Title

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Journal

Circulation Research, 130(4)

ISSN

0009-7330

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Publication Date

2022-02-18

DOI

10.1161/circresaha.121.319901

Peer reviewed

HHS Public Access

Author manuscript

Circ Res. Author manuscript; available in PMC 2023 February 18.

Published in final edited form as:

Circ Res. 2022 February 18; 130(4): 632–651. doi:10.1161/CIRCRESAHA.121.319901.

Sex-Specific Cardiovascular Risks of Cancer and Its Therapies

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Abstract

In both cardiovascular disease and cancer, there are established sex-based differences in prevalence and outcomes. Males and females may also differ in terms of risk of cardiotoxicity following cancer therapy, including heart failure (HF), cardiomyopathy, atherosclerosis, thromboembolism, arrythmias and myocarditis. Here, we describe sex-based differences in the epidemiology and pathophysiology of cardiotoxicity associated with anthracyclines, hematopoietic stem cell transplant (HCT), hormone therapy and immune therapy. Relative to males, the risk of anthracycline-induced cardiotoxicity is higher in pre-pubertal females, lower in pre-menopausal

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Disclosures:

JM has served on advisory boards for Bristol Myers Squibb, Pfizer, Takeda, Audentes, Deciphera, Janssen, ImmunoCore, Myovant, Cytokinetics, and AstraZeneca, ProteinQure, and Pharmacyclics. JCW is co-founder for Khloris Biosciences. BK has served as a consultant for Pfizer and Cytokinetics. NSW, SJR, MM, EJS, BKH, SA, and JWR have no additional disclosures.

females, and similar in post-menopausal females. For autologous HCT, several studies suggest an increased risk of late HF in female lymphoma patients, but sex-based differences have not been shown for allogeneic HCT. Hormone therapies including GnRH modulators, androgen receptor antagonists, selective estrogen receptor modulators and aromatase inhibitors are associated with cardiotoxicity including arrhythmia and venous thromboembolism. However, sex-based differences have not yet been elucidated. Evaluation of sex differences in cardiotoxicity related to immune therapy is limited, in part due to low participation of females in relevant clinical trials. However, some studies suggest that females are at increased risk of immune checkpoint inhibitor myocarditis, although this has not been consistently demonstrated.

For each of the aforementioned cancer therapies, we consider sex-based differences according to cardiotoxicity management. We identify knowledge gaps to guide future mechanistic and prospective clinical studies. Furthering our understanding of sex-based differences in cancer therapy cardiotoxicity can advance the development of targeted preventive and therapeutic cardioprotective strategies.

Keywords

Cardiovascular Disease; Women; Sex; Gender

Introduction

In both cardiovascular disease (CVD) and cancer, there are established sex-based differences in prevalence and outcomes [1, 2]. Risk of cancer treatment-related cardiotoxicity, as defined by heart failure (HF), cardiomyopathy, atherosclerotic vascular disease, thromboembolic disease, arrhythmias, or myocarditis, has been noted to differ according to sex as well. Certain malignancies, such as hormone-sensitive cancers, also have a sex predilection. The purpose of this review is to describe the sex-based differences in the epidemiology and mechanisms of cardiotoxicity of both conventional chemotherapies as well as targeted and immune therapies. Considerations for sex-based differences in the management of cardiotoxicity are also covered when data exist. We focus on four main treatment classes that are associated with clinically important cardiotoxicity risk: anthracyclines, hematopoietic cell transplantation (HCT), hormonal therapies, and immune therapies (Table 1).

Anthracyclines

Background

Anthracyclines are a cornerstone of chemotherapy used in the treatment of liquid and solid tumors both across children and adults. Anthracyclines include agents such as doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone, and these therapies are used in the treatment of acute leukemias, Hodgkin and non-Hodgkin lymphoma, Ewing sarcoma, osteosarcoma, neuroblastoma, and breast cancer, among others [3]. The most widely studied cardiotoxicity associated with anthracyclines is systolic dysfunction, ranging from asymptomatic declines in left ventricular ejection fraction to symptomatic HF.

Sex-based differences in epidemiology

Overall, the menopausal state and age of female patients appear to be key determinants of sex-specific differences in anthracycline-induced cardiotoxicity, with pre-pubertal females at increased risk [4–6], adult males at increased risk [7–10], and elderly males and post-menopausal women at similar risk [11].

Studies focusing on early-onset (<one year from diagnosis) anthracycline-induced cardiotoxicity in childhood cancer patients are limited, but support female sex as an adverse risk factor [4]. For example, in a retrospective study of 6,493 childhood cancer patients, females treated with anthracyclines had a two-fold risk (relative risk [RR] 1.89, 95% CI 1.28–2.78, p<0.01) of early-onset cardiotoxicity compared to males [4]. For young children receiving chemotherapy for hematologic malignancies, pre-pubertal females are at increased susceptibility of developing both early and late cardiovascular toxicity relative to males of the same age [4–6].

There are also several studies of longer-term (>one year) childhood cancer survivors that suggest females are at increased risk of anthracycline-induced cardiotoxicity. In a nested case-control study with 2,483 patients with Wilms' Tumor treated with doxorubicin, female sex was associated with an elevated risk of HF (RR 4.5, 95% CI 1.6–12.5, P=0.004) [12]. In a large retrospective cohort study of 14,358 anthracycline-treated 5-year survivors of various childhood cancers, the relative hazard of self-reported cardiac events including HF were significantly higher in females (hazard ratio [HR] 1.4, 95% CI 1.1–1.9, P=0.018) [13]. In another retrospective analysis of 20,483 survivors of childhood cancer who received anthracyclines, females had a higher rate of cardiac-related death than their male counterparts (standardized mortality ratio [SMR] 8.9, 95% CI 6.6–11.6, p=0.040) [14].

However, not all studies of long-term (>one year) childhood cancer survivors have found female sex to be an adverse risk factor [15–19], resulting in overall mixed conclusions regarding a sex predilection for cardiotoxicity in childhood cancer survivors. In a prospective cohort study of 514 5-year childhood cancer survivors who had received cardiotoxic therapies including anthracyclines, sex was not a risk factor for abnormal cardiac function as defined by change in left ventricular shortening fraction (LVSF) (male vs female, β=0.77, 95% CI −0.27–1.80) [15]. In a retrospective analysis of 458 anthracycline-treated childhood cancer survivors in a multiethnic Asian population, female sex was also not found to be associated with cardiotoxicity (OR 0.71, 95% CI 0.33–1.54, p-value = 0.390) [16]. In another retrospective analysis of 830 pediatric cancer patients treated with anthracyclines, female sex was not a significant risk factor for anthracycline-induced clinical HF (RR 1.46, 95% CI 0.62–3.43, p=0.39) [17]. Finally, a meta-analysis that included 14 studies totaling 2,813 osteosarcoma patients found female sex to be protective against anthracycline-induced cardiotoxicity (β= −0.796, S.E. 0.317, z = −2.509, p=0.012) [18].

