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REVIEW

Cardio-Oncology

Cardio-oncology: Emerging Concepts in Cardiovascular Sequelae of Cancer Therapies, Translational Research and Reverse Cardio-oncology

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Abstract

Cardio-oncology was established with the aim of defining primary and secondary prevention approaches through surveillance and the use of tools to stratify and diminish the cardiovascular risk to cancer patients. This branch of medicine also contributes to establishing a new field in translational medicine for cardiovascular disease by focusing on the interplay between cancer and heart disease. In this first article in the new cardio-oncology section of the journal, we explore the main concepts of emerging anti-cancer therapies and their plausible cardiotoxic effects and we will describe advances and gaps in knowledge, highlighting how cardio-oncology is contributing to translational cardiology. We will speculate on the complex interplay between cancer and heart failure and discuss an emerging concept known as reverse cardio-oncology. We also present the perspective that cardio-oncology represents a promising platform area of research, allowing the discovery of novel pathways involved in cardiovascular disease through the identification of toxicities induced by targeted cancer therapies.

Keywords

Cardio-oncology, translational research, heart failure, cardiovascular diseases, cancer

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Advances in effective systemic anti-cancer therapies have transformed outcomes for patients with cancer.[1,2] These achievements have come at a cost, with cardiotoxicity becoming progressively evident in clinical practice.[1–3] The need to treat cardiovascular complications of oncological therapies has resulted in the delineation of a new discipline called cardio-oncology.[4] This established branch of cardiology has progressively set the standards for primary and secondary prevention approaches through surveillance, as well as tools to stratify and diminish cardiovascular risk in cancer patients.[5] Cardio-oncology attempts to manage the adverse effects of anti-cancer treatments, in particular heart failure (HF), through guideline-directed medical therapy.[3,5] Once the relationship between oncological treatments and a decline in cardiovascular performance was clearly established, attention moved to the definition of the interplay between cardiovascular disease (CVD), cancer incidence and mortality.[6–8]

As reported by Moslehi, cardio-oncology now offers a unique opportunity for physicians and scientists because of the translatability of basic research that emerges from clinical observations.[1] Of importance, emerging oncological therapies are designed to modulate specific pathways that are critical to the development of tumours.[1] Consequently, cardiovascular sequelae observed in patients treated with these compounds may be linked to the perturbation of these pathways, which may sometimes lead to hypotheses that there may be a concealed role that these pathways play in CVD.

In this inaugural article of the new cardio-oncology section of the journal, we will explore the main research topics in cardio-oncology, shedding light on emerging anti-cancer therapies and their plausible cardiotoxic effects; we will describe advances and gaps in knowledge in preclinical science, highlighting how cardio-oncology is contributing to translational cardiology. We will finally speculate on the complex interplay between cancer and HF – a fascinating and emerging theme called reverse cardio-oncology.

It is hoped that readers will be encouraged by this article and this new section of the journal to submit original research, reviews and expert opinions on critical topics related to cardio-oncology.

Cancer Therapies and Cardiovascular Toxicities: From Anthracyclines to Emerging Compounds

While emerging cancer treatments have improved survival rates, their

side-effects do not spare any system and might carry significant risk of cardiovascular toxicity, necessitating collaboration between onco-haematologists and cardiologists.[2,5] Recently developed oncological therapies have been approved generally as second-line treatments and, therefore, are administered to patients who have already been exposed to potentially cardiotoxic drugs, such as anthracyclines.[3] The cardiotoxic effects of these compounds mainly lead to HF because of a dose-dependent effect.[3,9–11] While HF remains the primary focus of interest, cardiotoxicity can also manifest through other cardiovascular complications, including arrhythmias, hypertension, myocarditis or pericarditis, and coronary vasospasm or ischaemia.

