Cancer Treatment Related Cardiac Dysfunction - Unravelling the Mechanisms to Improve Breast Cancer Patient Care and Detailing the Need for a National Cardio-Oncology Network

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Breast Cancer Epidemiology and Current Treatment Paradigms

Currently one in eight Irish women are diagnosed with breast cancer during their lifetime. Breast cancer treatment has evolved to include personalised therapeutic approaches, with refined locoregional strategies including conservative surgical techniques, more patient and tumour specific radiotherapy regimens and the development of targeted systemic therapies informed by an improved understanding of tumour biology. The contemporary approach to breast cancer treatment aims to optimise oncologic outcomes, while minimising the negative sequelae of cancer treatment. This approach has been validated through the enhancement of oncological and survival outcomes, with National Cancer Registry data confirming five and ten year breast cancer survival of 90.3% and 83.8% respectively.

As breast cancer-survival continues to improve survivorship issues are becoming increasingly important. There is emerging evidence to suggest that female breast cancer survivors are more likely to die of cardiovascular disease (CVD) than their age-matched counterparts. This relates not only to a higher prevalence of risk factors for CVD in this population, but is increased exponentially by Cancer Treatment Related Cardiac Dysfunction (CTRCD). CTRCD refers to the cardiotoxic effects of cancer treatment which can occur acutely during cancer treatment, disrupting the treatment course, or later, negatively impacting the quality of life and survival of these patients (Figure 1). The combination of chemotherapy, radiotherapy and targeted therapy (anti-oestrogen and anti-human epidermal growth factor receptor-2 (HER2)) poses a significant cardiotoxic risk. These risks are even higher in an aging breast cancer population in whom pre-existing CVD is increasingly common. Therefore, in order to maximise anticipated clinical outcomes, it is critical that cardiovascular assessment and monitoring are considered for patients being treated for breast cancer. This article focuses on the need for clinical and translational research programme to inform care pathways dedicated to improving cardiac and oncological outcomes for breast cancer patients. It contextualises the national and international evidence and sets the scene for a necessary new national network being piloted at the National University of Ireland, Galway (NUIG).

Cancer Treatment Related Cardiac Dysfunction & Risk Factors

Contemporary breast cancer management is multimodal, involving surgical resection and the use of combined chemotherapy, radiotherapy and targeted therapies to maximise oncological outcomes. In the era of personalised therapy each of these therapeutic strategies carries their own risk of CTRCD, which highlights the requirement for care pathways to individualise and stratify according to the competing risks. Anthracycline-based chemotherapy leads to CTRCD in between 3 - 48% of patients. Cellular targeting of DNA topoisomerase IIB (TOP2B) is hypothesized to cause anthracycline-induced CTRCD, but the mechanism of myocardial cell injury remains unclear. Recently, Sandamali et al. outlined that 33.2% of patients being treated for invasive breast cancer developed subclinical CTRCD in the 6-months following treatment with anthracycline chemotherapies. Similarly, anti-HER2 therapies are known to be cardiotoxic: In their analysis of 931 patients being treated for HER2+ disease, Battisti et al. recently outlined that 16.6% of patients experienced CTRCD (defined as left ventricular dysfunction on echocardiogram or clinical manifestation of heart failure decompensation following treatment) to Trastuzumab (Herceptin©). Trastuzumab-mediated cardiotoxicity occurs due to TOP2B binding by Trastuzumab, highlighting the danger of Trastuzumab and anthracyclines synergistically inducing CTRCD.

The majority of patients are diagnosed with oestrogen receptor positive breast cancer, necessitating treatment with anti-oestrogen endocrine agents. There is some evidence that Tamoxifen may be cardioprotective compared to aromatase inhibition. A clinical study of 9,350 patients from Abdul-Qadir et al. previously illustrated an increased risk of myocardial infarction in postmenopausal women treated with aromatase inhibitors (AIs) versus tamoxifen (a selective estrogen receptor modulator) (hazard ratio: 2.02, 95% confidence interval (CI): 1.16 – 3.53). Interestingly, Khosrow-Khavar et al. performed a systematic review and meta-analysis of randomized controlled trials illustrating the cardioprotective value of Tamoxifen relative to placebo (rate ratio (RR): 0.67, 95% CI: 0.45 – 0.98) and increased risk of cardiac events with AI use (RR: 1.18, 95% CI: 1.07 – 1.34) relative to tamoxifen use. Similarly, a large study from the Surveillance Epidemiology and End Results (SEER) database observed radiotherapy-induced heart disease (RIHD) in 2% and 1% of those in receipt of left- and right- sided chest wall radiotherapy respectively. Consequently, there remains a current need to establish an algorithmic approach to identify those at risk of developing CTRCD from multimodal breast cancer treatment and delineate a risk benefit ratio for therapeutic effectiveness for the various interventions.

