Editorial

Disparate worlds drawing closer together - cardiovascular biomarkers predict outcomes in treatment naïve cancer patients

Cardiovascular disease and malignancy are the leading cause of death for approximately two-thirds of the population in developed countries. Over the last 5 decades both these clinical fields have observed major breakthroughs in various diseases, such as reperfusion for acute myocardial infarction and targeted molecular cancer therapies, leading to improved survivorship and significant reductions in disease-related morbidity. One area of intense focus for both fields has been the development of novel biomarkers for diagnosis, disease surveillance, targeting therapies with companion diagnostics, monitoring response to treatment and prognosis. The application of increasingly more varied, sensitive and sophisticated biomarkers has contributed to the major gains in healthcare outcomes for patients diagnosed with cardiovascular disease or cancer.

The adverse impact of some cancer therapies upon the cardiovascular system has been known for several decades, such as anthracycline-induced and radiation-induced cardiotoxicity. This problem has escalated in recent years with the growing number of targeted molecular therapies which significant efficacy upon specific cancers, but increasingly more complex cardiovascular toxicity profiles impacting upon outcomes in the cancer survivors. This has resulted in the rapid growth of ‘Cardio-Oncology’ as a new medical subspecialty to concentrate knowledge, understanding, education and care of the cardiovascular co-morbidities, risks and complications in cancer patients as they progress through treatment pathways with potential cardiotoxicity.

A new challenge has arisen relating to the potential impact of the cancer itself upon cardiovascular health. It has been recognised for many years that inflammation and various inflammatory cytokine profiles are elevated in cancer, and contribute to cancer disease progression. In parallel similar and overlapping pathways such as IL-1, IL-6 and TNFα are also activated in chronic cardiovascular diseases such as atherosclerosis and heart failure, where again they contribute to disease progression. In both cancer and chronic heart failure these pathways are drivers of skeletal muscle cachexia, and in cancer patients, preclinical models suggest that some of the most metabolically ‘toxic’ cancers can also drive maladaptive remodelling of the heart directly, leading to cardiac cachexia and dysfunction.

Modern cardiac biomarkers provide a potential toolkit to study cardiovascular health in cancer patients and have been applied in numerous studies to detect and monitor cardiotoxicity secondary to chemotherapy and targeted molecular therapies, with clinically applicable results, particularly regarding negative predictive value of normal cardiac biomarker profiles. However what has not been clear was how the underlying cancer pathophysiology may also impact upon cardiac biomarkers. In the issue of Heart Pavo and colleagues address this important question and report results from their study systematically measuring a panel of cardiovascular biomarkers measured in a cohort consecutively enrolled cancer patients in their centre, with biomarker measurement timed at baseline cancer diagnosis and prior to cancer therapy. (REF) Serum levels of a range of clinically
licensed (NT-proBNP, hs-TnT, CRP,) and exploratory (MR-proANP, MR-proADM, CT-proET-1, Copeptin, IL-6, serum amyloid A, fibronectin, haptoglobin) cardiovascular biomarkers were measured in 555 patients with a range of primary malignancies at first presentation to the oncology service, and recorded baseline cardiovascular risk factors. They excluded subjects with an abnormal baseline cardiac status defined as a significant structural cardiac abnormality on echocardiography which was performed in selected patients triggered by a reported history of cardiac disease, an abnormal baseline ECG or NT-proBNP>400pg/ml.

Their major and novel finding, at a median of 25 months (IQR 16-31), was the prognostic value of elevated cardiac biomarkers at baseline to predict all cause mortality. The biomarkers with most significant predictive value for mortality, independent of age, gender, cancer type, cancer stage and cardiac comorbidities on multivariate analysis, were NT-proBNP, hs-TnT, MR-proANP, MR-proADM, CT-proET-1 and Copeptin. In the examples of the two natriuretic peptides NT-proBNP and MR-proANP the effect size was impressive (HR 1.54 for NT-proBNP and 1.31 for MR-proANP). These cardiac biomarkers also displayed significant correlation with inflammatory biomarkers including IL-6 and CRP, although the latter were not independent predictors on an individual basis, and showed progressive increase with advancing tumour stage.