In the same way, monoclonal antibodies targeted against human epidermal growth factor-2 (HER2), such as trastuzumab and pertuzumab, approved for use in patients with HER2-positive breast cancer, are associated with cardiotoxicity, in particular asymptomatic left ventricular dysfunction and, rarely, overt HF.[5,12,13] The risk of cardiotoxicity is higher when these drugs are administered concomitantly or after anthracyclines, and cardiac function should be monitored regularly after their use so that treatment can be adjusted if significant reductions in left ventricular ejection fraction are detected.[12,13]

Other agents, such as fluoropyrimidines (e.g. 5-fluorouracil) and capecitabine, may cause coronary artery spasm and MI.[14–16] Early recognition of symptoms, such as chest pain and/or correction of risk factors for coronary artery disease is crucial for patients receiving these drugs.

Monoclonal antibodies designed against vascular endothelial growth factor (VEGF), such as bevacizumab and aflibercept, may cause hypertension, which is the most frequently observed cardiotoxic effect seen in patients receiving VEGF-targeting therapies.[5,15,17] This side-effect is often dose-limited and increases the risk of cardiovascular mortality in cancer survivors. Hypertension has many pathophysiological bases, including improper production of nitric oxide, oxidative stress, altered endothelin signalling and prostaglandin secretion, together with the alteration of the tone of vascular smooth muscle cells, increased vascular stiffness and microvessel rarefaction.[18]

Over the past decade, the advent of immunological therapies has revolutionised the treatment of solid and haematological malignancies.[19–21] These treatments activate the immune system to target cancer cells and include antibodies that inhibit immune checkpoint signalling, known as immune checkpoint inhibitors (ICIs), and therapies that take advantage of chimeric antigen receptor T lymphocyte (CAR-T) cells, natural killer (NK) cells and tumour infiltrating lymphocytes.[19–21] ICIs that target proteins such as programmed cell death protein 1 (PD-1), programmed cell death protein ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) are a key class belonging to immunotherapy. These drugs enhance the immune system's ability to recognise and destroy cancer cells but can also lead to immune-related adverse events (irAEs), including cardiovascular toxicities.[19,20] While cardiovascular events are less common than other irAEs, they can present with severe manifestations, including myocarditis, pericarditis and arrhythmias.[19,20] Myocarditis, though rare (ICI-related myocarditis has an incidence of <2% of cases [range 0.04–1.14%]), has a high mortality rate, amounting to 50% of patients affected by severe forms.

Myocarditis typically occurs within the first 3 months of treatment and early recognition and management are critical. ICIs can also cause pericardial disease and vasculitis, necessitating careful cardiovascular monitoring in at-risk patients.[19,20,22,23] The incidence of ICI-related myocarditis varies depending on several factors, including the treatment regimen, tumour type, pre-existing cardiovascular disease and sex.

CAR-T cell therapy, a type of adoptive cellular therapy, has shown remarkable efficacy in treating relapsed or refractory haematologic malignancies.[24] However, it has been associated with unique cardiovascular manifestations, primarily due to cytokine release syndrome (CRS).[24,25] CRS can cause severe systemic consequences, mediated by high-grade inflammation and leading to hypotension, arrhythmias, acute HF or cardiogenic shock.[26–31] Cardiologists need to be aware of the potential for rapid cardiovascular decompensation during CAR-T cell therapy, in particular in patients with pre-existing cardiac conditions.[24–31] Close monitoring and early intervention with dedicated treatments, such as the interleukin-6 inhibitor tocilizumab, are essential to mitigate these manifestations.[25,29–31]

Tyrosine kinase inhibitors (TKIs) are used for the treatment of a range of cancers, blocking the action of specific enzymes (tyrosine kinases) involved in cell growth and cancer progression.[32] However, they are also associated with several cardiovascular complications.[32] For example, VEGF inhibitors, such as sunitinib and sorafenib, are linked to hypertension, HF and arterial thromboembolic events.[32–34] Other TKIs, such as those targeting the BCR-ABL gene in chronic myeloid leukaemia (CML), such as imatinib and dasatinib, can cause pericardial effusion, pulmonary hypertension and QT prolongation.[5,35] Management strategies include aggressive blood pressure control and regular cardiac monitoring, especially in patients with pre-existing heart conditions.[5]