Predicting Tumour and Host Response to Treatment

The establishment of biomarker discovery programs is the cornerstone of improved personalised treatment strategies. These biomarkers can be present in the circulation or represented in clinical data such as available imaging. An enhanced understanding of the biological and genomic properties of cancers, factors which may leverage anticancer effects and produce less host toxicity is key to better survivorship.

Measurement of circulating biomarkers from venous sampling before, during, or after treatment have proven useful in deciphering those likely to respond favourably to the treatment as well as those at risk of CTRCD. For example, mi(cro)RNAs are small (19–25 nucleotides in length), endogenous, non-coding RNA understood to play important regulatory roles in governing gene expression and cellular activity. Aberrant miRNA expression profiles have been correlated with and provide valuable information in predicting patients likely to achieve favourable responses to (neo)adjuvant treatment for breast cancer. Interestingly, there is emerging in-vivo clinical trial data illustrating the predictive value of expression profiles of circulating miRNA such as miR-21 and miR-195 in predicting patients who will successfully achieve a pathological complete response to neoadjuvant chemotherapy in breast cancer. While these efforts have focused on tumour response to treatment, efforts to decipher patients at risk of CTRCD are also being explored: Silencing of miR-34a has been reported as key modulatory step in reducing doxorubicin-induced CTRCD while miR-215 has been identified as an informative biomarker of RIHD. Furthermore, there are several genetic biomarkers which have been associated with predicting treatment response and host toxicity to treatment: The seminal work of Zhang et al. first illustrated that cardiomyocyte-specific deletion of TOP2B protects cardiomyocytes from Doxorubicin-induced DNA double-strand breaks and transcriptome changes responsible for CTRCD. A recent systematic review outlined 88 genes and 154 single nucleotide polymorphisms (SNPs) perceived to be causative for chemotherapy-induced CTRCD and highlighted the importance of 6 key variants which were obviously associated with chemotherapy-induced CTRCD.