In adults, data on sex-specific differences in anthracycline-induced cardiotoxicity are derived primarily from studies on hematologic cancers that affect both men and women. Of these studies, nearly all support male sex as a risk factor for anthracycline-induced cardiotoxicity [7–10], although this association may be age dependent. One retrospective study of 615 adult Hodgkin lymphoma patients receiving doxorubicin-based therapy and radiation

therapy found that the estimated 15-year incidence rate of cardiac hospitalization was 16.5% in males and 7.3% in females [7]. Another retrospective analysis of 1,096 adult patients with Hodgkin lymphoma receiving doxorubicin-based therapy similarly found male sex to be a significant risk factor for cardiac hospitalization (HR 1.67, 95% CI 1.09–2.55, p=0.019) [8]. In a retrospective study of 141 patients with lymphoma treated with doxorubicin, male sex was associated with subclinical cardiomyopathy as defined by echocardiographic measures of decreased LV systolic function in the absence of clinical HF at least five years after treatment (β=1.201, 95% CI 0.50–1.90, p=0.01) [9]. In a larger retrospective analysis of 2,285 patients receiving anthracycline-based chemotherapy for cancer including hematologic malignancies and breast cancer, male sex was a significant risk factor for major adverse cardiovascular events, as defined by symptomatic HF and cardiac death (HR 1.84, 95% CI 1.14–3.01, p=0.013) [10]. Some studies also suggest that amongst elderly men and post-menopausal women greater than 65 years of age, there is no significant difference in cardiotoxicity risk according to sex [11].

From the available clinical data, conclusions regarding sex-based differences in anthracycline-induced cardiotoxicity vary based on the study population (i.e., pediatric, childhood cancer survivor, adult, or elderly), as well as the outcome of interest (i.e., asymptomatic or symptomatic disease). It is important to note that study definitions for cardiotoxicity and approaches to measuring cardiac dysfunction vary widely, ranging from echocardiography-based measures of asymptomatic LV systolic dysfunction to symptom-based measures of HF, as well differences in assessment timepoints after treatment. Studies also differed in terms of anthracycline treatment dosing and specific non-anthracycline chemotherapy regimens, and cancer type. Many of these studies also evaluated cardiotoxicity at different time intervals, which may in part explain the heterogeneity in conclusions regarding the impact of sex on treatment-related cardiotoxicity in this population.

Sex-based differences in mechanisms

Similar to the human level data in adults, most preclinical studies strongly support female sex as a protective factor against anthracycline-induced cardiotoxicity compared to males [20–28]. In one study, chronic intraperitoneal doxorubicin significantly increased cardiotoxicity as measured by echocardiography, histopathology, and molecular analyses, as well as mortality in wild type C57BL6/129SvJ/EMS +Ter male mice relative to females [20]. In two distinct studies, both using spontaneously hypertensive rats treated with intravenous doxorubicin, males experienced more severe cardiomyopathy and had higher serum levels of cardiac troponin (cTnT) than females [21, 22]. Two additional studies showed that male Wistar rats receiving intravenous doxorubicin had a higher mortality rate and more severe cardiomyopathy compared to females, while doxorubicin was found to have a sex-specific effect on cardiac phospholipids [23, 24]. In spontaneous hypertensive HF rats receiving doxorubicin via subcutaneous injection, male sex was associated with worse cardiotoxicity as quantified by echocardiography and higher cTnT versus females [25]. Male $B6CF_1$ mice receiving weekly intravenous doxorubicin for 6 to 9 weeks showed significantly increased cardiotoxicity compared to females across a range of cumulative dosing, based on measurement of myocardial cytoplasmic vacuolization and DNA damage

on necropsy 1 week after each consecutive final dose [26]. In addition, male C57BI/6 mice who received a single dose of doxorubicin intraperitoneally experienced more severe acute cardiotoxicity than females as measured by heart and body weight, cardiac histopathology, and mortality rate (55% in males versus 0% in females) 6-days post-treatment [27]. Most recently, a preclinical study of 10 distinct murine strains receiving intravenous doxorubicin showed that males, relative to females, had more severe cardiac pathology on histopathology and immunohistochemistry for most strains [28].

There are multiple mechanisms that could potentially explain sex-based differences in anthracycline-induced cardiotoxicity (Figure 1). First, preclinical studies suggest that mitochondrial dysfunction plays a key role in anthracycline cardiotoxicity, and that doxorubicin negatively regulates mitochondrial biogenesis in males. One possible mechanism for this sex difference is that the female sex hormone estradiol positively regulates gene expression of peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC-1), which itself promotes mitochondrial biogenesis [24]. A second possible mechanism is that AMP-activated protein kinase (AMPK), a kinase that stimulates ATP production and mitochondrial biogenesis, is downregulated in males relative to females who receive anthracyclines [24]. This may be related to increased body fat content in females and associated secretion of adiponectin, which activates AMPK and thus maintains mitochondrial biogenesis. Third, preclinical studies show that cardiolipin, a mitochondrial lipid, is decreased in male Wistar rats (but not females) treated with doxorubicin. Since cardiolipin plays an important role in mitochondrial respiratory chain functioning, ATP generation and energy metabolism, it leads to adverse cardiac remodeling when lacking [23]. These mechanisms may explain why females may be relatively protected against anthracycline-induced mitochondrial and subsequent cardiac dysfunction.

Second, sex differences in anthracycline-induced cardiotoxicity may be related to the role of sex hormones in oxidative stress. For example, estrogens attenuate doxorubicin-induced inflammation and oxidative stress through activation of the G-protein estrogen receptor (GPER) [29]. In a preclinical study in rats, ovariectomized females treated with anthracyclines exhibited increased markers of oxidative stress and cell damage in cardiac tissue. In addition, most preclinical studies in rodent models have shown that ovariectomized females who receive exogenous estrogen therapy exhibit reduced signs of doxorubicin-induced cardiotoxicity compared to reproductively normal females, as measured by echocardiography, histopathology, and markers of oxidative stress and cardiac injury [30–33]. However, one study in tumor-bearing spontaneously hypertensive rats treated with doxorubicin did not find differences in cardiotoxicity between ovariectomized and reproductively normal females [22]. Still, in this study, male rats were found to have increased sensitivity to doxorubicin-induced cardiotoxicity, as measured by echocardiography, histopathology and upregulation of genes involved in oxidative stress and apoptosis. This effect was notably annulled in castrated males, implying an injurious effect from testosterone rather than a cardioprotective effect of estrogen [22]. Overall, these studies suggest that sex hormones may influence doxorubicin-induced cardiotoxicity through their roles in either promoting or protecting against oxidative stress.