For multiple myeloma, proteasome inhibitors (PIs) represent a valid treatment option and include bortezomib and carfilzomib. Carfilzomib has been associated with a high incidence of HF and hypertension.[5,36–38] The mechanism through which these effects may be determined is not fully understood, but it is thought to involve increased oxidative stress and endothelial dysfunction.[2] Patients on PIs, particularly those with cardiovascular risk factors or previous cardiovascular history, should be closely monitored for signs and/or symptoms of HF.[5,37]

Poly (ADP-ribose) polymerase (PARP) inhibitors, including olaparib and rucaparib, are used for patients affected by BRCA mutation-related cancers, mainly breast and ovarian cancer.[2,5,39] While the cardiovascular side-effects of PARP inhibitors are less well-characterised than those of other cancer therapies, emerging evidence suggests they may contribute to QT prolongation, hypertension, HF and purely vascular complications. Cardiologists should be aware of these risks and manage cardiovascular health proactively in patients who are using PARP inhibitors.[2,5,39]

In summary, although advancements in cancer therapies have revolutionised treatment and significantly improved survival rates, they also pose a considerable risk of cardiovascular toxicity. It is crucial for cardiologists to be well-informed about these risks, closely collaborating with oncologists to manage and mitigate the potential heart-related side-effects of cancer treatments. Serum biomarkers, such as troponins and natriuretic peptides, may help to identify early signs of cardiotoxicity, allowing timely interventions. Imaging techniques, including echocardiography and cardiac magnetic resonance (CMR), are also valuable tools for characterising sub-clinical or manifest cardiovascular changes in these patients.

Translational Medicine in Cardio-Oncology

Evidence-based medicine is a cornerstone of modern clinical practice and

the role of translational research is to apply novel therapeutic strategies developed through experimentation to humans.[40,41] Translating preclinical knowledge to direct patient care can be challenging, particularly in cardio-oncology, where tumour and heart biology meld with comorbidities and the effects of cardiovascular drugs.[42,43]

Preclinical models used to study cardiotoxicity are divided into *in vitro* and *in vivo* models (*Table 1*).[42,43] *In vitro* models consist of cultured animal-derived cardiomyocytes or, more recently, human-induced pluripotent stem cell–derived cardiomyocytes (hiPSC-CMs), which have an advantage when modelling cancer therapies that target human proteins that don't have homologues in other species, such as trastuzumab, which specifically inhibits HER2.[42–45]

On the other hand, *in vivo* models consist of animal models, such as zebrafish, rodents or larger animals, such as rabbits or pigs, contributing to the elucidation of mechanisms of action that take part in the manifestation of specific cardiac phenotypes.[43–46] As an example, Sayour et al. attempted to better understand the pathomechanisms of HF, developing a mouse model of non-ischaemic HF with reduced ejection fraction (HFrEF) by treating mice with angiotensin-II infusion for 2 weeks.[46] This model was found to be reliable and easy to perform to identify novel HF mechanisms and therapeutic targets, which may be useful for cardio-oncology.[46]

When applying *in vivo* models in cardio-oncology, a key challenge is to create animal models that accurately mimic clinical scenarios, including the presence of cancer, comorbidities and also previous or concurrent therapies that have an impact on outcomes and development of potential cancer therapy-related cardio-vascular toxicity (CTR-CVT).[43,47]

For decades, anthracyclines have been the cornerstone of treatment for many solid and haematologic malignancies and have been used to study cancer therapy-related cardiac dysfunction (CTRCD).[3] Over the years, several *in vitro* and *in vivo* animal models have been developed to understand anthracycline cardiotoxicity mechanisms. They have proved to be complex and have not been fully elucidated, and involve mitochondrial damage, oxidative stress, dysregulation of iron metabolism, endothelial dysfunction, DNA damage and cell senescence.[3,43,48–50] For this purpose, Liu et al. focused on doxorubicin-induced cardiomyopathy in zebrafish and mice, aiming to identify molecular substrates that, if perturbated, may induce cardiotoxicity. It was found that cytochrome P450 family 1 (CYP1) played a role in doxorubicin cardiac damage and prevention of myocardial apoptosis and subsequent dysfunction in both models could be obtained through modulation of mitochondrial malate dehydrogenase.[51] Furthermore, in apoptosis and/or necroptosis-defective Ripk3$^{-/-}$, Mlkl$^{-/-}$, or Fadd$^{-/-}$ Mlkl$^{-/-}$ mice models, it was demonstrated that the iron-chelating activity of dexrazoxane enabled a cardioprotective approach against anthracycline cardiotoxicity.[52]