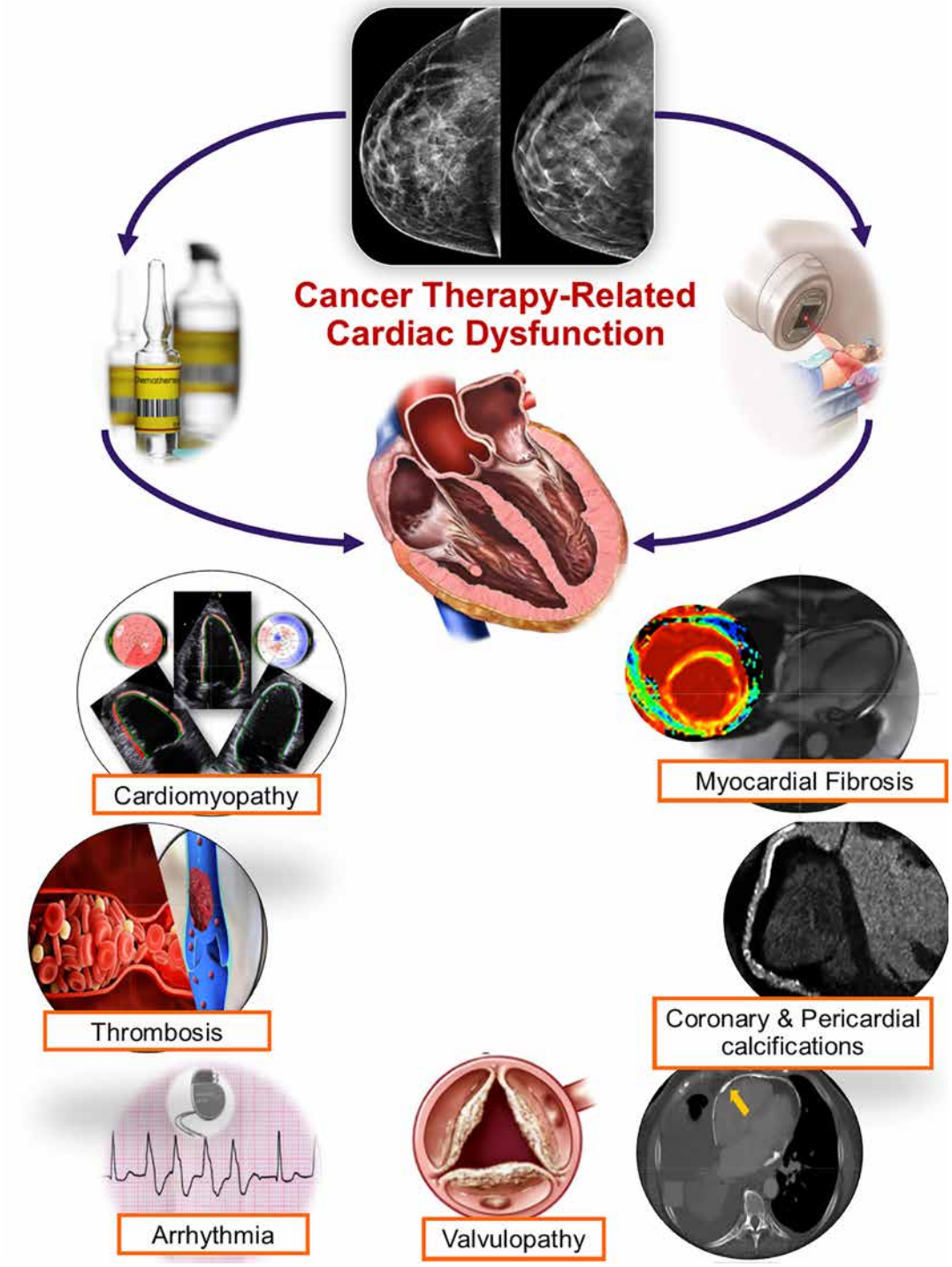

Figure 1. The potential impact of Cancer Treatment Related Cardiac Dysfunction (CTRCD) on patients being treated for cancer

Interestingly, radiogenomics (or radiomics) is an emerging field in medical imaging with potential to interrogate data from grey scale images from medical imaging to outline quantitative diagnostic and prognostic genomic information through high-throughput extraction of primary tumour features. Radiomics seems promising in deciphering host and tumour outcomes and the hypothesis has evolved to indicate that treatment naïve imaging may be practical in identifying those at risk of CTRCD. In the context of breast cancer treatment, Meshman et al. recently outlined the value of dose-weighted computed tomography radiomics for predicting patients likely to succumb to RIHD among those being treated for early breast cancer. While this concept remains in its infancy, refinement of artificial intelligence models looks promising in facilitating earlier detection rates of CTRCD in patients diagnosed with breast cancer.

Survivorship Needs

Quality of life is defined by the World Health Organization as “an individual’s perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, and standards and concerns”. Quality of life QoL comprises, among other elements, the sense of mental and physical well-being, opportunities for personal development, material status, social relationships, and functioning in the immediate environment. Health related

QoL, defined as the functional effect of physical, mental and social response to the disease and treatment, as perceived subjectively by the patient as well as the patient's assessment of their life situation during the treatment period. The determinants of Health Related QoL may include the disease itself, the resulting disability and the type of intervention performed. For patients undergoing multimodal treatment for breast cancer, there are multiple factors that may impact HRQoL including the effects of the disease itself but also the toxic sequelae of cancer treatment, including CRTCD. QoL assessment is an important consideration when optimising a care pathway or intervention. There is very little data reported on the impact that CTRCD has on HRQoL, with only qualitative data in small patient series, therefore there remains an unmet need to establish the current survivorship issues within patients who have developed CTRCD following treatment for breast cancer using current multimodal strategies.

Cardio-Oncology: The Irish Context

Breast cancer management requires a careful balance of adequate and appropriate cancer treatment while minimising cardiac risk and other toxicities. Despite over 3,000 new patients being diagnosed and treated for breast cancer in the Republic of Ireland each year, the relationship between breast cancer treatment and cardiovascular health has never been extensively investigated. Additionally, the scientific evidence upon which clinical decisions can be made is currently limited, with documented knowledge gaps in the area of Cardio-Oncology. Consequently, there is a lack of data regarding cardio-oncological incidence, causative factors, and clinical and survivorship outcomes, which further highlights the necessity for a multidisciplinary approach to both research and clinical management of breast cancer patients. Therefore, the involvement of both Cardiology and Oncology specialists is essential in the delivery of care and long-term surveillance of breast cancer patients.

