Late cardiovascular side effects of cancer treatment

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SUMMARY

Thanks to the enormous progress made in cancer treatment, there are more and more cancer survivors. Oncologists are now concerned with the long-term management of patients who have recovered from their cancer. Giving them the best chance of a healthy survival is a very important issue. However, in this context, epidemiological studies and registries have revealed that the prognosis of cancer survivors is marred by the onset of more frequent and earlier cardiovascular disease. The emerging cardio-oncology discipline is seriously concerned about this issue as the number of patients potentially affected is large and growing. The task consists of identifying patients at increased risk of cardiovascular events after cancer treatment. Patients at risk are those with pre-existing cardiovascular risk factors and heart disease, and those exposed to anticancer treatment with cardiac toxicity that appears during their follow-up. Identifying those high-risk patients is possible thanks to clinical, biological and imaging monitoring. Furthermore, this monitoring allows therapeutic interventions, ranging from lifestyle recommendations to pharmacological treatment. However, several important pending questions remain, including whether cancer survivors would benefit from a more aggressive approach than that used to treat non-cancer survivor patients for the same cardiovascular problem.

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INTRODUCTION: HOW BIG IS THE PROBLEM?

Cancer mortality is continuously decreasing, with over 80% of the young adult and childhood patients diagnosed with cancer currently surviving more than five years.[1] This is the result of remarkable advances in cancer screening, diagnosis and treatment. The current estimation is that about 5% of the general population today is a cancer survivor. This patient population did not exist just a few decades ago, and it is steadily growing. A very important issue is the management of this specific population, an important task that oncologists have integrated into their daily practice.

We currently know very well from epidemiological studies and registries that cancer patients have two uncertainties to deal with: cancer recurrence and cardiovascular disease (CVD). Regarding cancer recurrence, patients are very closely followed-up by oncologists with standardised clinical, biological and imaging monitoring. Regarding CVD prevention and screening, progress remains to be made. A large cohort of cancer survivors in the US with nearly 40-year of follow-up has recently been published.[2,3] The authors observed 1.4 times more CVD deaths in cancer survivors than expected in the general population, corresponding to 3.6 excess deaths per 10,000 person-years, data that are consistent with the results of a previous study concerning more than 200,000 UK 5-year cancer survivors.[4] The highest risk of cardiac mortality was experienced after Hodgkin's lymphoma with a standardised mortality ratio reaching 4.2, corresponding to over 20 excess deaths. The age group of 15-19 years at cancer diagnosis deplored the highest cardiac mor-

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tality compared to the other age groups.

This review paper addresses the CVD determinants in cancer survivors as a combination of pathophysiological processes related to the cancer itself. It also addresses the comorbidities of patients (cardiovascular risk factors, and previous CVD), and the toxicity of anticancer treatments. The various expressions of these cancer-related CVD will also be considered, and cutting-edge knowledge regarding optimal cardiovascular (CV) monitoring in terms of screening and care will be developed. Finally, concerns about unmet needs will close the reflection.

WHAT ARE THE DETERMINANTS OF CVD IN CANCER SURVIVORS?

Common risk factors can predispose to both CVD and cancer. A recent study pooled the data from 20,305 participants from two longitudinal cohorts of subjects, the Framingham Heart Study and the Prevention of Renal and Vascular End-Stage Disease study (PREVEND).[5] Patients were free of cancer at baseline and developed ascertained histology-proven cancer during the follow-up period (median time of fifteen years). Traditional CVD risk factors (mainly age, sex and smoking status), 10-year atherosclerotic risk score and natriuretic peptide concentrations were associated with an increased risk of future cancer. Conversely, a heart-healthy lifestyle was associated with a lower risk of future cancer. Pre-existing CVD and the development of interim CV events were not associated with higher risk of subsequent cancer. When it comes to the risk of developing cardiotoxicity after anticancer treatment, both pre-existing CV risk factors and CVD increase the risk. Therefore, patients with a combination of common CV risk factors, heart disease and a history of cancer face much higher CVD morbidity and mortality than non-cancer patients with same CV profile. It should be noted that cancer itself can also affect directly or indirectly the CV system. These indirect manifestations could be called paraneoplastic. Some are already well described, such as marantic endocarditis, but many others are not yet well understood or even described.