Anthracycline-induced cell senescence is gaining attention as a major contributor to CTRCD.[43,53,54] Senescent cells are characterised by cycle arrest and phenotypic alterations, including the expression of the pro-senescent, pro-fibrotic and pro-inflammatory senescence-associated secretory phenotype (SASP).[43,53,54] Senescent-like phenotype includes dysregulation of vascular tone, endothelial dysfunction, arterial stiffness and a reduction in mitochondrial biogenesis; at the same time, there are several *in vitro* studies demonstrating that doxorubicin causes cardiomyocyte senescence via oxidative stress, DNA damage and mitochondrial dysfunction.[55–58] According to this model, all these anthracycline-induced changes lead to a senescent phenotype featuring atherosclerosis, myocardial remodelling and vasomotor dysfunction.

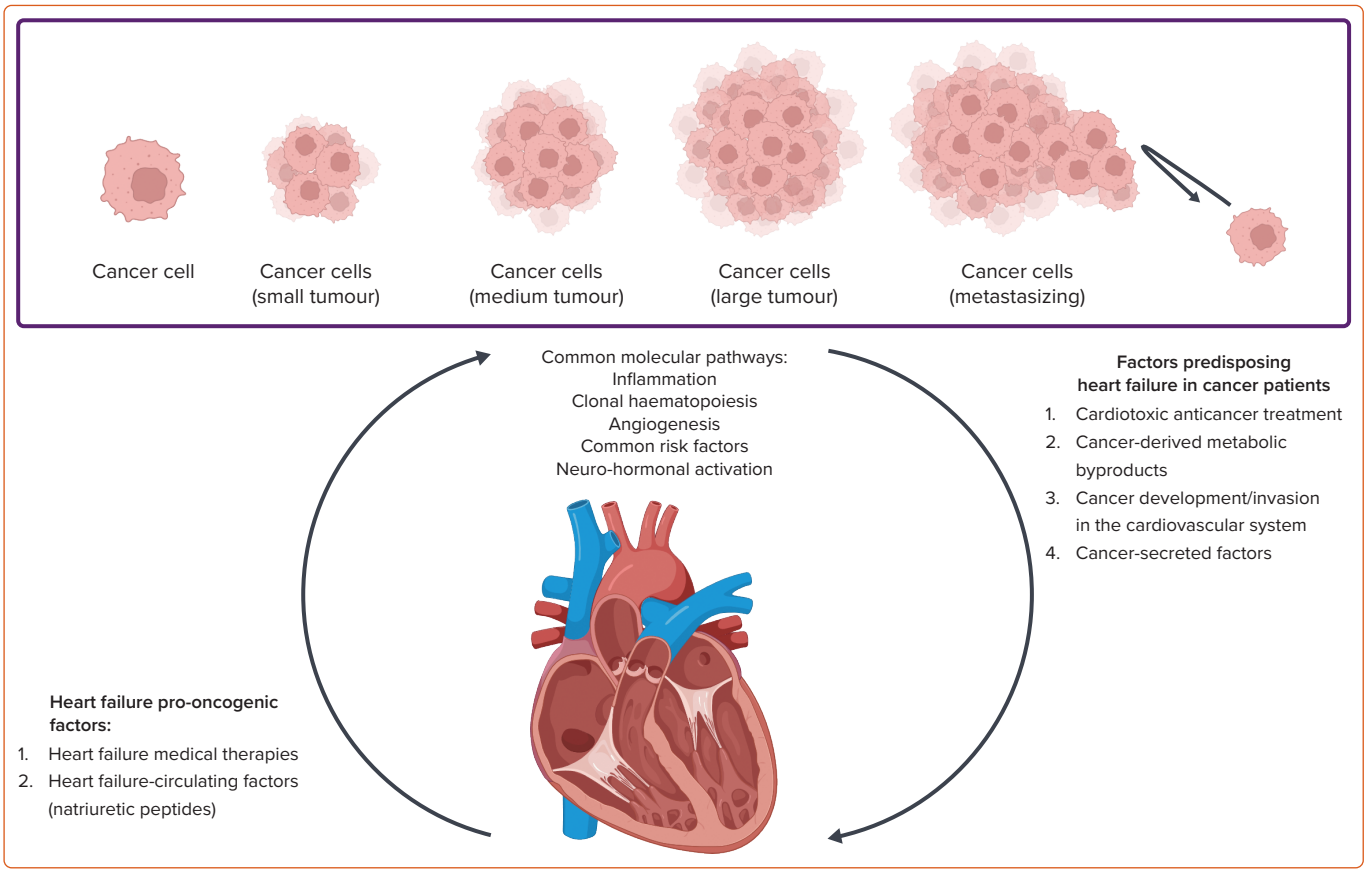
As stated, trastuzumab is a monoclonal antibody designed for patients with breast cancer with overexpression of HER2.[13] The interruption of HER2 signaling has shown significant repercussions on cardiac function in preclinical studies.[45] It was observed that in mice embryos carrying an ErbB2-null allele, the cardiac development was severely compromised and that the deletion of ErbB2 in murine models led to the development of spontaneous dilated cardiomyopathy, making the heart more sensitive

