab.

Figure 4: The immune system reacts to foreign and tumoral antigens with co-stimulatory signals to eliminate such antigens. Cancer induced checkpoint inhibitory signals PD1, PDL-1 and CTLA-4 cause immune tolerance and permits a proliferation of neoplastic cells. Inhibition of these check points PD1, PDL-1, and CTLA4 restores immune co-stimulatory signals eliminating in this way neoplastic cells.
APC = antigen presening cells, MHC = major histopatibility complex, TCR = T cell receptor, CD = cluster differentiation, CTLA-4 = cytotoxic T lymphocyte antigen-4, PD-1 = programmed death-1, PDL-1 = programmed death ligand-1.

- Tyrosin kinase inhibitors (TKI): Imatinib, dasatinib, nilotinib, erlotinib, sunitinib, pazopanib, lapatinib, ibrutinib.
- Proteasome inhibitors: bortezomib, carfilzomib.
- HDAC (histone deacetylase) inhibitors: panobinostat, romidepsin, vorinostat.
- CDK4/CDK6 (cycline dependent kinase) inhibitors: abemaciclib, ribociclib.
- mTOR (mammalian target of rapamycin) inhibitors: everolimus, temsirolimus.

Immuno-oncologic therapeutic agents *(Table 3)*

- Immune checkpoint inhibitors (anti CTLA-4, anti PD-1): ipilimumab, nivolumab, pembrolizumab, others.
- CAR T cell therapy.

CARDIOVASCULAR TOXICITY

Direct cardiotoxicity

Anthracyclines

Doxorubicin is probably the most common conventional chemotherapy drug used. Acute toxicity is rare and occurs in less than 5% of patients. Chronic cardiotoxicity is seen in 0 and 16% of users, depending on the population studied, dosing regimen, and years of follow up. The risk of subclinical cardiotoxicity can be as high as 57% of childhood cancer survivors.[16] Patients with anthracycline related cardiac toxicity may have reduced left ventricle (LV) function, heart failure, high grade ectopic ventricular beats with 8.2 increased risk of sudden death even 25 years after they received cancer treatment.[17] Risk factors for anthracycline cardiotoxicity are cumulative dose, extremes of age, female gender, cardiovascular comorbidities, adjuvant chemotherapies and thoracic radiotherapy.[18]

Non-anthracycline chemotherapy

Cyclophosphamide can cause hemorrhagic myocarditis. Platinum based monotherapy cardiotoxicity is rare with unknown prevalence. All-transretinoic acid has been associated in some cases with hipotension and myocardial depression.

Tyrosin kinase inhibitors

Trastuzumab, blocks signalling through NRG1/ERBB2 (HER-2) pathway involved in breast

cancer cell proliferation and apoptosis inhibition, this same HER-2 pathway is responsible for cardiomyocyte survival/cellular proliferation/apoptosis inhibition and if it is blocked by trastuzumab may result in cardiotoxicity.[9] 20% of breast cancer patients are HER2 positive and have an excellent response to trastuzumab therapy. Unfortunately, a high percentage of patients develop myocardial dysfunction and usually discontinue a useful cancer medication. Adverse events are more common in the real world than those observed in the clinical trials. Cardiac toxicity can develop as early as two weeks after beginning HER2 inhibitor, and this suggests it does not represent a cumulative dose-dependent issue.[9,19,20] The opening article in the first edition of the new specialized cardio-oncologic journal from the American College of Cardiology on September 1, 2019 was related to this topic, and showed that when cardiologist prescribed ACE inhibitors and betablockers it may be possible to prevent myocardial dysfunction and complete the full trastuzumab cycle without interruption.[21] Several small molecule tyrosine kinase inhibitors (TKI), most commonly sunitimib may be responsible for myocardial dysfunction, occurring in between 1-27% of patients.

