Mechanistic science in cardiovascular-oncology: the way forward to maximise anti-cancer drug effects and minimise cardiovascular toxicity

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Dramatic improvements in cancer survival have arisen because of the rapid development of novel anti-cancer therapies. The potential for cardiovascular toxicity associated with these drugs often reflects overlap between pathogenic cancer mechanisms and physiological pathways required for normal cardiovascular function. Clinical Science has, therefore, compiled a themed collection on Cardiovascular-Oncology. This collection examines the intersection between cancer treatments and their potentially harmful cardiovascular effects. By defining the mechanisms underlying unwanted cardiovascular effects of anti-cancer therapies, cardioprotective strategies can be developed. Only by doing so, will patients be able to achieve optimal cancer treatment at the minimum cost to cardiovascular health.

Recent decades have seen remarkable improvements in cancer survival. In the context of this success in cancer treatment, minimising the potential for competing cardiovascular risks has never been more important. Indeed, Cardiovascular-Oncology is now well-established as a clinical specialty and is receiving an appropriate increase in attention from the pre-clinical scientific community. Patients with cancer are more prone to cardiovascular comorbidity as a result of shared genetic predispositions [1,2] and risk factors including smoking, obesity and inflammation [2]. Furthermore, this heightened risk for cardiovascular disease may be further amplified by cancer therapies because of overlap between pathways required for normal cardiovascular homoeostasis and those involved in tumour initiation, growth and metastasis. Many targeted anti-cancer therapies have the potential to cause cardiovascular adverse effects by acting simultaneously upon physiologic and pathogenic pathways and mediators. Furthermore, there has been an associated reinvigoration to improving our understanding of the mechanisms and strategies to mitigate cardiovascular toxic effects of conventional chemotherapeutic agents, principally anthracyclines. In this themed collection on Cardiovascular-Oncology, these areas are addressed with particular focus on mechanistic pathways relevant to cardiovascular toxicity of anti-cancer therapies.

Targeted therapies

Although the association between anthracycline exposure and subsequent left ventricular dysfunction and heart failure has been recognised since the 1960s [3], the introduction of trastuzumab for the treatment of HER2-positive breast cancer prompted much more widespread concern from cardiologists. In early trials of patients treated with this monoclonal antibody directed against ErbB/neuregulin-1 (NRG-1), excellent anti-cancer effects were observed, the likes of which had not been seen before in this aggressive tumour
subgroup, but with a substantial incidence of cardiotoxicity (27% when given concomitantly with an anthracycline [4]; 7.2% in meta-analysis of subsequent trials [5]). By virtue of these clinical observations, reverse translation identified the important role of NRG-1 in myocardial physiology [6]. More recently, targeting tumour angiogenesis has become an important strategy in the treatment of many solid organ cancers, including renal, hepatocellular, thyroid and others. Vascular endothelial growth factor (VEGF) signalling is the primary target of these anti-angiogenic drugs. However, in contrast with the early situation with trastuzumab, the importance of VEGF in cardiovascular haemostasis and development had been well described for decades prior to therapeutic targeting. It is, therefore, not surprising that anti-VEGF drugs are strongly associated with unwanted cardiovascular effects including hypertension [7,8] and left ventricular dysfunction [9] which, at least partly, reflects microvascular dysfunction. It is notable that other therapies, including targeted inhibition of rapidly accelerated fibrosarcoma B-type (BRAF) and mitogen-activated extracellular signal-regulated kinase (MEK) for the treatment of cutaneous melanoma are also associated with a broad range of toxicities [10]. This is not unexpected given the well-known and important role of these mediators of the mitogen activated protein kinase (MAPK) signalling cascade in cardiovascular physiology. There is now a much greater appreciation that adverse effects of anti-cancer therapies extend far beyond ‘just’ left ventricular dysfunction and that a complex interplay exists between micro- and macro-vascular diseases with hypertension, direct myocardial toxicity and frequently a pro-inflammatory, pro-atherogenic environment [9].

**Immunotherapy**

Immunotherapy has provided impressive advances in cancer survival, including for patients with advanced and aggressive malignancies who would previously have had the most dismal of prognoses. In those patients who respond to immunotherapy, radiographic disappearance of advanced cancer may be achieved and survival for many years is possible. In a recent analysis, almost 40% of patients with cancer would currently be eligible for treatment with immunotherapy [11]. While the majority of treatment-related adverse effects are non-cardiovascular, myocarditis can be a devastating complication, with mortality at approximately 50% in early case series and registries. A range of other cardiovascular adverse effects is becoming clearer and includes atherogenesis and myocardial infarction as well as non-inflammatory cardiomyopathy, vasculitis and pericarditis [12]. Furthermore, there is growing evidence for the use of immunotherapy in combination with angiogenesis (VEGF) inhibitors. The cardiovascular consequences of more prolonged exposure to angiogenesis inhibition remain unknown, although these are a concern and require careful prospective ascertainment via longer term trial follow-up with appropriately defined cardiovascular endpoints and via dedicated cardio-oncology registries. Whether angiogenesis inhibition potentiates the cardiovascular toxic effects of immunotherapy, particularly atherogenesis and plaque inflammation remains unclear [13]. In more general terms, there is great potential for interaction between cardiovascular therapies and anti-cancer agents, especially via cytochrome P450 effects [14].

**Anthracyclines**

The growth of cardiovascular-oncology has stimulated better understanding of the cardiotoxic effects and mechanisms associated with anthracyclines. Attempts to prevent anthracycline-induced left ventricular dysfunction using conventional neurohormonal therapies including β-blockers and renin–angiotensin system inhibitors have been somewhat disappointing [15]. The established benefits of these drugs are in patients with the clinical syndrome of heart failure and consequent neurohormonal system activation. It is highly conceivable that a different approach targeting the direct myocardial toxic effects of anthracycline exposure would be more effective for the prevention or treatment of asymptomatic left ventricular dysfunction [16]. Dexrazoxane, an iron chelating agent with additional effects upon topoisomerase 2β, is approved for use in a narrow range of circumstances for the prevention of anthracycline-induced cardiotoxicity. However, better mechanistic understanding and alternative approaches would be valuable. The effects of a novel pro-drug (ICRF-193) has been elegantly explored by Kolláróvá-Brázdová and colleagues in a rabbit model of anthracycline-induced cardiotoxicity [17]. Carrera and colleagues provide an overview of the potential for manipulation of cytochrome 1B1 for the prevention of cancer therapy-associated cardiac dysfunction while simultaneously having the potential to sensitize anti-cancer effects, including in the context of anthracyclines [18].

**The future**

Clinical and basic science endeavours in cardiovascular-oncology have, historically, been reactive to the large and rapid successes in cancer treatment but are finally becoming increasingly pro-active. As a community, cardiologists
and cardiovascular researchers must work in closer collaboration with oncologists and cancer scientists and pay particular attention to defining the mechanisms underlying unwanted cardiovascular effects of anti-cancer therapies. Only by doing so will patients be able to achieve optimal cancer treatment at the minimum cost to cardiovascular health.

Competing Interests

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Abbreviations

NRG-1, neuregulin-1; VEGF, vascular endothelial growth factor.

References