Beyond that, several anticancer treatments present a very well described cardiac toxicity which can appear late during survival and contribute to a significant increase in CV mortality in these patients. A very wide variety of drugs have potential cardiotoxicity, but those with reversible toxicity do not seem to have the same important impact on late CV prognosis. The most widely described cardiotoxic anticancer treatments are anthracyclines and radiation therapy. Both share two general considerations: the concept of cumulative dose toxicity, (although cardiac damage can occur from the first exposure), and the delayed onset of the cardiac toxicity. However, it should be noted that new drugs are continually being introduced, some of which have been associated with unexpected cardiac toxicity. For example, in addition to the well-known risk of myocarditis when using immune checkpoint inhibitors, emerging data points to their potential involvement in accelerated atherosclerosis. This new data should be closely followed up by cardio-oncologists.

WHAT ARE THE LATE CV SIDE EFFECTS OF CANCER TREATMENTS?

The CV toxicity of anticancer treatment has been classified by the European Society of Cardiology (ESC) into nine categories: myocardial dysfunction and heart failure, coronary artery disease, valvular heart disease, arrhythmias, systemic arterial hypertension, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension and pericardial complications.[6] Focusing on the late CV side effects, the list can certainly be narrowed down to myocardial dysfunction and heart failure, coronary artery disease, valvular heart disease, systemic arterial hypertension, peripheral vascular disease and pericardial complications.

HEART FAILURE

Several studies have shown that left ventricular (LV) function can deteriorate after anticancer treatment due to direct drug cardiotoxicity. Heart failure is one of the most frequent but also feared late CV complications of anticancer treatment, and significantly contributes to non-cancer mortality and morbidity. This kind of cardiotoxicity is associated with numerous anticancer drugs, each one having its own specificities. The time point when cardiotoxicity becomes clinically relevant varies as well. Some treatments induce myocardial dysfunction early after exposure, while others generate cardiac injuries that become only clinically manifest years after exposure. Another important distinction comes from the fact that some drugs have cumulative cardiotoxicity, while others do not. Finally, some anticancer therapies are associated with reversible LV dysfunction, as is the case for trastuzumab, and therefore offer the opportunity to test rechallenge. However, it must be admitted that in practice, therapeutic regimens very frequently combine agents exhibiting cardiotoxicities that potentiate each other. In such situation, it becomes very difficult to make predictions about possible recovery.

Among cardiotoxic anticancer drugs, anthracyclines are clearly the pharmacological class for which the most data exist. Cumulative incidence is as high as 10.6% 40-year after childhood cancer.[7] The mechanism of anthracycline-induced cardiotoxicity is still not fully elucidated, but current opinion suggests that oxidative stress is implicated. The

role of topoisomerase-2β, an enzyme required for DNA transcription, replication and recombination, seems to be crucial. When bound to anthracyclines, topoisomerase-2β leads to breaks of double-stranded DNA that result in p53 activation, mitochondrial dysfunction, generation of reactive oxygen species, cell dysfunction and finally death.[8] This cardiomyocytes damage and death lead to subclinical, followed by, in some cases, overt LV systolic dysfunction that can progress to heart failure.