Immune checkpoint inhibitors

Immune checkpoint inhibitors have increased overall survival in otherwise very aggressive forms of cancer such as melanoma, renal cell carcinoma, non-small lung cancer and Hodgkin disease. Unfortunately, these immune based therapies are often associated with adverse immune based side effects in more than 50% of patients. Cardiovascular toxicity related to ICI includes myocarditis, *tako-tsubo*, arrhythmias, pericarditis, coronary artery disease/vasculitis and hypertension.[10] Myocarditis that occurs as a consequence of ICI is the most common cardiovascular adverse effect and has a bad prognosis with major adverse cardiac effects (MACE) in 50% and mortality in 17% of cases. Clinically, it may express itself with dyspnea, palpitations, acute heart failure and cardiogenic shock. Myocarditis May occur in 1.3% of patients treated with the anti-PD1 pembrolizumab, and 0.6% treated with nivolumab. Anti-CTLA-4 (ipilimumab) combined with anti-PD1 increases the percentage of myocarditis to 2.4%.[22-24]

CAR T-cell therapy

The main adverse effect after infusion of CAR T-cells is the cytokine release syndrome with

Table 1: Conventional chemotherapy.

	Arrhythmia	Cardiomyopathy	Arterial vascular disease	Pulmonar hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Conventional chemotherapy							
Anthracyclines (doxorubicin, epirubicin)		+					
Alkylating agents (cyclophosphamide, melphalan)	+	+	+				
Antimetabolites (5 fluoruracilo, capecitabina cytarabine)		+	+			+ cytarabine	
Microtubule binding agents (paclitaxel)	+		+				
Platinum based therapy (cisplatinum)			+		+		
Antibiotics (bleomycin)			+	+			
Immunomodulatory drugs (thalidomide)	+						

Table 2: Targeted therapy agents.

Target agents	Arrhyth-mia	Cardio-myopathy	Arterial vascular disease	Pulmonar hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Proteasome inhibitors (bortezomib, carfilzomib)		+	+		+		
HDAC inhibitors (vorinoztat)	+						
CDK4/CDK6 inhibitors (ribociclib)	+						
mTOR inhibitors (target of rapamycin) (everolimus)	+	+	+		+		
HER2 inhibitors (pertuzumab, trastuzumab)	+						
VEGF inhibitors (bevacizumab, sunitinib)		+	+		+		
BCR-ALB1 inhibitors (dasatinib, nilotinib, ponatinib)	+		+	+ Dasatinib			
BTK inhibitors (ibrutinib)	+						
ALK inhibitors (alectinib, nilotinib, ponatinib)	+		+				
BRAK inhibitors (dabrafenib)	+	+					
MEK inhibitors (MAPK/ERK kinase) (binimetinib, cobimetinib, trametinib)	+	+		+			

the liberation of interferon-gamma, granulocyte macrophage colony-stimulating factor, interleukin-6, and interleukin-10.[25]

Arrhythmias

Conventional chemotherapy

Atrial fibrillation has been described in 8% of patients on melphalan or busulfan and < 2% of patients on paclitaxel, mostly in the elderly, but also, it has been described in several cases of young patients without risk factors.[26] Paclitaxel and thalidomide have been associated with bradycardia. Arsenic trioxide used in some leukemias blocks repolarizing K currents (Ikr and Iks) and causes QTc prolongation above 500 ms in 65% of patients according to Bazzet QT corrective formula and 24-32% using Fridericia's. This latter formula is preferred in cancer patients because fewer overcorrection occurs at high heart rates, the issue that could lead to inappropriate cancer treatment interruption.[27] Torsade de Pointes usually does not occur in patients on Arsenic trioxide (probably because it also activates repolarizing K-ATP dependent current) unless there are electrolyte abnormalities, sudden death is infrequent.[28]

Tyrosin kinase inhibitors

Ibrutinib, an inhibitor of Bruton tyrosine-kinase (BTK) is used for chronic lymphocytic leukemia, it is associated with atrial fibrillation and ventricular arrhythmias, also sinoatrial arrest and asystole have been reported.[29] (BTK) is a regulator of PI3K-Akt signalling pathway and BTK inhibition by Ibrutinib is the postulated mechanism of the 8% risk of atrial fibrillation with this TKI.[30]

Another pro-arrhythmia related issue is QTc prolongation. Several small molecule TK inhibitors may increase QTc, especially in the context of K, Ca or Mg abnormalities, so these should be corrected before initiating these drugs. Some of the several TKI that may cause

QTc prolongation include lapatinib, sunitinib, nilotinib, sorafenib, vandetanib, the list is long and surely it will increase in the near future.

