Managing the cardiovascular risk in cancer therapy: a paradigm shift?

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Dr. Zaha will not be discussing off-label uses in his presentation.

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Biographic Information

Dr. Zaha is leading the Cardio-Oncology Clinic within the Clinical Heart Center, provides multimodality cardiovascular imaging diagnosis, including Echocardiography, Nuclear Cardiology and Cardiac MRI, and acts as a Liaison for the Center for Translational Medicine at the Advanced Imaging Research Center at UT Southwestern Medical Center. His research and clinical interests involve non-invasive cardiac mechanical and metabolic phenotyping for early diagnosis and guidance in the management of cardiomyopathies using multi-modality cardiac imaging modalities such as echocardiographic strain imaging, radioactive PET tracers, and multi-parametric cardiac MRI, as well as the development of novel non-radioactive hyperpolarized carbon-13 MRI spectroscopic imaging methodology for translational cardiac investigations.

Purpose & Overview

The purpose of this presentation is to describe recent advancements at the interface of cardiology and oncology that support the cardiovascular health of cancer patients who receive treatments with potentially cardiotoxic effects.

Cardio-oncology / onco-cardiology is a new interface subspecialty that bridges cardiology and hematology-oncology to support the cardiovascular health of patients with hematologic and oncologic malignancies. Tremendous progress in the early diagnosis and treatment of cancer has resulted in the last 5 decades in a significant increase in cancer survival. Life with and after cancer is a reality for many more patients, so that by 2026 there will be more than 20 million cancer survivors nationwide. The ages of these survivors will span a wide spectrum, as more than 80% of children treated for malignancies survive more than 5 years. Unfortunately some of the therapies effective to treat malignancies have long term cardiovascular toxicity, decreasing life expectancy after surviving cancer. Therefore, significant efforts have been made to develop a focused approach to the diagnosis and management of cardiovascular complications of cancer treatment. Recognizing the vulnerable population and the potential cardiotoxic therapeutic classes, and implementing guideline based approaches, including referral to a cardio-oncology clinic, can help to improve cardiovascular outcomes in this patient population.

Educational Objectives

1. Recognize characteristics of the patients vulnerable from cardiovascular perspective
2. Recognize the major categories of cardiotoxic oncotherapies
3. Integrate clinically current guideline recommendations for screening and management of cardiovascular complications
4. Recognize the rapid progression of molecular targets in cancer and their potential cardiovascular side effects
5. Appreciate future research direction in early diagnosis of cardiotoxicity

The intersection between cardiology and oncology

Cancer and cardiovascular disease remain the two most common causes of mortality in the United States, although survival for both conditions has improved steadily over the last 5 decades. By 2026 the number of cancer survivors is estimated to reach more than 20 million in US[1]. The death rate for all cancers declined by 22% between 1991 and 2011, driven by both earlier diagnostic and improved therapeutic modalities[2]. It is increasingly recognized that many cancer patients experience cardiovascular complications as a result of their therapies. This includes the development of newly diagnosed cardiovascular problems, or the exacerbation of underlying cardiovascular disease. Rates of cardiotoxicity from cancer-related therapeutics have been reported to be in excess of 30%, but their impact depends on the type of anti-cancer therapy utilized , with some events occurring several decades after the completion of treatment[3, 4]. Cardiac toxicity is the second most common cause of morbidity and mortality in cancer survivors[5].