For a long time, it has been thought that anthracyclines cause irreversible cardiomyopathy in a dose-dependent manner, manifested as LV dysfunction and heart failure long after patient exposure. Therefore, they used to have one of the worst prognosis among the different aetiologies of acquired cardiomyopathies. This belief has been gradually challenged in light of recent advances. First, concerning the dose-dependent toxicity, *Feijen et al.* demonstrated that there is no safe dose of anthracyclines.[7] Consequently, the validation of alternative anthracycline-free treatment regimens without compromising the chance of cure is very important. This dose-dependent toxicity is probably the result of the existence of risk factors that potentiate their cardiotoxicity. Among those, we are already able to cite: age (<18 years and >65 years), conventional CV risk factors and pre-existing CVD, combination of cardiotoxic treatments such as association of anthracycline and left thoracic radiation therapy, and genetic predisposition (an area in which much progress is currently being made). On the other hand, the late onset of cardiotoxicity should be defined as the delayed diagnosis of an acute damage, as demonstrated by *Cardinale et al.*[9] This study analysed the outcomes of 2,625 patients that received anthracycline-based chemotherapy for breast cancer or non-Hodgkin lymphoma. *Cardinale et al*[9] demonstrated that cardiotoxicity, defined as a decrease in LV ejection fraction (EF) >10% to a value <50%, occurred within the first year in 98% of patients (mean time between end of chemotherapy and LVEF decline of 3.5 months). Moreover, treating these patients with enalapril plus carvedilol or bisoprolol resulted in an impressive LVEF recovery rate of 82%, contrasting with the previous opinion that anthracyclines were associated with irreversible cardiac damage. In their study, the crucial determinant of cardiac recovery seems to be the time of onset of the cardioprotective therapies. A higher response rate was observed when the treatment was started within the first one to two months after chemotherapy compared with a treatment introduced later than four to six months. These findings stress the major interest of a cardiac monitoring allowing early detection and treatment of anthracycline-induced cardiotoxicity as incorporated in the most recent guidelines.[10] It is henceforth recommended to monitor asymptomatic patients receiving anthracycline treatment with baseline normal LVEF for early detection of cardiac toxicity. The recommended timing of LV function surveillance is after a cumulative dose of doxorubicine 250 mg/m^2, or its equivalent anthracycline, after each additional 100 mg/m^2 and at the end of therapy, even if total dose is less than 400 mg/m^2 (level of evidence I, grade of recommendation A).[10] Importantly, a highly reproducible, quantitative volumetric, non-irradiating imaging is recommended (quantitative 2D/3D echocardiography and cardiac magnetic resonance), using the same imaging modality chosen for serial testing. Transthoracic echocardiography offers the advantage of myocardial deformation imaging using 2D speckle tracking technology, which may facilitate early detection of subclinical cardiac dysfunction. Periodic measurement of cardiac biomarkers (troponin I or troponin T, BNP or NTproBNP) is also suggested unless the exact timing of sampling lacks standardisation (level of evidence III, grade of recommendation C).[10] In many instances, standard cardiac-based therapy should be introduced as soon as possible, since it can stabilise or correct abnormalities, allowing the completion of the prescribed anticancer therapy.

Another important aspect about anthracycline-induced cardiomyopathy has recently been published by *Fornaro et al.*[11] These authors showed that patients with anthracyclines-induced cardiomyopathy treated with optimised heart failure therapy had comparable overall survival rates than patients with idiopathic dilated cardiomyopathy at five and ten years. These findings contradict the previously published data reporting a considerably worse survival rate in anthracycline-induced cardiomyopathy, below 50% at five years. The recent findings of *Fornaro et al.* certainly reflect the progress made in optimising the treatment of heart failure in cancer survivors.

In addition to anthracyclines, late occurrence of heart failure is also a concern after left chest radiation therapy delivered for lung, oesophageal and left breast cancer as well as Hodgkin lymphoma. To some extent, this is due to incidental irradiation of the heart, owing to its proximity with the target volume. The precise incidence of radiation-induced cardiotoxicity is difficult to estimate for several reasons. The main ones are the long delay between radiation exposure and the onset of clinically objective cardiac damage; the continuous improvements in radiotherapy techniques; and the synergistic cardiotoxicitywhen radiation therapy is delivered together with cardiotoxic chemotherapies, which frequently occurs. Among cancer survivors, the risk of heart failure after mediastinal radiation therapy has been shown to be increased by 4.9-fold compared with the general population.[6] Radiation-induced heart failure can manifest as systolic (heart failure with reduced EF, HFrEF) or diastolic dysfunction (heart

failure with preserved EF, HFpEF), as the consequence of interstitial myocardial fibrosis, and is also frequently associated with concomitant radiation-induced coronary artery and valvular disease.

Many other traditional chemotherapies (cyclophosphamide, cisplatin, ifosfamide, taxanes, etc.) and targeted cancer therapies (HER2 inhibitors, VEGF signalling pathway inhibitors, proteasome inhibitors, etc.) can induce myocardial dysfunction. Myocardial dysfunction typically occurs within days of drug administration and long-term follow-up data seem reassuring in terms of absence of late-onset heart failure.

CORONARY ARTERY DISEASE

Acute coronary syndromes can manifest during the anticancer treatment as the consequence of endothelial injury, vasospasm or procoagulant status, but a kind of late cancer therapy- related cardiotoxicity is also frequently encountered. In this setting, chronic coronary artery disease and associated potential myocardial ischemia or infarction are the result of a premature and accelerated atherosclerosis in relation to anticancer-treatment induced-changes in lipid metabolism and/or, chronic activation of inflammation in response to acute endothelial damage.