This report raises a number of interesting questions. The first is why are these ‘cardiovascular’ biomarkers elevated at baseline diagnosis in cancer patients? From a cardiovascular perspective we consider these biomarkers as functional hormones (NT-proBNP, MR-proANP, MR-proADM, CT-proET-1) or markers of cardiac injury (hs-TnT) from myocardial or vascular origin. This could imply the cancer is able to induce a direct or indirect toxic effect on the heart or vasculature to a degree that is clinically relevant. Preclinical studies of the hearts from rodent cancer models provide mechanistic clues which could explain this direct cancer-related cardiotoxicity, particularly via the cancer-related cytokines. However the biology appears much more complex, as many of these hormones are also directly involved in the pathogenesis of malignancy, whether relating to angioneogenesis in the tumour as part of the metastatic development, or in modification of the tumour microenvironment which ultimately support tumour progression. In addition many patients have overt or occult sepsis at presentation with malignancy as a confounding factor which could raise these biomarkers, and it is not clear if patients with infection were actively excluded. Whether the biomarker source is the heart and general vasculature or from the cancer itself remains to be determined.

A second issue is what these elevated biomarker levels are predicting. Unfortunately the cause of death was not reported, as acknowledged by the authors, and therefore it is not clear whether these biomarkers are predicting cancer death, cardiovascular death in cancer survivors (albeit over a short time window) or a composite. Give the heterogeneity of cancers, cancer staging and treatment pathways in this real world cohort, it is impressive that these biomarkers can maintain a strong predictive prognostic potential. These biomarkers have established role in clinical cardiology for diagnosis and in some cases prognostic value. More recently there is increasing knowledge that in some tumours these biomarkers may drive the malignant and metastatic potential. For example adrenomedullin has a direct role in the development and progression of angioneogenesis in tumours, and could be a therapeutic target as well as a biomarker of activity and metastatic potential. There is also a growing body of evidence that some tumour cells express natriuretic peptide receptors on their surface membrane, and ligand binding increases transformation to the
malignant phenotype. Conceivably these biomarkers could in one subgroup reflect cancer activity and metastatic potential, and thereby cancer prognosis, whilst in another subgroup perhaps identify a group with either pre-existing cardiovascular disease which is destabilised by the cytokines released by the cancer and/or a group with higher susceptibility to cardiotoxic side effects of certain treatment pathways, and thereby predict cardiovascular mortality.

A few practical observations and questions arise from this study. Cardiovascular risk factors and medication were common at baseline in this unselected cancer population e.g. 45% hypertension, 8% diabetes mellitus, 31% ACE inhibitor or angiotensin receptor blocker use, 22% beta-blocker use, and therefore was the screening protocol sufficiently rigorous to exclude all patients with established cardiovascular disease? Approximately 7% of patients had a history of heart failure, and details of the baseline echocardiography and the cut off values for various echocardiographic parameters for inclusion versus exclusion would be helpful to ensure there was not a skew based on subclinical but significant pre-existing cardiovascular disease.

There was also a relatively high 2 year mortality of 34% in this unselected cancer population, reflecting ~50% of the cohort with a tumour at stage 3 or 4 at presentation. Whether this represents an unusually high risk cancer population remains to be determined, and so caution is required before extrapolating these results to more common but lower risk cancer populations.

This study opens the potential for new management strategies integrating cardiology and oncology. Treating overt and perhaps subclinical cardiac dysfunction may improve outcomes in cancer patients, and possibly improve progression-free cancer survival based on optimising cancer treatment and preventing interruptions. These biomarkers could serve as a surveillance strategy for both cardiologists and oncologists. It would be equally tantalising to know whether treating the cancer effectively improves cardiac outcomes, but this will be more challenging to unravel if the cancer treatment imparts potential cardiotoxicity.

The key next stage will be to reproduce these findings in a prospectively designed multicentre study with larger numbers in order to validate the conclusion, collect the mode of death and also consider whether serial biomarker assessment adds further predictive power. Pavo and colleagues should be congratulated on bringing to our attention the widening complexity of biomarker biology, and the potential to identify single biomarkers with the unique properties to predict both cardiovascular and oncology outcomes. This result could help pave the way to inform both oncology and cardiology clinical communities regarding the mechanistic value of this risk prediction in order to help target escalation of cancer therapy or target cardiovascular prevention strategies, in our combined ongoing goal of risk stratification to guide cost-effective personalised medicine.

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