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Viewpoint

Cancer Therapy-Related Cardiac Dysfunction: Unresolved Issues

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ABSTRACT

An increasing awareness of chemotherapy and radiotherapy as preventable causes of cardiac failure among large numbers of patients surviving cancer has contributed to the development of cardio-oncology as a subspecialty. Perhaps the most important driver has been that the aging of the population undergoing cancer therapy has provided an increasing number of patients at risk for the development of heart failure. Cardio-oncology has many unresolved questions. In this article the 6 most important unresolved issues requiring additional research are discussed: (1) the frequency of overt heart failure as a manifestation of cardiotoxicity; (2) the optimal diagnostic approach to cardiotoxicity in the context of large numbers of patients requiring repeated testing; (3) the need for better risk prediction; (4) alternatives to the use of ejection fraction as the cornerstone of evaluation; (5) definition of the best strategy for protection; and (6) the need for evidence-based algorithms to guide late follow-up. When this evidence base is mature, we will have a better understanding of the magnitude of the problem of cardiotoxicity, who best to screen (and how), who justifies the use of cardioprotective therapy, and how all at-risk patients should be followed over the decades following cancer therapy.

RÉSUMÉ

Le fait que la chimiothérapie et la radiothérapie soient de plus en plus reconnues comme des causes évitables d'insuffisance cardiaque chez un grand nombre de survivants du cancer a contribué à l'émergence de la cardio-oncologie comme sous-spécialité. Le facteur le plus important a peut-être été celui du vieillissement de la population traitée pour un cancer, ce qui a fait croître le nombre de patients présentant un risque d'apparition d'une insuffisance cardiaque. Or, la cardio-oncologie comporte de nombreuses questions non résolues. Cet article traite des six plus importants problèmes non résolus pour lesquels des recherches supplémentaires s'imposent : (1) la fréquence de l'insuffisance cardiaque patente comme manifestation d'une cardiotoxicité; (2) la méthode optimale pour diagnostiquer la cardiotoxicité chez un grand nombre de patients nécessitant des analyses répétées; (3) la nécessité d'une meilleure prédiction du risque; (4) la recherche de solutions de rechange à l'utilisation de la fraction d'éjection comme pierre angulaire de l'évaluation des patients; (5) la définition de la meilleure stratégie de protection; et (6) la nécessité d'algorithmes s'appuyant sur des données probantes qui guideront le suivi à long terme. Lorsque cet ensemble de données probantes sera constitué, nous aurons une meilleure compréhension de l'ampleur du problème de la cardiotoxicité, du ciblage optimal des patients à soumettre au dépistage (et des meilleures méthodes de dépistage), des critères justifiant le recours à un traitement cardioprotecteur et de la façon dont tous les patients à risque devraient être suivis pendant les décennies qui suivent un traitement anticancéreux.

The associations of common cardiac diseases (heart failure, myocardial dysfunction, pericardial disease, valvular heart disease, and ischemic heart disease) with previous cancer therapies have been known for decades and are recorded in most cardiology textbooks. The development of the topic of cardio-oncology and the resulting multidisciplinary programs[1] reflect several new developments.[2] First, cancer has become a survivable disease, so that these cardiac problems represent a facet of cancer survivorship.[3] Second, as the population ages, the frequency of cancer in the elderly is increasing, and these patients have levels of comorbid disease, which have been less common in previous eras of cancer management. Third, in addition to the roles of radiotherapy and anthracyclines, a new generation of tyrosine kinase inhibitors and small molecules have shown benefit in the treatment of cancer, but with potential side effects on the heart. Although in this issue of the *Canadian Journal of Cardiology* highlights many of these aspects, there are many unresolved questions in cardio-oncology (Table 1), and some are embarrassingly basic. Ongoing research will be needed to complete the evidence base in a number of areas.

A fundamental uncertainty relates to the frequency of overt heart failure as a manifestation of cardiotoxicity, because this end point is the driver of investment in early diagnosis and

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Table 1. Unresolved issues

Frequency of heart failure in target populations
• Age and comorbid disease subgroups
• Early vs long-term follow-up
Definition of cardiotoxicity
• Distinction of heart failure from LV dysfunction
• Developing a non-EF-based definition
• Understanding the balance of cardiotoxic and other contributors
Risk prediction
Diagnostic testing
• Roles of tissue characterization and strain
• Biomarkers
Cardioprotection
• Situation-specific selection of particular agents
• Imaging-based vs universal strategy
Evidence-based algorithms for long-term follow-up

EF, ejection fraction; LV, left ventricular.