Third, cardiac mast cells may also partly explain sex differences in anthracycline-induced cardiotoxicity. One preclinical study in spontaneously hypertensive rats treated with doxorubicin found more severe cardiomyopathy in males than females, and cardiotoxicity was associated with an increased number of cardiac mast cells and percentage of cardiac mast cells undergoing degranulation [21]. In this same study, female rats that were ovariectomized had more severe cardiomyopathy, which was comparable in severity to doxorubicin-treated males, indicating that the effect on cardiac mast cell function could potentially be estrogen-mediated [21]. A more recent study showed that ovariectomized female rats receiving anthracyclines exhibited reduced cardiotoxicity when treated with cardiac mast cell stabilizers, as measured by left ventricular systolic function on echocardiography, and its cardioprotective effect was comparable to exogenous estrogen [34]. These preclinical studies indicate that stabilization of mast cells and associated reduction in cardiac inflammation, which may be estrogen-mediated, may help attenuate anthracycline-induced cardiotoxicity.

Fourth, matrix remodeling is likely to play an important role in sex-dependent differences in anthracycline-induced cardiomyopathy. One preclinical study showed that wild type male mice were more sensitive to doxorubicin cardiotoxicity than female mice [20]. However, the differences between sexes were even greater in knockout mouse models lacking thrombospondin 2, a protein known for its matrix-preserving function in part via inhibition of matrix metalloproteinase 2 [20]. This is clinically relevant as other preclinical studies have shown greater cardiac matrix metalloproteinase activation in males than females at baseline [35, 36]. This may be related to estrogen-mediated inhibition of matrix metalloproteinase 2, which was demonstrated in an *in vitro* model of adult rat cardiac fibroblasts, thus implicating a potential mechanistic role for matrix remodeling proteins in the decreased sensitivity of female mice to anthracycline-induced cardiotoxicity [37].

Finally, differences in pharmacokinetics between males and females may play a minor role in sex differences in anthracycline-induced cardiotoxicity but are unlikely to be primary drivers. In mice, doxorubicin was shown to modulate cardiac cytochrome CYP gene expression in a sex-dependent manner, leading to the generation of cardiotoxic metabolites in male mice and cardioprotective metabolites in female mice [27]. As a result, female mice showed signs of milder doxorubicin-induced cardiotoxicity than males based on histopathology [27]. In contrast, sexual dimorphism in body fat content and fat patterning typically results in women having a higher percentage of body fat. It has been speculated that doxorubicin may have both low accumulation in fat depots and decreased clearance in the setting of increased body fat, thus increasing the probability of cardiotoxicity in females [6].

In summary, female sex appears to be a risk factor for early-onset cardiotoxicity in children receiving anthracycline-based treatment. In contrast, female sex appears protective against anthracycline-induced cardiotoxicity in most preclinical and adult clinical studies. Post-menopausal females may have similar risks as elderly men. Studies in long-term childhood cancer survivors have included varying proportions of pediatric, adolescent, and adult patients, likely contributing to discordant conclusions regarding the role of sex in anthracycline-induced cardiotoxicity. Based on study design and mechanisms

of anthracycline-induced cardiotoxicity, there may be several possible explanations for these differing results. First, most preclinical studies investigated the pathophysiology of anthracycline-induced cardiotoxicity in adult rather than juvenile rodents. Second, pre-pubertal women are at increased risk for anthracycline-induced cardiotoxicity relative to males of similar age, but pre-menopausal women are at decreased risk and some studies suggest no sex-specific differences in post-menopausal women and older men [11, 38, 39]. This suggests that the role of female sex in anthracycline-induced cardiotoxicity is likely age dependent. Third, preclinical studies provide a mechanistic basis for the cardioprotective effects of estrogen, including increased mitochondrial biogenesis, protection from oxidative stress and apoptosis, reduced inflammation via stabilization of cardiac mast cells, and promotion of favorable matrix remodeling. Data supporting sexual dimorphism in the pharmacokinetics of anthracyclines are mixed and deserving of further investigation. Finally, differences between studies in terms of outcomes, anthracycline dosing regimens, size, design, types of cancer studied, heterogeneity in the age of onset of cardiotoxicity in studies of childhood cancer survivors, and lack of control for possible confounding factors may also explain observed differences in epidemiologic studies.

Sex-based differences in management

Dexrazoxane is an iron chelator that has been shown to decrease the incidence of HF and systolic dysfunction in clinical trials in patients receiving anthracycline-based therapy [40]. Several studies have demonstrated sex differences in response to dexrazoxane. One prospective, randomized multi-center clinical trial compared 66 pediatric patients with high-risk acute lymphoblastic leukemia treated with doxorubicin to 68 patients treated with both doxorubicin and dexrazoxane [41]. A subgroup analysis found that female patients receiving dexrazoxane and doxorubicin experienced improved left ventricular shortening fraction (LVSF) at five years relative to females receiving doxorubicin alone (LVSF = 1.17, 95% CI 0.24–2.11, p=0.04) [41]. Notably, this improvement was not observed in male patients. In a retrospective cohort study of 85 pediatric patients with sarcoma receiving high-dose doxorubicin, females experienced greater cardioprotection from dexrazoxane than males as measured by LVSF (p=0.019), cavity size in diastole (p=0.002) and systole (p<0.001), and these changes largely persisted for one to two years post-treatment [42]. The differential response to dexrazoxane observed in pediatric female patients is incompletely understood but may be related to sex differences in dexrazoxane pharmacokinetics and/or the increased underlying susceptibility of pre-menopausal females to doxorubicin cardiotoxicity.