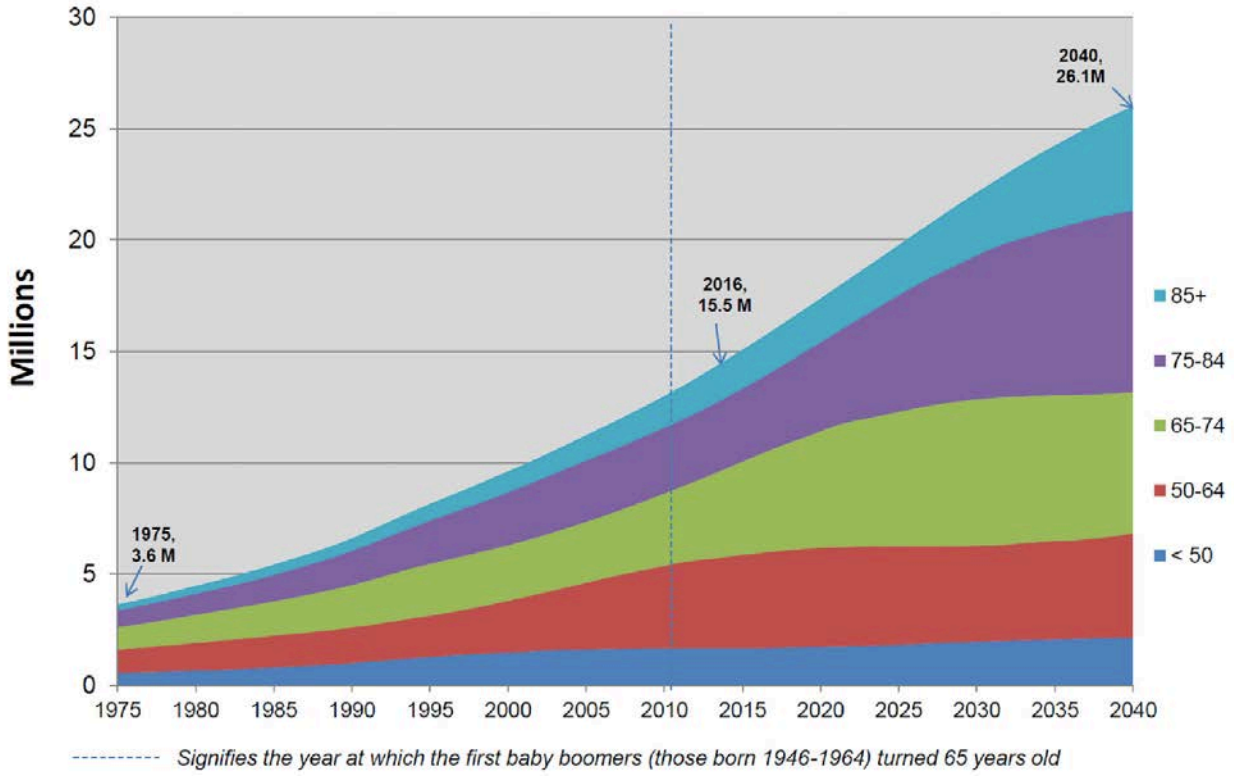

Fig 1. Estimated cancer prevalence by age in the US population from 1975 (216 M) to 2040 (Bluethmann SM, et al. *Cancer Epidemiol Biomarkers Prev*. 2016;25:1029-1036)

Cardiovascular complications of cancer therapy can be divided into nine main categories[6]:

- myocardial dysfunction and heart failure (HF);
- coronary artery disease (CAD);
- valvular disease;
- arrhythmias, especially those induced by QT-prolonging drugs;
- arterial hypertension;

- thromboembolic disease;
- peripheral vascular disease and stroke;
- pulmonary hypertension and
- pericardial complications.

Professional guidelines

Practice guidelines have recently been published to summarize the current experience and best practice strategies for addressing the cardiotoxic effects while maximizing anti-cancer therapy[6, 7]. Cohort studies in childhood cancer survivors have shown that modifiable risk factors have a multiplicative effect on development of major cardiac events in cancer survivors[8]. Risk factor control is recommended as an important early strategy. Detection of early cardiac function changes and sensitive biomarkers have also been investigated[9, 10]. Further research is though required to understand the underlying risk profile at individual level.

Risk factors
• Cumulative dose
• Female sex
• Age
- >65 years old
- Paediatric population (<18 years)
• Renal failure
• Concomitant or previous radiation therapy involving the heart
• Concomitant chemotherapy
- alkylating or antimicrotubule agents
- immuno- and targeted therapies
• Pre-existing conditions
- Cardiac diseases associating increased wall stress
- Arterial hypertension
- Genetic factors

Table 1. Factors associated with risk of cardiotoxicity following treatment with anthracyclines (Zamorano J. *Eur Heart J*. 2016;37:2739-2740).

Anti-cancer therapies with cardiotoxic potential

Utilized successfully for cancer treatment over the last 5 decades, anthracyclines and radiation, are still effective in several cancers, but well known to cause cardiovascular complications[11]. Anthracyclines are associated with cardiotoxicity, including heart-failure symptoms, in a progressive, dose-dependent manner. Radiation therapy (especially targeting the chest) has been associated with myocardial, valvular, pericardial, and vascular toxic effects[12]. In the case of anthracyclines, investigators have gained mechanistic insights into such cardiotoxicity[13].

However, the expansion of the molecular approach in cancer has resulted in new mechanisms of cardiotoxicity. During the past two decades, a better understanding of the molecular pathways that are involved in tumor progression has led to the introduction of more selective, mechanism-based therapies, such as kinase inhibitors.