Supradiaphragmal radiation therapy is associated with a higher incidence of ischemic heart disease through the development of severe atherosclerotic disease, complicated by plaque rupture and thrombosis, which can lead to chronic ischemic cardiomyopathy, acute coronary syndrome or sudden cardiac death.[6] An important study has demonstrated that women who underwent radiotherapy for left breast cancer had higher rates of coronary artery disease than those who underwent radiotherapy for right breast cancer, with a dose-effect correlation based on the mean dose to the entire heart. They found a relative increase in the rate of major coronary events of 7.4% per Gy of radiation, without any apparent safe threshold.[12] This dose-effect relationship has been validated by van den *Bogaard et al.* in an independent cohort of breast cancer patients.[13] Moreover, the authors demonstrated that the volume of the left ventricle receiving more than 5 Gy, which is a dose distribution parameter, was a better prognostic parameter than the mean heart dose. Indeed, the location of the irradiation field is important, as it is the location of the target structures. Another study also demonstrated that it is mainly the coronary arteries located in the target area of radiotherapy (mid and distal part of left anterior descending artery, distal diagonal branch in case of left sided radiotherapy to the chest wall or breast, and proximal right coronary artery in case of right internal mammary chain) that carry an increased risk of clinically significant coronary artery stenosis. This outcome emphasises the need to consider coronary artery as a structure at high risk of damage. Therefore, every effort should be made to avoid irradiation to the coronary arteries.[14]

Considering chemotherapies, cisplatin-treated survivors of testicular cancer have a higher incidence of coronary artery disease, with an absolute risk of up to 8% over 20 years. Among immune and targeted therapeutics, those inhibiting the vascular endothelial growth factor (VEGF) signalling pathways have an increased risk for coronary thrombosis, but the impact of these treatments on the late incidence of coronary artery disease is not yet known.

Immune checkpoint inhibitors have recently been associated with potential accelerated atherosclerosis of clinical relevance. Indeed, in a recent work, *Poels et al.* have demonstrated that combination therapy with anti-CTLA-4 and anti-PD-1 antibodies in mice induces T cell-mediated plaque inflammation and drives plaque progression.[15]

VALVULAR HEART DISEASE

Chemotherapeutic agents do not directly affect cardiac valves, but radiation-induced valvular heart disease has been reported as common, affecting around 10% of treated patients. Left-sided valves are more commonly involved, with the aortic valve being more frequently involved than the mitral one, and insufficiency being more frequent than stenosis. Pathophysiology includes fibrosis and calcifications of aortic valve cusps, mitral valve annulus and the base and mid portions of the mitral valve leaflets, sparing the mitral valve tips and commissures.

PERICARDIAL DISEASE

Delayed pericardial disease can develop six months to fifteen years after exposure to mediastinal radiation therapy, and includes chronic pericardial effusion and pericarditis, which can turn into constriction after exposure to very high radiation doses.

HYPERTENSION AND METABOLIC SYNDROME

Hypertension, obesity, dyslipidaemia and diabetes, clustered together as the metabolic syndrome, are established risk factors for CVD. Childhood cancer survivors seem to be at particular increased risk of developing metabolic syndrome as a consequence of the cancer treatment, especially childhood leukaemia survivors and survivors treated with cranial radiotherapy.[16] Childhood cancer survivors are also shown to have substantially less exercise capacity than community controls as evaluated by maximal cardiopulmonary fitness testing, which may contribute to worse adherence to regular physical activity and potentiate the risk of metabolic syndrome occurrence.

KEY MESSAGES FOR CLINICAL PRACTICE

1. Cancer survivors are at increased risk of cardiovascular morbidity and mortality.
2. Common risk factors may predispose to both cardiovascular diseases and cancer. Common risk factors and heart diseases predispose to cardiotoxicity.
3. Late cardiovascular side effects of cancer treatment that are currently observed are mainly the consequence of previous exposure to anthracyclines or radiotherapy. However, given the continued emergence of unexpected cardiotoxicity with new anticancer treatments, that could of course change in the future.
4. All cancer survivors, and even more those who have been exposed to cardiotoxic drugs or did develop acute cardiotoxicity during cancer management, require a cardiovascular risk stratification. Based on the result, they may also need an individualised cardiovascular follow-up program.