Pre-pubertal women are at increased risk of cardiotoxicity, and this risk persists through pregnancy. In a systematic review and meta-analysis of 6 studies encompassing 2,016 pregnancies in cancer survivors, the median age of cancer diagnosis was 12.1 years, median age of first pregnancy was 21.8 years, and 66.5% were exposed to anthracyclines with a mean cumulative dose of 234.0 mg/m^2 [43]. Key risk factors for cardiac dysfunction during pregnancy included a younger age at cancer diagnosis and longer time from cancer treatment to pregnancy in those with no prior history of cancer therapy-related cardiac dysfunction (CTRCD) [43]. In those with a known history of CTRCD, the risk of HF during pregnancy was 28.4% (OR 47.4, 95% CI 17.9–125.8, p<0.001). Therefore, in patients with either (a) a history of CTRCD or (b) who develop CTRCD during pregnancy, specialized

care should be considered. This includes preconception counseling, consults to cardiology, maternal fetal medicine and obstetric anesthesia, cardiac surveillance during pregnancy, and cardiac monitoring during labor, delivery and post-partum in women with significant cardiac dysfunction [43].

Hematopoietic Cell Transplant

Background

HCT is a potentially curative therapy for many malignancies, marrow failure syndromes, and other inherited disorders [44, 45]. HCT entails eradicating recipient bone marrow through chemotherapy and/or radiation (conditioning regimen), followed by infusion of either donor-derived hematopoietic progenitor cells (allogeneic HCT), or patient-derived hematopoietic progenitor cells collected prior to chemotherapy (autologous HCT), which eventually re-populate the bone marrow [44]. Cardiovascular complications of HCT may consist of a complex interplay between 1) pre-HCT risk factors (existing cardiac disease cardiotoxic exposures [e.g., anthracycline chemotherapy or radiation], or other coexisting chronic conditions); 2) acute toxicities occurring during the initial transplant course; and 3) late effects of treatment that may take several years to emerge. As conditioning toxicities and supportive care for HCT have improved over time, a greater number of older patients with more co-morbid conditions are undergoing transplantation [46, 47]. Pre-existing conditions such as coronary artery disease, obesity, and diabetes may not only put patients at greater risk for decompensation during the acute transplant period, but these conditions have also been associated with cardiovascular late effects long after HCT [48, 49]. Prior anthracycline chemotherapy and radiation may further predispose patients to poor cardiovascular outcomes during and post-HCT [50, 51].

Acute cardiovascular complications occurring in the initial post-HCT period include dysrhythmias, angina and acute myocardial infarction, HF, pericardial effusion, pulmonary hypertension, and thromboembolic disease [44, 52–57]. Although many of these acute toxicities will resolve with time, some may predispose HCT recipients to chronic cardiovascular conditions. Allogeneic recipients appear more likely to develop late CVD than those undergoing autologous HCT, suggesting factors intrinsic to the allogeneic HCT process may further increase long-term risk [58, 59]. The potential mechanisms of this have not been elucidated, though some have proposed that increased corticosteroid use, endothelial dysfunction, or the inflammatory state associated with allogeneic HCT may be responsible [58–60].

HF, premature coronary artery disease, valvular heart disease, and arrhythmias occur frequently and are associated with increased mortality in long-term survivors [59–61]. HCT survivors are at increased risk for diabetes and metabolic syndrome, and these complications also likely potentiate CVD [48, 49, 58, 62]. Among long-term survivors, arterial disease presents more frequently as coronary or cerebrovascular disease, and isolated peripheral vascular disease is much less common [61]. Venous thromboembolism (VTE), in contrast, is common in HCT survivors, particularly in those that develop chronic GVHD and those with plasma cell diseases (who may continue to receive thrombogenic anti-cancer therapies) and is associated with adverse outcomes [55, 63, 64]. While several sex-based differences

in CVD have been described in the general population, the impact of sex in transplant and subsequent CVD is not as well known.

Sex-based differences in epidemiology

Differences in outcomes based on sex in the first years post-allogeneic HCT are reported with men experiencing worse HCT outcomes compared to females. Kim et al. studied outcomes in 11,797 adults undergoing allogeneic HCT recipients between 2008 and 2010. The 4-year overall survival for males was 41% vs 45% for females (P=0.001) [65]. Multivariate analysis confirmed worse overall survival (HR 1.11, P<0.0001), progression-free survival, (HR 1.10, P<0.0001), relapse (HR 1.06, P=0.04), and non-relapse mortality (HR 1.09, P=0.032) [65] in males. These inferior outcomes by sex are partly explained by donor-recipient matching. Chronic GVHD risk is thought to be increased with discrepant matching of donor and recipient sex, potentially due to differences in minor histocompatibility antigens, which may in turn be associated with cardiovascular complications [65, 66]. In males receiving stem cell grafts from females, non-relapse mortality is greater than those with male grafts, whereas there is no difference for females receiving either male or female grafts [65]. Other potential causes of increased mortality in males may be related to pre-HCT comorbidities which may be more frequent and severe in men [67].

Several studies have evaluated sex as a risk factor for cardiovascular disease outcomes post-HCT. In the early post-HCT period, sex has not generally been found to impact the risk of early-onset cardiomyopathy or other early cardiac complications [48, 68, 69]. In studies of longer-term allogeneic and autologous survivors, sex has also not been associated with coronary artery disease or cardiomyopathy risk [48, 58, 70]. However, in a nested case-control study of 2,938 autologous HCT survivors, females had an increased odds of developing HF (Odds Ratio 4.6, p = 0.05) [71]. Intriguingly, sex-based differences in HF may be specific for the lymphoma population, where the cumulative incidence has been observed to be higher for females (14.5% ± 2.3%) compared to males (6.1% ± 1.3%) [72].

Specific chemotherapy agents commonly used in HCT conditioning regimens may also play a role in sex-based differences. Acute thiotepa cardiotoxicity is a rare occurrence, but has been associated with female sex [73]. Alidina, et al. studied 171 HCT patients who received thiotepa as part of their conditioning regimen. Of these patients, 9 (5.3%) developed clinical HF in the first 30 days post-HCT. Eight of 9 patients developing HF were female, whereas 89/171 (52%) of the cohort were female (p=0.04). Overall, the heterogeneity of cardiovascular outcomes and timeframe studied make comparisons across different studies challenging. Longitudinal, prospective studies are needed to elucidate sex-based differences in the future. Ideally, these studies would adjust for cumulative anthracycline exposure, reviewed above with known sex-based differences, as well as hormonal status (i.e., pre- or post- menopausal, receiving testosterone replacement, etc.)

VTE is a common complication after HCT and is associated with increased mortality [74, 75], with mixed data regarding sex-based differences. VTE may occur both in the acute period post-HCT, which is characterized by inpatient hospitalization, immobility, thrombocytopenia, and central venous catheters; as well as in long-term survivors, which

appears to be strongly associated with development of chronic GVHD [74, 76]. Among a cohort of 2,276 consecutive recipients undergoing allogeneic HCT, 7.1% required anticoagulation for VTE at 2-years post-HCT [74]. In this study, neither patient sex nor hormone replacement therapy among females were associated with thrombosis risk. Likewise, Martens, et al. studied risk factors for VTE in days 30 through 100 post-HCT and found no difference in risk based on sex [56].