Kinases also play a critical role in cardiovascular homeostasis, including vascular, metabolic, and myocardial regulation. Therefore, it is not entirely surprising that kinase inhibition may result in cardiovascular toxicity. In unexpected instances the specific kinase that is inhibited is not known to have a biologic role in the cardiovascular system, resulting in on-target toxicity. Also, multitargeted small-molecule inhibitors can result in off-target effects[14, 15].

Multitargeted Tyrosine Kinase Inhibitors

Small-molecule inhibitors that can block multiple tyrosine kinases expanded the arsenal of targeted cancer therapies. Imatinib, the first such multitargeted tyrosine kinase inhibitor, inhibits the ABL1 kinase, a tyrosine kinase that is activated in chronic myeloid leukemia (CML), as well as proto-oncogene receptor tyrosine kinase (KIT) and platelet-derived growth factor receptor alpha (PDGFRA), which are mutationally activated kinases in gastrointestinal stromal tumor, turned fatal cancers into manageable chronic conditions[16, 17].

Next-generation tyrosine kinase inhibitors were initially developed to overcome imatinib resistance, with more rapid and profound molecular responses, but also broader cardiovascular side effects. Four such drugs — dasatinib, nilotinib, bosutinib, and ponatinib — serve as such examples in CML.Whereas imatinib showed minimal cardiovascular complications, dasatinib was associated with cardiopulmonary issues, especially pulmonary hypertension; both nilotinib and ponatinib were associated with vascular events.Ponatinib, a unique drug owing to its potent activity against ABL1 kinase mutations that remain resistant against other tyrosine kinase inhibitors, was even briefly removed from the market in the United States because of substantial vascular events. CML has become a chronic disease, with a predicted 5-year survival rate of more than 90%[18].

Newer generations of tyrosine kinase inhibitors are tested for various types of cancer. Although many tyrosine kinase inhibitors appear to have cardiovascular side effects, it is unclear whether such events are clinically significant. For example, ibrutinib, which inhibits Bruton’s tyrosine kinase, has shown considerable efficacy in certain types of B-cell cancers. In a recent trial, 3% of the patients who received ibrutinib had grade 3 or higher atrial fibrillation requiring hospitalization or invasive intervention, as compared with none of the control patients who received an alternative agent[19, 20].

HER2 Inhibitors

Trastuzumab, a humanized monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2), a receptor kinase that is overexpressed in a subgroup of breast cancers, dramatically improved the prognosis of women with HER2-positive breast cancer. However, in the first pivotal study, either symptomatic heart failure or asymptomatic cardiac dysfunction developed in an alarming 27% of patients who received trastuzumab with traditional chemotherapy (doxorubicin and cyclophosphamide)[21].

Subsequent trials and clinical experience with trastuzumab showed a lower incidence of cardiomyopathy, perhaps in part owing to closer cardiac monitoring and recognition of

cardiac toxicity. In breast-cancer trials, the incidence of symptomatic heart failure in trastuzumab-treated patients was 2 to 4%, and the incidence of cardiac dysfunction was 3 to 19%.[13-15] Basic studies showed a critical, unexpected role for HER2 in cardiac biologic features, which suggested on-target toxicity[22].
A number of newer HER2-targeted therapies have been approved and can be used in combination with trastuzumab. The cardiotoxic effects of such combination therapies are less clear, although early studies have suggested a reasonable safety signal. Another confounding factor is that clinical trials of trastuzumab largely excluded patients with a history of cardiac disease or heart failure; such exclusions do not apply once a drug is approved. As such, several retrospective analyses with the use of publicly available databases have suggested a higher rate of trastuzumab-associated cardiotoxicity than what is reported in the breast-cancer clinical trials[23].

An important unanswered question is the long-term clinical sequelae of such subclinical cardiomyopathies. In 2016, the survivorship guidelines of the National Comprehensive Cancer Network emphasized early recognition and prevention of heart failure in patients who had received anthracyclines. They also advised that high-risk survivors should undergo a thorough clinical screening for heart failure within 1 year after completion of anthracycline therapy.