Immune check point inhibitors

Ventricular arrhythmias ocurrs in patients on ICI and these finding can increase mortality to 40%. Other forms of cardiac toxicity are AV or other conduction defects observed in 10% of patients and are associated with 50% mortality. These arrhythmias have been related to inflammatory cell infiltration of the myocardium and may be one of the manifestations of myocarditis.[22,31]

Vascular toxicity

Myocardial ischemia

Some antimetabolites, such as fluoropyrimidines may cause myocardial ischemia through coronary vasospasm even in the absence of angiographic disease.[32] 5-fluorouracil may cause coronary vasospasm in 1 to 68% of cases and capecitabine in 3-9% of patients.

Several new molecular agents signaling VEGF may cause vascular toxicities/arterial ischemia such as myocardial infarction, stroke, and/or limb ischemia.[33]

Platinum compounds are agents that may induce vascular toxicity and have been associated with hypertension, myocardial infarction, stroke, peripheral artery disease, and Raynaud phenomenon.[34,35] Chest pain may occur in 38% of testicular cancer patients treated with combination therapy that includes cisplatin, vinca alkaloids and bleomycin.[36]

Hypertension

Angiogenesis/VEGF (vascular endothelium growth factor) inhibitors: several VEGF inhibitors through vascular/capillary rarefaction and increased vascular resistance induce systemic hypertension. A relatively common used VEGF inhibitor used is bevacizumab.[37,38]

Radiotherapy induced cardiotoxicity

More than 50% of patients with cancer receive radiotherapy during some part of there treatment. Vascular structures are susceptible to radiation-induced injury, and it may cause endothelial dysfunction and inflammatory cells infiltration.[39] The cardiomyopathy observed after radiation therapy is often restrictive and manifests as heart failure with preserved ejection fraction. Patients with Hodgkin disease or breast cancer who recieved thoracic radiation may have premature atherosclerosis.[40] Long term radiation effect on the heart are heterogenous and include coronary heart disease (especially ostial/proximal disease), valvular heart disease, myocardiopathy with systolic and more commonly diastolic dysfunction and conduction defects. Also observed are pericardial and valvular fibrotic disease with calcification in the long term.[41-47]

DIAGNOSIS

Clinical syndrome

Cardiac toxicity may be asymptomatic, so, according to risk factors and specific antineoplastic therapy, we need to monitor potential toxicity issues as disclosed in next sections.

Table 3: Immunotherapies and other agents.

	Arrhythmia	Cardiomyopathy	Arterial vascular disease	Pulmonar hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Immunotherapies							
Immune check point inhibitors	+	+	+	+		+	
CAR T cell therapy	+	+	+	+		+	
Other therapies							
Radiotherapy	+	+	+	+		+	+

Patients may refer data related to heart failures such as dyspnea, pulmonary or systemic venous congestion, palpitations or dizziness/syncope related to arrhythmia/conduction defects, chest pain caused by ischemia/pericarditis, or data of acute heart failure/cardiogenic shock.

Electrocardiogram

The electrocardiograma is a very useful, inexpensive and available instrument to monitor patients under cancer treatments. Arrhythmias and conduction defects may be detected. Anthracycline cardiotoxicity occurs with ECG changes in 20-30% of patients, arrhythmias in 3% such as sinus tachycardia, supraventricular tachycardia, heart block and ventricular arrhythmias.[15] Also, it is necessary to monitor QTc and modify (QTc>450 ms) or temporal suspensión (QTc>500 ms) of antineoplastic treatment that increases QTc. Small progressive declining R wave amplitude voltage may be an indication of pericardial fluid accumulation related to pericarditis.

Biomarkers

Cardiac troponin (cTn) is an extremely useful biochemical marker of cardiac injury. It is elevated in 94% of established ICI myocarditis cases, and also it has important positive predictive value for potential left ventricular dysfunction in the setting of anthracycline therapy. Several years ago, a well done study measured cTn before, 72 hours, and one month after anthracycline therapy and showed that cTn elevation after this antineoplastic drug correlated with left ventricular (LV) dysfunction in the future. Also, the same study demonstrated the protective effect of angiotensin converting enzyme (ACE) inhibition in patients receiving this chemotherapic drug.[48,49] Brain natriuretic peptide (BNP) or amino-terminal pro-brain natriuretic peptide (NT-pro-BNP) also have value as a prognostic biomarker of myocardial injury.