In contrast, among long-term allogeneic survivors, male sex has been associated with VTE, though no difference by sex was seen in autologous HCT survivors [64, 77]. The reason for these differences is not entirely clear but may be based on a different set of risk factors for thrombosis in the immediate post-HCT setting (e.g., immobility, central venous catheter), compared to longer-term survivors (e.g., chronic GVHD, lifestyle factors), as well as lower overall rates of thrombosis in long-term autologous survivors. As thrombosis is clearly linked to worse outcomes in HCT patients, further investigation into sex-based differences is warranted. Prospective trials evaluating VTE as an outcome measure may provide additional information if adjustments are made for hormonal status and hormone replacement therapy. Additionally, murine chronic GVHD models examining VTE would help elucidate the impact of sex hormones on incident thrombosis.

Sex-based differences in mechanisms

Cardiac complications from HCT may be due to direct cardiac injury from treatment (i.e., radiation, anthracycline), due to acute complications of HCT (i.e., sepsis, concomitant medications), or from less well understood long-term mechanisms [78, 79]. In addition to myocardial damage, radiation may also cause direct vascular injury, which is characterized by endothelial dysfunction, smooth muscle cell proliferation, fibrosis, and lipid deposition [77]. Immunosuppressive drugs such as corticosteroids, calcineurin inhibitors and mTOR inhibitors used to prevent and treat GVHD can increase risks of insulin resistance, hypertension, and hyperlipidemia.

Mechanistically, arterial CVD after HCT is thought to be related to an accelerated atherosclerotic process, attributed to prior therapy as well as transplant conditioning chemoradiation, further amplified by both pre-existing and incident cardiovascular risk factors (hypertension, diabetes, hyperlipidemia) post-HCT [80] (Figure 2). Atherosclerosis is characterized by an inflammatory process resulting in endothelial injury, and several aspects of transplant may further compound this. The exact mechanisms by which conditioning regimens and specifically radiation therapy increase risk of cardiovascular risk factors such as diabetes and metabolic syndrome are unclear, and there remains a paucity of data investigating the role of sex in the pathogenesis. Studies have suggested a role for radiation-induced hepatic or pancreatic injury in contributing to insulin resistance and metabolic syndrome [81]. The subsequent development of chronic GVHD can further lead to microvascular disease caused by infiltration of alloreactive cytotoxic T lymphocytes and further endothelial injury, suggesting that immunological mechanisms contribute to coronary artery disease [82]. While some data indicates that females may be more likely to develop sustained allo-immune tolerance, reducing their risk for chronic GVHD [83]; the

relationships between specific sex differences, GVHD, and cardiovascular disease has not been studied.

Sex-based differences in chemotherapy metabolism and hormones may play a role in cardiac toxicity. In adolescent and young adults, differing body mass composition and pubertal status play a role in tolerance and effectiveness of certain chemotherapy agents [84]. Anthracyclines are typically not given as part of HCT conditioning, but many patients with hematologic malignancies receive these agents prior to HCT. The role of sex on anthracycline-induced cardiomyopathy and potential mechanisms have been reviewed extensively above. Cyclophosphamide, which is often used both prior to HCT and as part of HCT conditioning regimens, may also be associated with acute cardiac toxicity [52, 85] and evidence suggests that the variable kinetics may be influenced by sex [86, 87]. Future studies of cyclophosphamide kinetics and HCT outcomes would benefit from close examination of cardiac outcomes, and the role of sex.

Gonadal failure is also very common after HCT [88, 89]. The lack of exposure to physiologic hormones, particularly in younger patients, may alter long-term cardiac health. The impact of hormonal deprivation therapy for cancer treatment and the risk of CVD is discussed further below. In men, testosterone deficiency is a risk factor for CVD in the general population, and testosterone replacement has been associated with potential cardiac benefits, although there are conflicting data [90–92]. Estrogen deprivation increases CVD risk and risk of cardiovascular death in women with primary ovarian insufficiency [93–95]. The role of gonadal failure and impact on CVD has not been studied specifically in the HCT population. In general, however, it is recommended that all women, who do not have a contraindication, receive hormone replacement therapy mimicking physiologic gonadal function to lower the risk of CVD and other comorbidities [94]. For subjects exposed to chemotherapies prior to puberty with evidence of gonadal failure, hormone replacement therapy may be used for puberty induction, which is recommended to start at approximately age 12 [96]. Underdiagnosis of hormonal deficiency is common in pediatric cancer survivors, and failure to appropriately diagnose and treat HCT survivors may contribute to the higher rates of CVD in this population [97].

Well-designed mechanistic and clinical studies with particular emphasis on sex-based factors (i.e., donor recipient sex matching, menstrual status pre- and post- HCT, parity, concomitant testosterone or estrogen deficiency, sex- and gender- based variability in lifestyle, metabolism) are needed to further elucidate sex-based differences in outcomes. Several gaps remain, including studies further evaluating differences in metabolism, hormonal changes post-HCT and their impact on acute and chronic cardiac complications post-HCT.

Sex-based differences in management

Currently, guidelines regarding CVD surveillance and treatment for patients undergoing HCT or in long-term survivors do not necessarily vary by sex. It is important to note, however, that atherosclerotic CVD risk guidelines that are used to determine lipid management goals in the general population incorporate sex in prediction models [98]. While studies in the general population may suggest sex differences in health behaviors and

management of CVD; there are little data in the HCT population. Continued awareness of the burden of CVD risk factors and differences in both men and women and its implications for morbidity and mortality are needed. There is an unmet need for further investigation to evaluate sex-based differences in the treatment and management after HCT.