management of at-risk patients. Discerning whether early and late cardiotoxicity are separate phenomena is similarly of importance because a commonality between these entities would suggest that early surveillance with sensitive tests has a role in controlling late manifestations. If these are separate entities, then the issue of long-term follow-up intervals becomes more important, because it would suggest that a process for early detection at the time of cancer chemotherapy will not avoid the transformation into overt disease after exposure to other stimuli—perhaps because early diagnosis is insensitive to subclinical disease. The diagnostic approach to cardiotoxicity is also unresolved. Because of the numbers of patients, and the requirement for repeated testing, expensive imaging tests are probably not optimal, and a biomarker-based screening strategy with confirmation using imaging would seem more feasible, although the question remains as to whether this is actually practicable. The optimal agents for protection against cardiotoxicity remain uncertain, with similar effect sizes for statins, dexrazoxane, angiotensin inhibition and blockade, and β-blockade. More importantly, the appropriate choice between trying to protect all patients vs targeting cardioprotection at those at higher levels of risk or preclinical disease remains unresolved.

Epidemiology

Cancer has changed from a fatal to a usually survivable disease, with an increasing number of cancer survivors. Breast and hematological malignancies are among the 5 most common causes of cancer in men and women—these conditions are associated with chemotherapy that is commonly linked to cardiotoxicity, and likely to stay among the most common cancers for the foreseeable future.[4] Likewise, radiotherapy remains a cornerstone of cancer therapy, despite its cardiac complications.[5] These risks provide challenges not only with respect to the early surveillance of patients during therapy, but also the surveillance over long-term follow-up over several decades.

Clearly, the frequency and severity of heart failure in chemotherapy patients is an important determinant of how intensely surveillance is undertaken, and clearly plays into decision-making regarding potential preventive strategies. However, estimates of the frequency of heart failure and left ventricular (LV) dysfunction are widely variable, and understanding the drivers of this heterogeneity is important.[6] Although overt heart failure from cardiotoxicity is believed to carry a very adverse prognosis, the anecdotal information from heart failure centres performing transplantation and ventricular assist devices is that few of these patients with advanced heart failure have a cancer-related etiology. Likewise, clinical trials have shown a relatively low incidence of heart failure ($< 5\%$) or LV dysfunction ($< 10\%$).[7] Older studies show that the frequency of heart failure in the follow-up of patients treated with anthracycline appears to have increased from the initial risk reports of approximately 1% to reports of $> 10\%$. Moreover, epidemiologic studies have shown the development of heart failure and LV dysfunction in $> 20\%$ of patients.[8,9] There has been discussion about the degree to which this might represent the age and comorbidity differences between clinical trial and the "real world" of population health studies.[10] This difference could also reflect the presence of standardized clinical evaluations in clinical trials, rather than administrative coding of the diagnosis of many clinicians, without reference to a standardized protocol, in epidemiologic studies. Finally, the difference might also reflect the effect of duration of follow-up and the propensity of elderly patients (with or without a cancer history) to develop heart failure, the lifetime risk of which is 20%.[11]

Defining Cardiotoxicity

A definitive diagnosis of cardiotoxicity would involve clinical evidence of heart failure that is temporally associated with exposure to a potentially cardiotoxic agent. Because the outcome of heart failure in this setting is so poor, such a presentation is usually considered to be a failure of surveillance, prophylaxis, or both. The definition of cardiotoxicity is arbitrary, on the basis of an arbitrary reduction of LV function—a 10% decrease to subnormal function (< 0.53) in an asymptomatic patient and a 5% decrease to subnormal function in a symptomatic patient.[12] It should be recognized that the diagnosis of cardiotoxicity encapsulates 2 scenarios that are potentially quite different—the recognition of toxicity that has actually occurred, and the recognition of the patients at risk for the development of toxicity.

Asymptomatic LV dysfunction is associated with increased risk of subsequent heart failure and might be used as reasonable grounds for initiating prophylactic therapy. However, LV dysfunction is an ambiguous signal—it might be reversible (eg, trastuzumab), attributable to other causes, and limited by image quality (especially with echocardiography). The definition of LV dysfunction is probably better made in the context of a known baseline evaluation than from a single study. Thus, the term, cardiotoxicity, needs to be modified or staged so that asymptomatic LV dysfunction is differentiated from clinical evidence of heart failure.