Inhibition of VEGF Signaling Pathway
Vascular endothelial growth factor A (VEGFA), which is secreted by tumors, plays a critical role in angiogenesis through binding VEGF receptors and activating the VEGF signaling pathway.VEGF signaling inhibitors have been approved for a number of different cancers, with more than 10 therapies that have been approved by the Food and Drug Administration (FDA). From a cardio-oncology perspective, VEGF signaling inhibitors have been associated with a vast array of cardiovascular issues, including hypertension, vascular toxic effects, and cardiomyopathy.Nearly all the patients who have been treated with VEGF signaling inhibitors have an increase in blood pressure, often in a dose-dependent and transient manner, within 1 week after treatment. The overall incidence of hypertension ranges from 20 to 25% with bevacizumab and sunitinib (the initially approved drugs in this class) to more than 50% with newer approved agents. Both systolic and diastolic blood-pressure levels have been affected[17].

Immuno-oncologic therapies
Immune checkpoint inhibitors to treat cancer
An important part of the immune system is its ability to tell between normal cells in the body and those it sees as “foreign.” This lets the immune system attack the foreign cells while leaving the normal cells alone. To do this, it uses “checkpoints” – molecules on certain immune cells that need to be activated (or inactivated) to start an immune response.

Since the approval of the first PD-1 checkpoint inhibitor, **Pembrolizumab**, in 2014, there has been an explosion of the numbers of trials testing these drugs, both alone and

in combination. The latest figure, coming from the **Cancer Research Institute** (CRI) in the US, sets the number in over 1,500 trials.

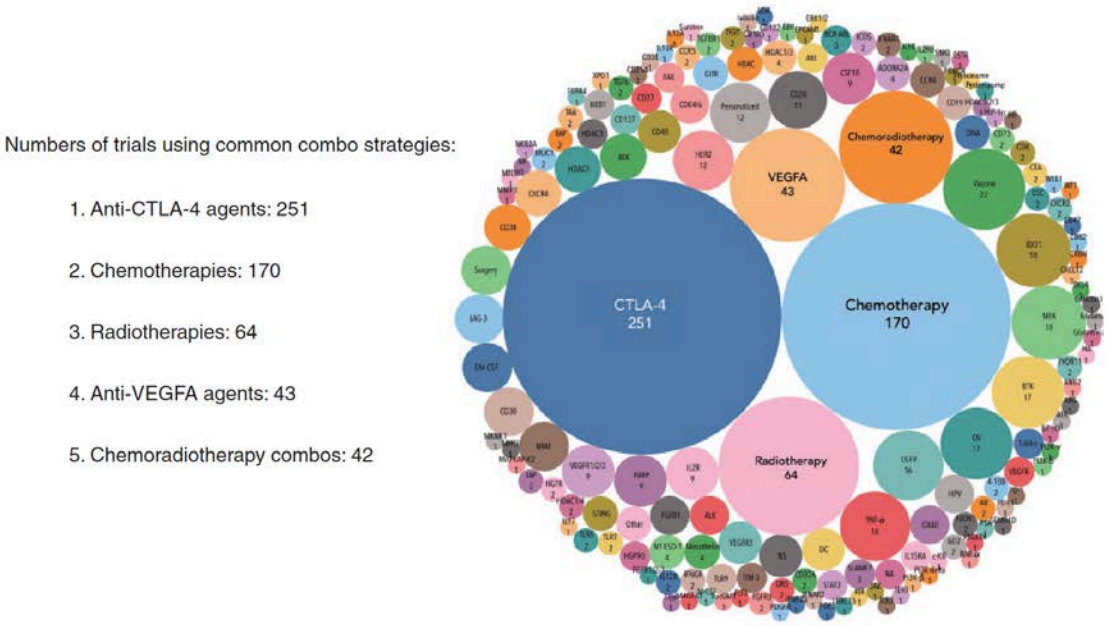

Fig 3. Targets of anti-PD-1/L1 combination trials. The size of the bubble correlates to the number of trials (Tang J, et al. Ann Oncol. 2018;29:84-91).

Drugs that target PD-1 or PD-L1

PD-1 is a checkpoint protein on immune cells called T cells. It normally acts as a type of "off switch" that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells. When PD-1 binds to PD-L1, it basically tells the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1, which helps them evade immune attack. Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost the immune response against cancer cells.

PD-1 inhibitors: Examples of drugs that target PD-1 include:

- **Pembrolizumab (Keytruda)**
- **Nivolumab (Opdivo)**

These drugs have been shown to be helpful in treating several types of cancer, including melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma.

PD-L1 inhibitors: Examples of drugs that target PD-L1 include:

- **Atezolizumab (Tecentriq)**
- **Avelumab (Bavencio)**
- **Durvalumab (Imfinzi)**

These drugs have also been shown to be helpful in treating different types of cancer, including bladder cancer, non-small cell lung cancer, and Merkel cell skin cancer (Merkel cell carcinoma).