Imaging

Echocardiography has an important role in monitoring the cardiotoxicity of antineoplastic drugs. In patients with previous cardiac risk factors or established heart disease, it is important to obtain a baseline echocardiogram. This study might influence to decide for potential chemotherapy drugs in the case of abnormal cardiac structure/function. The follow-up timing of subsequent echocardiographic studies will depend on clinical characteristics and risk factors of the patient, pre-existent cardiac abnormalities, chemotherapy chosen and cumulative drug dose. In general, chemotherapy related left ventricular dysfunction is classically defined as LV ejection fraction declines of more than 10% compared with baselines studies, or if it goes under 50% after chemotherapy cycles. Lately, strain/deformation myocardial imaging has significantly contributed to earlier detection of LV dysfunction, even before a fall in LV ejection fraction occurrs. Echo studies should include evaluation of different strain modalities such as global longitudinal (GLS), radial and circumferential. A GLS relative change above 15% represents subclinical left ventricular dysfunction. Echo is also excellent in the evaluation of pericardial disease, including effusion or hemodynamic compromise related to the pericardial fluid.

Multigated acquisition (MUGA) based left ventricular functional studies are used less often now, and have been widely substituted by echo imaging.

Magnetic resonance (MR) is actually the gold standard for the non-invasive evaluation of myocardial structure and function. Unfortunately, it is expensive, may be time consuming, and more critically or claustrophobic patients may not tolerate it. These logistical reasons make it also inappropriate for repeating follow up studies. Anyway, we might need MR studies in cancer patients on chemotherapy, it is extremelly useful when we suspect drug related myocarditis. It may provide diagnostic clues in favor of myocarditis or alternative diagnosis, it also gives us cardiac related prognostic information measuring extracellular matrix expansion of myocardium. A recent article provides excellent information related to MR to detect cardiovascular effects of cancer therapy and describes useful diagnostic sequences:[50]

1. Anatomical sequences, cine-volume and function,
2. T2 sequences-Edema,
3. Native T1 and T2 mapping-Edema/fibrosis,
4. Early Gadolinium Enhancement-Edema/ Late Gadolinium Enhancement-Fibrosis,
5. Post-Contrast T1 mapping/ECV-Fibrosis

Computed tomography (CT) or PET/CT: useful for detection of cardiac structure, coronary disease, cardiac primary/secondary neoplasm, it has an unwanted side effect: ionizing radiation.

PREVENTION

Screening is an important part of prevention, anticipating/early detection of declines in LV.

The American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACI) recommend in anthracycline-based therapy assess left ventricular ejection fraction (LVEF), GLS, and cTn after therapy and six months, and if the cumulative doxorubicin dose is above 240 mg/m^2 repeat LVEF, GLS and cTn before each additional dose of 50 mg/m^2. For non-anthracycline therapies, the ASE/EACI recommendation is to repeat these measurements every three months during therapy. Patients on TKI or vascular endothelium growth factor (VEGF) inhibitors should be evaluated at one month.

Modifying cardiovascular risk factors, including exercise and statins, is an established way to reduce susceptible patients for cardiac toxicity. In high-risk patients of developing cardiotoxicity, there is evidence of certain beta-blockers as carvedilol that also has antiapoptotic and antioxidant effects[51] and nebivolol as a measure to prevent LV functional decline. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are also useful,[21,48] in part through lowering blood pressure and potential overload mediated myocardial damage, and also inhibiting angiotensin II inducing NADPH oxidase oxidative stress. One study showed that the combination of the ACE inhibitor enalapril plus carvedilol prevents decline in LV ejection fraction.[52]

In the setting of anthracycline cardiotoxicity, dose reductions, prolonged infusions rates of doxorubicin instead of bolus and/or use of liposomal formulations reduces cardiac toxicity.

If trastuzumab is indicated, avoid concomitant anthracycline. Desraxozane, an iron chelator that interacts with topoisomerase IIb has been used successfully to prevent anthracycline myocardial injury,[7,53] but such preventive therapy is infrequently used in several countries because it is usually unavailable and economic issues.