LV dysfunction as a marker of cardiotoxicity works well in patients early after chemotherapy, but the connection is more difficult in late follow-up. Very commonly, heart failure has multiple etiologies; it is possible for a patient to be exposed to anthracycline in middle age, endure a lifetime of hypertension and diabetes mellitus, develop heart failure in old age, and have this presentation labelled as being due to cardiotoxicity. If there is subclinical LV dysfunction early after

chemotherapy, attribution of heart failure to cardiotoxicity might be expected on the basis of a relentless process initiated by chemotherapy, perhaps potentiated by "multiple hits" of heart failure risk factors over decades. Although it is possible that exposure of patients to cardiotoxic agents sensitizes the heart to other insults, in the absence of evidence of early LV dysfunction, the attribution of heart failure to cardiotoxicity seems more difficult.

Thus, additional efforts are required to align previous chemotherapy with diagnosis of heart failure before the conclusion is made that the cause is cardiotoxicity. A meaningful attribution of heart failure to cardiotoxicity will need somehow to account for other causes, especially when late cardiotoxicity is being considered.

Risk Prediction

The effective prevention of problems on a population-wide basis is heavily dependent on accurate assessment of risk. Unfortunately, appreciation of risk of cardiotoxicity is rudimentary. As in other situations of calculating risk, it is paradoxical that numbers of low-risk patients developing cardiotoxicity outweigh the higher proportion of small numbers of high-risk subjects. Much attention has been devoted toward defining a threshold dose of anthracyclines, but it has been apparent from the earliest reports that cardiotoxicity might occur from low doses of anthracyclines; there is no universally safe dose of anthracycline from the standpoint of heart failure risk.[13]

An assessment of risk is also strongly dependent on other potential drivers of heart failure and cardiotoxicity. Large administrative databases have been used to develop risk scores on the basis of age, type of chemotherapy, and comorbidity (coronary disease, atrial arrhythmias, diabetes mellitus, hypertension, and renal failure).[14] The problem at the moment is that although this process has identified levels of risk, it has not identified a low-risk group who could be followed with less extensive surveillance.

Diagnostic Testing

As mentioned previously, the current criteria for cardiotoxicity involve consideration of symptoms, change of ejection fraction (EF), and criteria of "abnormal" EF. In addition to the ambiguity of heart failure symptoms in the cancer patient, the EF criteria of the cardiotoxicity diagnosis are problematic. Other challenges include the variability of testing that arises from changing physiology from time to time as well as the limits of measurement of EF. In fact, the 95% confidence intervals for repeated measurements using 2-dimensional means for measurement of EF have been reported to be as high as 12%.[15] Several other limitations of measurement of EF are well known (Table 2). There are 2 main imaging strategies for prevention, detection, and management[16]:

(1) A functional definition could be used with techniques of higher accuracy and lower variability. Cardiac magnetic resonance (CMR) is the reference standard for the measurement of cardiac volumes and EF. Although susceptible to poor image quality, 3-dimensional measurement of EF also overcomes the variability that arises from the use of different imaging planes, and as a consequence, shows less variability than 2-dimensional measurement.[17] Fundamentally, however, there are inherent disadvantages in the use of EF—especially the limited prognostic value of EF when it is close to the normal range, and the effect of loading conditions on EF. Measurement of myocardial deformation (or strain imaging) provides an alternative technique, which is more sensitive to minor changes of function.

Table 2. Limitations to prognostic value of ejection fraction

Technical
• Geometry-dependent
• Difficulties posed by high and low heart rate
• Left bundle branch block
• Mitral regurgitation
• Expertise
Load dependence
Insensitivity to change
Test-retest variability

Myocardial strain is usually measured using speckle tracking echocardiography, but can also be assessed using CMR. A number of studies have documented that this is a sensitive marker of minor change, which seems to precede the deterioration of EF by several months,[18] thereby suggesting the ability of this technique to recognize patients in early-stage disease who might be amenable to cardioprophylaxis. This technique has been shown to provide prognostic information superior to EF in other settings. Although it appears to be robust, the transition of strain from research to clinical tool is still in progress, and the learning curve is unclear.[19] Differences in software between vendors appears to be less important than previously thought.[20,21] However, whether its use changes overall patient outcome remains to be proven, and this is the topic of an ongoing multicentre study.

(2) Approaches to the early detection of cardiotoxicity could be on the basis of tissue characterization, predominantly using CMR. The use of gadolinium late enhancement has not shown high value in the recognition of toxicity,[22] presumably because the process is diffuse. However, T1 and T2 mapping appear to be markers of early disease in the setting. Although the disadvantage of these strategies is that they will likely be difficult to translate to large numbers of patients at risk of cardiotoxicity, research using this technology might facilitate the more efficient diagnosis of the condition with more widely available technologies.