Table 1: Preclinical Models Application According to Potentially Cardiotoxic Drug Categories.

Cancer Therapy	Reported Cardiovascular Toxicities	Proposed Pathways	Preclinical Models
Anthracyclines	Cardiomyopathy Arrhythmias	Mitochondrial damage Oxidative stress Dysregulation of iron metabolism Endothelial dysfunction, DNA damage Cell senescence	hiPSC-CMs Zebrafish Rodents Swine
Fluoropyrimidines	Coronary vasospasm Acute coronary syndrome Cardiomyopathy Arrhythmias Pericarditis	Apoptosis and autophagy Endothelial dysfunction Oxidative stress Mitochondrial damage	Rodents Rabbits
HER2-inhibitors	Cardiomyopathy	Alterations in cellular and metabolic pathways	hiPSC-CMs Primary cardiomyocytes Mice
Immune checkpoint inhibitors	Myocarditis Pericarditis Atrial and ventricular arrhythmias Cardiomyopathy	IgG autoantibodies T-cell activation	Mice
CAR-T therapy	Cardiomyopathy Pericarditis Vasculitis Vascular leak Thrombosis Tachyarrhythmia Cytokine release syndrome	T-cell activation	Mice
BTK inhibitors	AF Hypertension Heart failure Ventricular arrhythmia/sudden death	AF Hypertension Heart failure Ventricular arrhythmia/ sudden death	Mice
VEGF inhibitors PDGF inhibitors	Cardiomyopathy Vascular disease Hypertension Thrombotic microangiopathy QT prolongation	Capillary rarefaction Induction of HIFs in the myocardium Suppression of PI3K signaling Decreased NO production	hiPSC-CMs Primary cardiomyocytes Mice

BTK = bruton tyrosine kinase; CAR-T = chimeric antigen receptor-T; DNA = deoxyribonucleic acid; HER2 = human epidermal growth factor 2; HIF = hypoxia-inducible factor; hiPSC-CMs = human-induced pluripotent stem cell-derived cardiomyocytes; Ig = immunoglobulins; NO = nitric oxide; PDGF = platelet-derived growth factor; PI3K = phosphoinositide 3-kinases; VEGF = vascular endothelial growth factor.

Figure 1: Common Pathways between Heart Failure and Cancer.