Patients with pre-existent AV or other conduction defects usually also have other structural heart disease or cardiac risk factors, they might be at increased risk of bradycardias or heart blocks with antineoplastics drugs such as crizotinib, paclitaxel, thalidomide, and pazopanib. In such a situation, avoid, or if needed, carefully monitor non-dihydropyridine calcium antagonist as verapamil or diltiazem, beta-blockers, and digoxin.

In case of radiotherapy, especially in mediastinal or left breast cancer, reduction of dose exposure is the best intervention, use of protective shielding, specific positioning, or proton beam may be helpful measures to prevent radiation-induced cardiac toxicity. Some experimental studies have suggested statins and ACE inhibitors to prevent radiation-induced cardiotoxicity, unfortunately, not clinically proven.

TREATMENT

For LV dysfunction, follow guideline-based treatments, including betablockers as carvedilol, ACE inhibitors, ARB, and spironolactone. Sometimes it may be necessary to reduce or stop anticancer therapy, or modify administration protocol, or switch to less cardiotoxic regimes.

In the case of vascular induced cardiac toxicity (type II cardiotoxicity) by 5-FU or capecitabine that act as vasoconstrictors, the treatment is with vasodilators, nitrates may be useful on epicardial coronaries, and long acting nifedipine is a better strategy at the coronary microvascular level.

As previously disclosed VEGF inhibitors are associated with the development of hypertension, no specific quidelines are indicating the best antihypertensives in these situations. But we should have a target blood pressure less 130/80. In general terms, it is better to avoid the

calcium antagonist verapamil or diltiazem because potential drug-drug interaction through CYP3A4, better to use ACE inhibitors or the dihydropyridine amlodipine.[54]

Immune checkpoint inhibitors/myocarditis

ICI inhibitors related to myocarditis or ventricular tachycardia/fibrillation are life treating and require stopping the antineoplastic drug and initiate immunosuppressive agents. Also, AV block and conduction defects might be expressions of myocarditis, these, together with pericarditis or coronary vasculitis related to ICI is a clear indication to begin immunosuppressive therapy, the most common immunosuppresive therapy used are steroids. It is important to begin early immunosupression, ideally, before 24 hours of myocarditis diagnosis, patients recieving treament after 72 hours have the worst prognosis, and high dose corticosteroids are associated with the best outcomes. These indicate that myocardial damage may improve with early and intensive corticosteroid therapy.[55] If after initial evaluation the patient is asymptomatic and has only mild abnormal screening test, it may be appropriate to resume ICI under close monitoring. If the patient is symptomatic, we have to suggest to discontinue ICI permanently. If mildly symptomatic, oral prednisone 1-2 mg/kg/day may resolve toxicity. If severe cardiotoxicity symptoms develop it is necessary to progress to IV methylprednisolone 1 g/day for 3-5 days and then continue oral steroid until the cardiac function returns to baseline, then, taper over 4-6 weeks. Manage arrhytmias as needed. The intensive and rapid escalation of immunosuppressants are often required and may include intravenous immunoglobulin, thymocyte anti-globulin, anti-TNF (infliximab), mycophenolate mofetil or tacrolimus. Plasmapheresis has been used (eliminates the drug and autoreactive antibodies). It may be particularly useful to eliminate chemotherapic drugs that have long half-lives (14.5 days ipilimumab, 25 days pembrolizumab, and 27 days for atezolizumab).[7,56,57] Sometimes, and if neoplastic relatedlLife expectancy is favorable, advanced heart failure management, including support with ventricular assist devices may be indicated.

CONCLUSIONS

Half a century ago, in the 1970s began the relation between oncology and cardiology with the recognition of the cardiotoxicity of the antineoplastic drug doxorubicin. Since then, there have been significant advances in both areas, oncology and cardiology. As a result, we have witnessed increased life expectancy in cancer patients and longer lives in cardiac patients. The increased survival in cancer patients brought with it the recognition of the short and long term effects of several of the different modalities of anticancer therapy, and now, it is common to see in a general cardiology practice several cancer patients survivors, many of them with cardiac pathology. In the late part of the XX century cardio-oncology units appeared in the world, mainly in the setting of large academic/university-based hospitals.

There will not be special cardio-oncology units all around the globe, so, it will be necessary to include this area in cardiology teaching programs, acquire skills, and training cardiologist in this important issue so they will be able to collaborate with the oncologist in the management of the cardiovascular aspects of these patients.

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