Hormone Targeted Therapies

Background

Hormonal therapies are a cornerstone for treating hormone-sensitive cancers, including prostate and breast cancers, which are the most common non-cutaneous cancers in the US in men and women, respectively [99]. An estimated 12% of men in the US will be diagnosed with prostate cancer during their lifetime and as of 2017, more than 3.1 million men were living with prostate cancer in the USA. Similarly, studies suggest that 1 in 8 women (i.e., 12%) will develop breast cancer during their lifetime and there are approximately 2.8 million breast cancer survivors among the general population in the US [99, 100]. While hormonal therapies such as androgen receptor (AR) antagonists, GnRH modulators, selective estrogen receptor modulators (SERMs), and aromatase inhibitors (AIs) have significantly improved the survival of hormone-sensitive cancer patients, they have also been associated with an increased risk of cardiovascular morbidity and mortality [101]. Regarding prostate cancer, AR antagonists and GnRH modulators have been related to broad-spectrum cardiometabolic complications such as increased LDL-C and triglyceride levels, increased visceral fat, increased insulin resistance, and decreased cardiopulmonary fitness [102, 103]. Additionally, these therapies have been associated with an increased risk of acute myocardial infarction, HF, and arrhythmias [99, 101, 104, 105]. Regarding breast cancer, SERMs have been associated with an increased risk of VTE events, whereas AIs have been associated with an overall higher risk of cardiovascular events when compared with tamoxifen [101]. In addition, AIs have been linked to metabolic syndrome, dyslipidemia, and hypertension [99, 101, 105, 106]. These cardiovascular complications of hormone therapies highlight how sex hormones modulate one’s cardiovascular risk.

Sex-based differences in risk factors

Patients with pre-existing CVD or risk factors at baseline have been found to be more vulnerable to subsequent cardiovascular events when treated with hormonal therapies [99, 101, 106]. Meanwhile, hormonal therapies themselves can augment cardiovascular risk factors, which may in turn increase downstream risk of CVD in this population either additively or synergistically. The burden of cardiovascular risk factors differs by sex, which further modulates their cardiovascular risk of hormonal therapies. Data from the National Health and Nutrition Examination Survey (NHANES) suggest that the prevalence of high blood pressure is greater in women than men aged >65 years [2]. Similarly, diabetes mellitus is more prevalent in women than men ≥20 years of age (8.3% versus 7.2%) and women are also more likely to have higher total cholesterol values [107]. On the other hand, cigarette smoking remains more common among men than women (23.1% versus 18.1%). Men are also more likely to be overweight than women (72% of men and 64% of women) as defined by body mass index [108]. Collectively, these sex-based differences in cardiovascular risk factors further complicate one’s cardiotoxicity risk with hormonal therapies.

Sex-based risk of arrhythmias

Experimental models suggest increased susceptibility to drug-induced arrhythmia with high estradiol levels, while testosterone and progesterone confer protection against arrhythmia [109]. Consistent with this observation, in healthy individuals, QTc is longer in women than in men from puberty to menopause, due in part to testosterone's effect to shorten QTc, thus placing women at higher risk of long QT syndrome (LQTS) and Torsades de Pointes (TdP) [110]. Accordingly, the threshold for sex-specific diagnosis of LQTS includes approximately QT_C >440 ms for adult males and >460 ms for adult females [111, 112].

Mounting evidence suggests that androgen deprivation therapy (ADT) used for treating prostate cancer may increase the risk of ventricular arrhythmia (e.g., TdP) by prolonging QTc [113]. In 2020, Lazzerini et al. investigated the prevalence of ADT in a consecutive cohort of 66 TdP patients collected over 10 years, and reported that 4 patients (6%) were treated with ADT with two developing cardiac arrest [113]. They further noted that ADT represented the second most frequently administered QT-prolonging medication in males associated with TdP (4/24, 17%) [113]. Similarly, Gagliano-Jucá et al. reported significantly higher rates of increasing QTc durations >440 ms among male patients treated with ADT compared to those who were not [114]. In 2019, Salem et al. used the World Health Organization's global database of individual case safety reports, VigiBase, and determined an association between ADT and drug-induced LQTS, TdP, and/or sudden death [110].

Hormonal therapies for breast cancer have also been linked to QT prolongation and risk of arrhythmia. Specifically, tamoxifen, a SERM with an antagonist effect on the breast tissue and agonist effect on metabolism and cardiovascular organs, has been shown to increase QTc duration and subsequent risk of TdP when compared to AIs [115]. In 2018, Grouthier et al. reported that SERMs were associated with increased cardiovascular adverse drug reactions, specifically related to LQTS, TdP, and ventricular arrhythmias, when compared with AIs based on analyses of the European database of suspected adverse drug reaction (ADR) reports [116].

Sex-based differences in mechanisms

Endogenous estrogens may influence both tonic and phasic effects regarding cardiovascular homeostasis in premenopausal women while also preventing the development of CVD [5]. More specifically, estrogen receptor activation regulates the stimulation of PI3K/Akt signaling converging on nitric oxide (NO) synthases and provides cardioprotective effects such as preventing atherosclerosis, reducing ischemia/reperfusion injury, and maintaining vascular tone (Figure 3) [5, 117]. As such, increased susceptibility of cancer therapy-related cardiovascular complications has been described among prepubertal girls as well as post-menopausal women [5]. This risk appears to be further heightened when post-menopausal patients are treated with AIs which inhibit the peripheral conversion of testosterone into estradiol, thus further decreasing estradiol while increasing testosterone levels [104, 115, 118]. Various clinical trials with AIs have provided some evidence of an increase in cardiovascular events, but the underlying reasons for this finding are not fully understood [119]. AIs are hypothesized to reduce circulating estradiol and/or alter lipid metabolism, thus eliminating the cardioprotective effect [119].

Mounting evidence also suggests beneficial effects of testosterone in cardiovascular health. Testosterone has been shown to elicit cardioprotective effects through multiple intracellular mechanisms, including anti-apoptosis, regulation of leukocyte migration, decrease in reactive oxygen species generation, and enhancing NO-cGMP pathway (Figure 3) [58, 120, 121]. Additionally, various studies report that testosterone enhances insulin sensitivity and glucose uptake in the heart, thereby leading to an increased cardiac energetics [46, 47, 58]. Data also suggest that testosterone promotes mitochondrial function in cardiac cells by coordinating the expression of mitochondrial genes [48, 58]. As such, direct androgen receptor (AR) antagonists, often used in metastatic prostate cancer, have been associated with an increased risk of adverse cardiovascular events.

Despite these favorable effects of endogenous testosterone, various retrospective studies and randomized trials report that supplemental testosterone may enhance the risk of CVD [114]. In a study evaluating a large cohort of 55,593 men receiving intramuscular testosterone therapy from an insurance database, Finkle et al. found that the risk of CVD (i.e., nonfatal MI) following testosterone prescription increased by 36% [114, 122]. However, it is important to note that epidemiological data thus far are conflicting, with some retrospective studies supporting the beneficial effect of testosterone replacement therapy on cardiovascular mortality, whereas other studies report increased risk of serious cardiovascular events by testosterone [114].