Finally, the development of a biomarker-based approach would seem to be the most feasible screening strategy for a relatively uncommon condition with a large number of patients at risk. Indeed, troponin appears to be a sensitive marker of myocardial damage, which is of value in type I and type II cardiotoxicity.[23] However, the release of troponin appears to be inconsistent through time, so a sampling strategy needs consideration. Nonetheless, it does appear that a negative component result in the setting of normal strain has a very high negative predictive value. Some evidence suggests that the treatment of patients after troponin release allows the salvage of ventricular function in most but not all patients.[24] The implications of the use of high-sensitivity troponin are

unclear. The value of troponin for the recognition of cardiotoxicity late after chemotherapy is questionable.

Other biomarkers have been studied, including type B natriuretic peptide. The value of this as a marker of early cardiotoxicity is controversial, and the test is currently under evaluation in a large randomized trial.

In summary, the optimal diagnostic approach for cardiotoxicity remains to be defined. The attraction of EF appears to be limited to its historical use and perhaps will be displaced by other tests. The epidemiologic challenges of screening large numbers of individuals need to be kept in mind.

Cardioprotective Strategy

A number of agents have been shown to protect against the development of cardiotoxicity. They can be grouped into 3 major categories, including those that interfere in the mechanisms whereby myocytes are damaged by cardiotoxic agents, those that reduce the workload on the heart, and ones that reverse the processes of injury, which compromise ventricular function.[25] As reviewed by Moudgil and Yeh, the rational selection of cardioprotective agents depends on understanding the underlying mechanisms of injury.[26] Although this has mainly focused on the myocardium, the role of the vasculature should not be neglected.[27]

Type I cardiotoxicity, related to anthracyclines, seems likely to involve free radicals and the inhibition of DNA repair by topo-isomerase. Observational and limited clinical trial data suggest that statins are cardioprotective, and if this is the case it seems likely that the mechanism involves protection against free radicals. Dexrazoxane is also thought to provide protection against free radicals, and this cardioprotective agent appears to work by protection of the DNA repair pathway. Whether this process is confined to the myocardium or includes tumor tissue, which could compromise the activity of anthracyclines, remains an issue of contention.

Observational studies and clinical trials have suggested that agents such as angiotensin-converting enzyme inhibitors and β-blockers are cardioprotective. Although both of these agents might have antioxidant properties, their effect seems more likely to relate to unloading the heart and interrupting inappropriate feedback loops, which potentiate fibrosis. Other agents such as mineralocorticoid antagonists might act as antifibrotic agents, although it is unclear as to whether fibrosis is an important early component of cardiotoxicity. Recent analyses suggest that a similar level of protection is available with each of these agents, but more research is needed to identify the optimal protective therapy.

A more fundamental controversy relates to how cardioprotection should be used. At present, measurement of EF is used to identify the presence of preclinical disease, and the agents are initiated in response to this. The preceding discussion about the limitations of EF measurement suggest that another technique—for example, assessment of myocardial strain—might be more effective for this purpose. However, an alternative strategy would be to initiate prophylactic treatment of all at-risk individuals undergoing chemotherapy. Certainly, some small clinical trials have used this strategy and shown benefit with a high level of patient acceptance. A modelling comparison of these approaches, including assessment of cost effectiveness, suggests that this selection might need to be tailored to the type of cancer.[28] However, recalibration of this modelling will be required in the development of exercise as an alternative, nondrug preventive strategy to the emergence of cardiotoxicity.[29]

Long-term Follow-up

A striking aspect of cardiotoxicity is that patients who present with heart failure usually do so years after the initial insult with a cardiotoxic drug. As discussed previously, this likely reflects loss of cardiac reserve due to subclinical cardiac damage, as well as the coexistence of multiple etiologies, including common causes of heart failure and cancer,[30] direct effects of cancer on the heart, and the effect of acute and chronic cardiac insults after successful chemotherapy. This latent interval between treatment and the onset of heart failure is perhaps most apparent in patients undergoing radiotherapy. It seems likely that a better understanding of the interaction between myocardial damage related to cancer, and common causes of heart failure will shed light on the risk evaluation of this problem and how best to avoid it.

Conclusions

Awareness of the adverse cardiac consequences of cancer chemotherapy and radiotherapy has been present for decades. The recent upsurge of interest in this area pertains to the increasing survivorship from cancer, as well as the availability of new, sensitive markers for LV impairment that might precede the development of heart failure. Ongoing research is required to better understand the number of patients at risk, the optimal means of recognizing the problem, the most effective cardioprotective agents and the best strategy for their use, as well as the optimal timing of long-term follow-up.

Disclosures

The authors have no conflicts of interest to disclose.

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