CV = cardiovascular; HF = heart failure. Created using BioRender.com.

to pressure overload and, of course, to anthracyclines.[59–61] In studies conducted with hiPSC-CMs, trastuzumab exposure led to impaired contractile function, calcium handling and cardiac energy metabolism, allowing a better understanding of the pathophysiology behind trastuzumab-induced cardiotoxicity.[45]

The approval of ICIs in a wide range of tumour types has brought an increased reporting of immune-related toxicities, with ICI-induced myocarditis being an uncommon, although highly fatal, adverse event.[19] Preclinical and translational research has studied different potential mechanisms of ICI-related myocarditis, such as molecular mimicry and autoreactive T cells activated by ICI and directed against the heart. In a murine model with ICI myocarditis, anti-alpha myosin T cells were detected in the heart, showing higher levels of PD-1 compared with the other T cells.[62–64]

Translational research in cardio-oncology presents different fields to explore, involving the role of genetics in CTR-CVT risk stratification scores, the mechanisms behind the arrhythmogenesis of cancer therapies and the potentially actionable pharmacodynamic pathways for the prevention of cardiotoxicity.[65] For example, sodium-glucose cotransporter-2 (SGLT-2) inhibitors are under investigation, thanks to their promising mechanisms of action.[47] Preclinical *in vitro* and *in vivo* studies have demonstrated different pharmacological mechanisms of SGLT-2 inhibitors that are able to counteract anthracycline-mediated cardiotoxicity, such as regulation of macrophage phenotype expression, downregulation of inflammasome, interference with cardiac metabolism through upregulation of ketone body release and downregulation of ferroptosis, paving the way to clinical studies aiming to evaluate the cardioprotective effects of SGLT-2 inhibitors in patients undergoing potentially cardiotoxic therapies.[47]

The Interplay Between Cancer and Heart Failure

Cardio-oncology research has focused on the complex intersections between HF and cancer incidence and mortality, including the implications for patients' care (*Figure 1*).[6,66–68] In patients with cancer, CVDs are the leading causes of death unrelated to cancer.[6] A study conducted in the US examined the mortality risk for CVD in cancer patients and analysed the risk of dying from CVD among cancer survivors. The mortality rate was calculated on the basis of calendar year, age at diagnosis and follow-up time after cancer diagnosis. It was observed that 61% of all cancer patients who died from CVD were diagnosed with either breast, prostate or bladder cancer. It was also shown that cancer patients were perpetually at elevated risk of dying from cardiovascular problems compared to the general population, and this risk was negatively associated with age at diagnosis. Of interest, the greatest risk of CVD mortality was in the first year after a cancer diagnosis.[69]

Cancer and HF now appear to be closely connected: on one hand, an increased risk of cancer development has been recognised in patients with HF, indicating a potential pro-oncogenic substrate given by HF.[6,67,68,70] On the other hand, there is evidence of an increased incidence of HF in cancer patients.[68] The reduced risk of death due to improvements in cancer therapies and management has led to an increased comorbidity burden, including CVD and therefore HF.[70] Moreover, HF is one of the main manifestations of cardiotoxic effects induced by commonly used antineoplastic therapies.[3]

Several epidemiological studies have shown that patients with HF have a higher incidence of cancer compared to controls.[70–74] This may be linked to the close medical observation that HF patients receive, which increases the likelihood of radiological and laboratory tests that identify malignancies.[66,67] In a systematic review and meta-analysis, 515,041 patients with HF were compared with a control group of 1,365,452 patients without HF and were found to have a significantly increased incidence of cancer. Furthermore, there was no difference in mortality rates due to cancer between HF and non-HF patients, which was probably linked to the lack of studies providing hazard ratios for cancer-related death.[70]

This evidence has formed the foundation for the budding concept of 'reverse cardio-oncology', which focuses on the reciprocal relationship between CVD (in particular HF) and cancer pathogenesis.[75]