Given the complex, potentially cardioprotective effects of sex hormones, sex differences in cardiotoxicity in patients receiving hormonal therapies may be better understood by comparing common treatments used for both prostate cancer and breast cancer, notably GnRH modulators (Figure 3). Through their actions on the hypothalamus-pituitary-testicular/ovarian axis, GnRH modulators can effectively reduce endogenous estrogen/testosterone levels thereby preventing cancer growth as well as disease recurrence. Moreover, GnRH agonists have been shown to directly exert anticancer activity. While GnRH modulators have become an important hormone therapy, they have also been associated with significant cardiovascular morbidity and mortality. In prostate cancer, multiple comprehensive meta-analyses and cohort studies have identified an elevated risk of cardiovascular events following hormonal therapy, particularly with GnRH agonists [99, 105, 123]. In a randomized phase 3 trial involving 930 male patients with advanced prostate cancer comparing GnRH antagonist (relugolix) to agonist (leuprolide), Shore et al. observed a more than two-fold increased risk of major adverse cardiovascular events with GnRH agonists versus antagonists [124]. In addition, combined treatment of a GnRH agonist and AR antagonist has been associated with enhanced cardiovascular toxicity in men with preexisting cardiovascular conditions [106]. The mechanism by which GnRH agonists increase cardiovascular risk compared to GnRH antagonists remains elusive but it is hypothesized that GnRH agonists may promote plaque destabilization and rupture. In breast cancer, GnRH agonists are used to suppress ovarian function which may theoretically increase cardiovascular risk via estrogen suppression in premenopausal women, although the risk may differ according to host factors associated with the comparatively younger age of females, and detailed clinical data regarding longer term cardiovascular outcomes remain sparse.

Sex-based differences in management

Sex hormones, testosterone, and estradiol are essential to cardiovascular health. Therefore, drugs to antagonize their effects, such as AI, AR antagonists, and GnRH modulators, have been linked to increased rates of adverse cardiovascular events. Current guidelines regarding CVD prevention and treatment for patients on hormonal therapies do not have sex-specific recommendations. Therefore, it remains important to apply and follow standard guidelines and recommendations to lower CVD risks in cancer patients treated with hormonal therapies. As hormonal therapies overall place patients at higher risk of CV events relative to the general population, a lower threshold to monitor and manage cardiovascular risk factors and disease should be warranted. Additionally, sex hormones modulate the expression and properties of iron channels which lead to differences in QT duration and arrhythmogenicity. While no specific guidelines exist regarding arrhythmia monitoring and management based on sex and hormone therapy status, it is important to be aware of potential drug-induced LQTS and arrhythmia when patients are treated with SERM for breast cancer or ADT for prostate cancer. Finally, continued research to improve the management of cardiovascular risk factors and disease is warranted to optimize the cardiovascular health of patients receiving hormonal therapies.

Immunotherapy

Background

Harnessing the immune system has revolutionized cancer therapy in the last decade. Of these therapies, immune checkpoint inhibitors (ICI) have proven to be highly versatile with an estimated 50% of cancer patients now eligible for treatment [125]. ICIs are monoclonal antibodies that target immune brakes or “checkpoints” – either CTLA-4 or PD-1 (expressed on T cells and other immune cells) or PD-L1 (ligand for PD-1, expressed on host cells, including tumor cells). While treatment with ICI has significantly improved the survival of patients across many different cancers, activating the immune system by ICI has also led to immune-related adverse events (irAEs), including colitis, pneumonitis, thyroiditis, encephalitis and hepatitis, among other adverse effects affecting multiple organ systems [126]. Acute cardiovascular toxicities associated with ICI include myocarditis, pericarditis, cardiomyopathy/HF, vasculitis, and arrhythmia, with recent data suggesting a possible predisposition to atherosclerosis [127, 128]. ICI-associated myocarditis, although uncommon, has been best studied and is characterized by electrocardiographic disturbances, T cell and macrophage infiltration of the myocardium, and predilection for concomitant myositis. Fulminant myocarditis can be fatal with mortality over 50%, though recent improvements in treatments have significantly improved outcomes [129–131]. A major risk factor for the development of ICI-associated myocarditis is the use of combination ICI-therapies, for example, ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) [132].

Sex-based differences in epidemiology

Sexual dimorphism in ICI efficacy and irAEs is still not well understood. The low representation of female patient population in clinical trials have limited the scope of data. Three malignancies where ICI have been most widely tested and used are melanomas, lung cancers, and kidney cancers, are each more prevalent in males compared to females [133].

In a case series of 101 patients with ICI-myocarditis, 66% were male and 77% of cases were reported in melanoma, lung cancer or renal cancer patients [134]. In a meta-analysis of 20 randomized control trials of ICIs, mostly in melanoma and lung cancer, female patients comprised less than a third of the overall population [135]. The authors of the paper concluded that male patients have a larger treatment effect from ICI compared to female patients (p=0.0019 for difference in efficacy between female and male); however, the unequal representation of female and male patients in the trials may have affected the results [135]. Recent clinical trials of ICI have attempted to increase study sample sizes with more robust representation of female patients. An updated meta-analysis that included more recent clinical studies did not demonstrate any difference in efficacy and outcomes between female and male patients treated with ICI [136]. In this meta-analysis, males comprised most participants (9322 males vs. 4399 females). However, 5 of the included studies had more than 40% female participants, an improvement from approximately 30% females in previous trials.

Despite this sex imbalance in treated patients, studies evaluating sex-based differences in irAEs have either shown increased risk in females or no difference between the sexes [137–140]. A single-center retrospective study of 91 non-small cell lung cancer (NSCLC) patients (57% females) did not find any association between sex and incidence of irAEs [140]. On the contrary, another single-center retrospective study with a larger sample size, including 245 metastatic melanoma patients (39.6% females) and 231 NSCLC patients (45% females), showed that female patients, especially pre-menopausal women, are more likely to experience irAEs compared to male patients [137]. Similarly, a prospective observational study of melanoma patients (38.6% females) treated with ipilimumab, a CTLA-4 inhibitor, found increased risk of irAE in female patients [138]. However, a meta-analysis of 13 clinical studies did not show any statistical differences in irAE risk between males and females [139]. Currently, sex-based differences in irAEs are largely speculative. The ongoing prospective observational study (G-DEFINER) will recruit 400 participants, and hopefully will shed more light on the gender difference in irAEs [141]. In addition, JOCARDITE (JOint use of database to identify risk factors of CARDiovascular toxicity induced by Immune Checkpoint Inhibitors (NCT04294771), the international ICI-myocarditis registry, will further assess sex-differences in ICI-related cardiovascular issues [142].