In Ireland, there is currently no established Cardio-Oncology clinical pathway or network which may enhance detection. Moreover, there is limited data outlining the cardiovascular and survival outcomes in those being treated for breast cancer. Prior et al. recently described the competing risks of cardiovascular and oncological 10-year mortality in their recent analysis of 102 patients diagnosed and treated for stage I-III breast cancer who underwent resection with curative intent. Interestingly, the authors report a decrease in CVD-related risk of mortality at 10-years from 26.5% to 9.9% in high-risk patients through risk factor optimisation. While these authors report predictive CVD outcomes in a small Irish cohort, there remains a paucity of data in relation to the risk of, biomarker prediction, and survivorship outcomes associated with CTRCD in Irish patients. Furthermore, there remains a lack of established services dedicated to enhancing Cardio-Oncology patient care in the Republic of Ireland.

Informing the development of a Cardio-Oncology Clinical Network - European and International Guidelines

The primary aim of establishing a Cardio-Oncology Clinical Network is to manage and optimise CVD in the cancer treatment-naïve patient, to minimise the risk of CTRCD, and to treat those who succumb to CTRCD as a sequalae of their cancer treatment. To achieve this, a multi-faceted, multi-disciplinary, and collaborative approach from several specialists is required and the preliminary data from the United Kingdom is overwhelmingly positive: Overall, 94% of the total number of cancer patients referred with left ventricular CTRCD observed an improved ejection fraction with appropriate therapies and 88% were fit to continue their treatment following intervention by Cardio-Oncology services. Therefore, it seems imperative that efforts are made in the Republic of Ireland to provide these services to our prospective cancer patients: Guidelines from the European Society of Cardiologists (ESC) recently outlined several template structures which Cardio-Oncology programs can be run, which encompass several local and regional circumstances. Interestingly, the ESC emphasize the importance of a tight-knit multi-disciplinary approach in developing and ensuring the provision of Cardio-Oncology services to a region, irrespective of local infrastructure and resources. Ghosh et al. provide a concise review of their experience in establishing the Bart's Heart Centre and University College London Hospital cardio-oncology services in the United Kingdom. Similarly to the ESC, these authors highlight the value of the multi-disciplinary team in ensuring benchmark care, while emphasizing the clinical importance of research, clinical audit, education and training in ensuring the provision of the service to their population. These principles echo the fundamental philosophy outlined by the British Cardio-Oncology Society, which was established to enhance cardio-oncological patient services in 2012. Finally, the American College of Cardiologists (ACC) provide an extensive review and guideline outlining the key stakeholders expected to partake in providing Cardio-Oncology services. The ACC demonstrate the necessity of Cardio-Oncology-specific cardiologists, other cardiologists, oncologists, specialist nurses, research nurses, cardiac physiologists, secretarial support, and cardio-oncology management staff to ensure adequate provision of cardio-oncology services in a centre of excellence. Of note, the ACC uses the Bart's Heart Centre to exemplify the key requirements needed to establish Cardio-Oncology clinic in a new centre.

Precision Cardio-Oncology Research Enterprise (P-CORE)

The Precision Cardio-Oncology Research Enterprise (P-CORE) at NUIG is a multidisciplinary collaboration of cardiologists with specific expertise in advanced cardiac imaging which has the potential to identify early signs of CTRCD, working closely with surgical and medical oncologists responsible for biomarker discovery programmes to individualise breast cancer treatment delivery and surveillance. The P-CORE principle investigators are as follows (Figure 2): Professor Aoife Lowery (Professor in Translational Research & Consultant Breast Surgeon), Professor Osama Soliman (Professor of Cardiovascular Research & Consultant Cardiologist), Professor William Wijns (Professor of Interventional Cardiology) and Professor Michael Kerin (Chair of Surgery and Managed Clinical and Academic Network Director).

References made available upon request from the Corresponding Author

Figure 2: Principle investigators from the Precision Cardio-Oncology Research Enterprise (P-CORE) at the National University of Ireland, Galway (NUIG). Clockwise from top: Professor Michael Kerin, Chair and Professor of Surgery at NUIG; Professor Aoife Lowery, Associate Professor of Surgery at NUIG; Professor William Wijns, Professor of Interventional Cardiology at NUIG; and Professor Osama Soliman, Professor of Cardiovascular Research at NUIG.