Among modifiable CV risk factors, hypertension is the foremost one, with a reported prevalence of 40% in cancer survivors over 50 years, versus 26% in siblings. It has also the strongest association with all cardiac events and mortality compared to diabetes, dyslipidaemia and obesity.[17,18] However, obesity is associated with a 4-fold increased risk of hypertension. Hypertension can be directly induced by the anticancer treatment (vascular endothelial injury), or indirectly, through anticancer treatment nephrotoxicity and secondary chronic kidney disease. Concerning chemotherapy, prior treatments with high-dose corticosteroids, cyclophosphamide, ifosfamide, cisplatin, vinblastine, gemcitabine, anti-VEGF and tyrosine kinase inhibitors (TKI) have been associated with the development or exacerbation of hypertension through isolated direct, or combined direct and indirect mechanisms. Radiation therapy has also been incriminated through abdominal radiation and renal artery stenosis or neck irradiation and secondary baroreflex failure. Finally, radical nephrectomy for kidney cancer is also associated with the development of hypertension, with partial nephrectomy potentially attenuating this risk.

WHICH PATIENTS REQUIRE A CV FOLLOW-UP?

All cancer survivors, and even more those who have been exposed to cardiotoxic drugs or have developed acute cardiotoxicity during cancer management, require a CV risk stratification and, based on the result, an individualised CV follow-up program.[19,20] However, today the way in which this CV surveillance should be organised is not the subject of universal recommendations in the absence of strong evidence, while many efforts have already been made to standardise the monitoring and diagnosis of acute CVD. The presented study followed the long-term surveillance program established by the 2016 European Society of Cardiology (ESC) position paper on cancer treatments and CV toxicity.[6] A very important issue is to ensure that all cancer survivors benefit from guideline-led cardioprotective therapies, both as primary or as secondary prevention. For paediatric cancer survivors, follow-up should be organised with smooth transition from paediatric to adult onco-cardiologists. A recent cross-sectional observational study conducted in a cardiology unit of a large tertiary hospital in Australia shows that the management of modifiable CV risk factors in patients with a history of cancer is still suboptimal.[21] Cardioprotective therapies, especially statins and antiplatelet agents were under-prescribed in this population compared with patients without a history of cancer and with a comparable CV risk profile. Given that cancer survivors are already inherently at increased CV risk, this issue is of considerable public health importance. Furthermore, so far and unfortunately, no study has assessed whether cancer survivors would benefit from a more aggressive approach than non-cancer survivors.

CONCLUSIONS

The increased CV issues that arise in cancer survivors are, in a way, a positive sign. It reflects the increasing number of cancer survivors due to the improvements in cancer treatment. However, the CV cancer survivor issues should begin at the time of diagnosis, not years after the completion of the treatment. Indeed, at present, we consider as unethical for an oncologist not to consider the CV future of the patients, knowing that the probability of recovery is high. Based on the current evidence that common risk factors may predispose to both CV diseases and cancer, and increase the risk of cardiotoxicity occurrence during cancer treatment, fighting

these risk factors, as soon as the cancer has been diagnosed, should have an impact on both the risk of CV disease and the cancer itself. Moreover, the added value of a cardio-oncology support during the cancer treatment will help prevent cardiotoxicity requiring anticancer treatment modification.

There is an urgent need of more studies addressing the effectiveness of lifestyle interventions and CV risk factors management on CV diseases in childhood cancer survivors to convince and increase adherence to survivorship programs focused on CV prevention.

Enhancing survivorship care has been established as one of the top ten priorities to actualise for cardio-oncology during the global cardio-oncology summit on October 2019, in Sao Paulo, Brazil.[22] The challenge is to build a survivorship clinic, so that cancer survivors can have access to personalised and comprehensive care delivered by experienced clinicians who are aware of the late complications of cancer therapies. Currently, various barriers still exist and prevent the widespread implementation of survivorship care, including the lack of trained providers, and general practitioners and patients lack of knowledge of lifelong risk.

In the near future, multivariable risk prediction models will implement our daily practice, identifying potentially high-risk patients requiring preventive measures and optimal monitoring, reducing the risk of cardiotoxicity and even guiding therapy decisions.

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