Drugs that target CTLA-4

CTLA-4 is another protein on some T cells that acts as a type of “off switch” to keep the immune system in check.

Ipilimumab (Yervoy) is a monoclonal antibody that attaches to CTLA-4 and stops it from working. This can boost the body’s immune response against cancer cells.

This drug is used to treat melanoma of the skin. It is also being studied for use against other cancers.

Checkpoint inhibitors can cause serious or even life-threatening auto-immune side effects. Compared to drugs that target PD-1 or PD-L1, serious side effects seem to be more likely with ipilimumab[24].

Other immuo-oncologic therapies

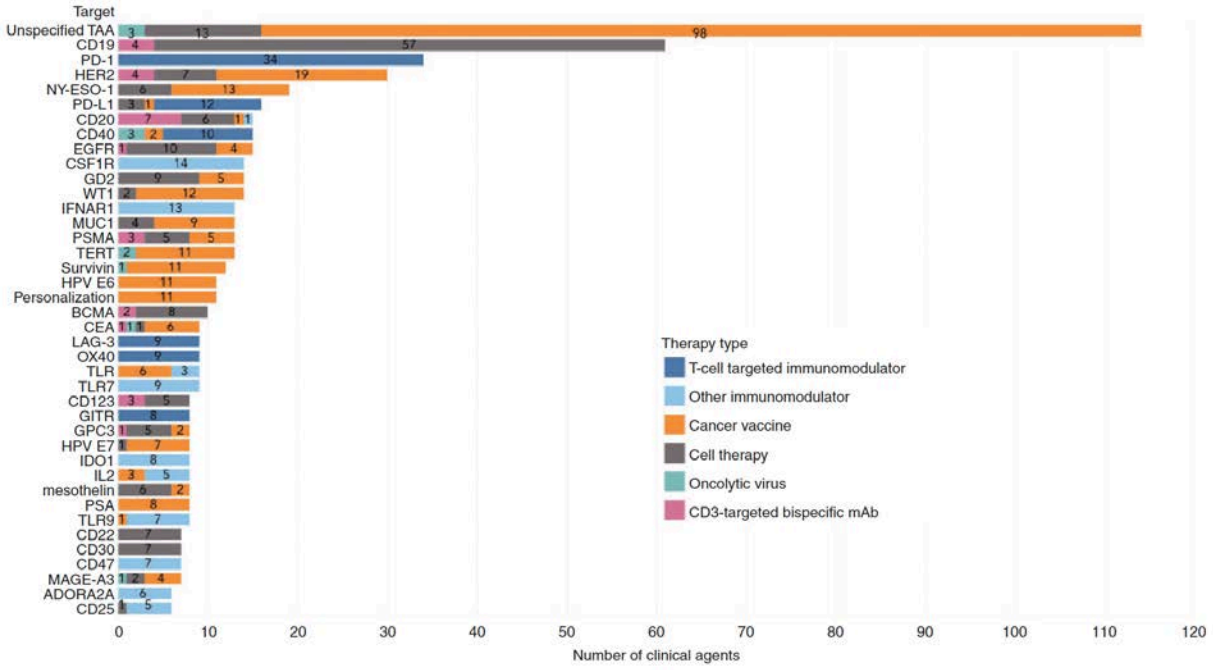

Fig 4. The top 40 targets with the most clinical-stage immuno-oncology agents. (Tang J, et al. Ann Oncol. 2018;29:84-91).

Conclusions

The current experience with cardiovascular toxic effects associated with cancer therapies introduces several important points that are pertinent to clinical care and future therapeutic developments:

1) personal risk profile and modifiable risk factors are very important for established therapies;
2) refer high risk individuals to cardio-oncology clinics for early diagnosis of side effects;
3) define drug-related toxic effects versus cardiovascular events that are not related to these drugs;
4) cardiovascular toxic effects that are identified with new cancer therapies must also be balanced against the prognosis of the cancer, existing therapies, and the net benefit of therapy; 5) cancer clinical trials often exclude patients with a previous cardiovascular history and many clinical trials do not prospectively evaluate cardiac measurements, such as left ventricular dysfunction, so cardiovascular events may be higher in the real-world population
6) a closer collaboration between cardiologists and oncologists is necessary, both in clinical trial design and in adjudicating cardiovascular end points
7) when a drug-associated toxicity is identified, it is important to understand the precise mechanisms of cardiovascular toxicity to help identify patients at risk for cardiovascular events
8) further research is required to develop early diagnostic tools

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