The intersection between cancer and HF has solid pathophysiological foundations.[68] HF generates a pro-neoplastic *milieu* characterised by secretion of oncogenic factors and neurohormonal activation, which in turn promotes tumour development.[65,68,75] Moreover, HF is characterised by low-grade systemic inflammation and cytokine cascade that predisposes to neoplastic transformation and progression.[75] Supporting the role of inflammation in the development of tumours and HF, the CANTOS study has demonstrated the effectiveness of canakinumab, an anti-interleukin-1β antibody, in reducing cardiovascular events and hospitalisations for HF, as well as reducing the incidence and deaths from lung cancer.[76,77] Moreover, studies have highlighted the key role of inflammation as a mediator of tumour cell development, metastasis and epithelial-mesenchymal transition.[75]

At the same time, some risk factors appear to be shared by HF and cancer, making them closely associated.[4] Over the past decades, risk factors identified with the development of HF, including age, sex, hypertension, diabetes, obesity, diet, sedentary lifestyle and smoking, might appear to be responsible for the development of various cancers as well.[4]

Genetic predisposition may mediate the development of cancer and HF. It has been demonstrated that somatic mutations acquired in haematopoietic cells can lead to the development of leukaemia and increase the risk of HF and the progression of coronary artery disease.[78]

Clonal haematopoiesis of indeterminate potential (CHIP) exemplifies a key element of the intersection between CVD and cancer.[79] CHIP arises from somatic mutations in haematopoietic stem cells that yield clonal progeny of mutant leukocytes in the blood.[79] Individuals with CHIP have an increased risk of ischaemic heart disease and stroke, together with worsened HF outcomes independent of traditional precipitating factors. In this context, studies have demonstrated that certain genetic mutations common in CHIP, particularly in genes such as TET2 and DNA methyltransferase 3 alpha, are associated with an increased incidence of HF and poorer prognoses.[80,81] At the same time, the absence of the driver gene TET2 in animal models resulted in accelerated progression of atherosclerosis and heightened susceptibility to cardiac dysfunction.[80] All in all, the recognition of CHIP as a non-traditional risk factor challenges specialists from haematology/oncology and from cardiovascular medicine.[81–83]

Finally, there are also close connections between HF and cancer in terms of therapies: numerous preclinical studies, meta-analyses and trials have highlighted how various therapies recommended in HF guidelines can have positive or negative effects on outcomes and the incidence of different cancers.[65]

For ß-blockers, preclinical studies have shown their anti-tumour effects, through inhibition of tumour growth, reduction of metastasis development and suppression of tumour angiogenesis.[65] However, in clinical studies, ß-blockers have been shown to exert various effects, depending on tumour types: for breast cancer, lung cancer and melanoma, they appear to increase overall survival, while for others, such as prostate cancer, they seem to worsen it.[65]

Dysregulation of the renin–angiotensin–aldosterone system (RAAS) appears to underlie cancer development.[65] Since various RAAS components are expressed in tumour cells and are part of the tumour microenvironment, RAAS-blocking drugs, which are recommended as first-line treatments for HF, seem to have anti-neoplastic effects.[65]

Glucose is one of the main metabolites required for the growth and survival of tumour cells. Therefore, SGLT2 inhibitors, which mainly block glucose uptake at the renal level, seem to affect tumour cell metabolism and may be protective against cancer.[47]

Lastly, there are opposing studies on the effects of angiotensin receptor-neprilysin inhibitors on tumour growth. *In vivo* and *in vitro* studies have shown that natriuretic peptides may inhibit the growth of tumours and may also be the products of tumour cells.[65]

Conclusion

This review illustrates new frontiers in cardiovascular toxicities induced by oncological therapies, as well as how this branch of cardiology may now configure as a novel platform for translational research into the connections between cancer and the cardiovascular system. Research and dedicated education in cardio-oncology appear to be necessary if we are to guarantee cancer patients optimal surveillance and management of any complications that arise from their treatment. From a clinical perspective, as recently proposed for cardiomyopathies, a 'cardio-oncology mindset' should be proposed, with new-generation cardiologists being prepared to recognise and deal with different clinical scenarios concerning oncology patients with cardiovascular manifestations. ❑

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