The relationship between sex and ICI-myocarditis, one of the uncommon but potentially severe forms of irAEs, has not been extensively investigated. However, one study suggested a female predilection for ICI-myocarditis [143]. Zamami and colleagues analyzed 107 patients with ICI-myocarditis in the FDA FAERS database; female patients were 1.92 times more likely to have ICI-myocarditis compared to males (OR 1.92, 95% CI 1.24–2.97, p=0.004) [143]. On the other hand, retrospective case series all reported more cases of ICI-myocarditis in males compared to females [144–146]. These data should be interpreted with caution, given they were not designed to determine if sex-based differences exist. In addition, males are more represented in both ICI use and clinical trial enrollment, and thus more male cases of ICI-related cardiotoxicity are to be expected [146]. In the retrospective cohort study by Salem et al., 67% of ICI-myocarditis occurred in males [144]. In other case series, Mahmood and colleagues reported that males comprised 71% patients of the

total cohort of 35 patients with ICI-myocarditis, and Escudler and colleagues reported 77% males in the cohort of 30 patients with ICI-related cardiotoxicity [145, 146]. In contrast, more balanced studies (>44% female) do not suggest a difference in CV events according to sex [125]. Overall, these descriptive studies do not necessarily indicate that males have a predisposition for ICI-myocarditis and pericarditis, and the results are largely mixed. Additional studies are needed to establish the relationship between sex and the incidence of ICI-myocarditis, as the current data are not sufficient to definitively conclude that there is any sex predilection to cardiotoxicity.

Sex-based differences in mechanisms

Preclinical mouse models of ICI-myocarditis are limited but suggest a sex difference in ICI-myocarditis [147]. In a mouse model of ICI-myocarditis, with a single copy loss of *Ctla4* (encoding CTLA4) and complete loss of *Pdcd1* (encoding PD-1), which can be extrapolated to represent patients on combination anti-CTLA4 and anti-PD-1 therapies, mice die prematurely due to myocarditis, which clinically and pathologically recapitulates ICI-myocarditis. Mortality secondary to myocarditis is higher in female mice compared to males – the 100-day mortality rate was about 25% in male mice and more than 50% in female mice [147]. Data with other preclinical models of ICI-myocarditis are less clear in terms of sex differences [129]. A focus on development of preclinical animal models and mechanistic studies may help better understand the relationship between sex and ICI-myocarditis.

Though the manifestation of sex differences in clinical outcomes and irAE (especially myocarditis) with ICI remains inconclusive, there is sufficient theoretical plausibility for differential immune responses between male and female patients. In general, females mount stronger innate and adaptive immune responses compared than males [148]. Antibody- and cell-mediated immune responses are more vigorous in females than males after either infection or vaccination [149]. Correspondingly, females tend to have a higher incidence of autoimmune disorders than males [150].

Genetic mediators play an important role in this gender and immune system discrepancy. Sex chromosomes, especially the X chromosome, contain many genes that regulate immune function, including the interleukin 2 receptor, the interleukin 3 receptor, and the toll-like receptor 7, etc. [148, 151]. Two copies of X chromosomes in females lead to X chromosome inactivation, in which one of the X chromosomes is permanently and randomly inactivated in cell populations early during embryological development. In males, only one X chromosome is present. Thus, all cells in males will express the X-linked gene mutations while only half of the cells will in females. Therefore, males are more susceptible to X-linked diseases, and the resultant cellular mosaicism in females leads to added physiologic diversity and stronger immunity [152]. Another genetic factor is the sex-based difference in gene expression. Genes related to immune responses in T cells are overexpressed in females than males, resulting in stronger inflammatory and cytotoxic T cell responses, which can lead to increased risk of irAEs in females [153]. Studies of other cardiomyopathies also demonstrated distinct gene expression in males compared to females, suggesting a sexual dimorphism of gene expression in ICI-myocarditis [153].

Humoral differences also contribute significantly to discrepancies in immune responses based on sex. In both nonhuman primates and mice, females exhibit increased antibody titers and memory B cells following vaccinations [154]. This is also true in humans – genes expressing B cells are significantly upregulated in females compared to males, resulting in a more robust humoral response in females [155]. Sex hormones also have a profound influence on humoral immunity. Estradiol stimulates antibody production by B cells [156]. Progesterone, produced during menstrual cycle and at high levels during pregnancy, has broad anti-inflammatory effects and can promote skewing of CD4+ T cell responses [157]. Androgens such as dihydrotestosterone and testosterone, which occur in higher concentrations in males than in females, have also been shown to cause increased anti-inflammatory responses, and suppress pro-inflammatory responses [158–160]. Furthermore, studies on animal models have suggested that sex hormones can modulate the PD-1-PD-L1 pathway, which plays a major role in regulating immune responses [160, 161].

Much of the discussion above is focused on ICI, the class of immunotherapies that have been tested in a wider range of patients. However, immunotherapies contain other types of therapies including cellular therapies, such as chimeric antigen receptor T (CAR-T) cells, bispecific molecules, cytokines, vaccines, and oncolytic viruses, are expanding and each can have diverse cardiovascular sequelae [162, 163]. There are limited data regarding the role of sex in immunotherapies other than ICI, likely because many of these immunotherapeutic approaches are still in early development phase with few existing clinical trials. One recent retrospective observational study looked at the ADR profiles after CAR-T therapies using the US FAERS (Food and Drug Administration Adverse Event Reporting System) and European EudraVigilance databases [164]. In both databases, about 30% of the reported ADRs occurred in females (28.6% were females in EudraVigilance and 30.4% in FAERS). Although about 20% of the reports did not have the patients' sex available, the authors did not find a significant difference between male and female patients [164]. However, as the indications and use of these therapies expand to a wider group of patients, future studies should especially focus on the potential sex differences not only in efficacy, but also in short- and long-term immune-based toxicities, including cardiovascular ones.

Conclusions and Future Directions

Increasing data support sex-based differences in the epidemiology and mechanisms of cardiotoxicity associated with cancer therapy. To date, epidemiologic and mechanistic studies suggest that anthracyclines, stem cell transplant, hormone therapies, and immune therapies have sex-specific differences (Table 1). However, there are significant knowledge gaps as it relates to a deeper and more robust understanding of these differences. Well-designed, preclinical mechanistic studies are necessary to elucidate the biologic basis behind these relationships. Moreover, prospective longitudinal clinical studies with standardized collection of data, longer term follow-up, and a focus on sex-based differences with the consideration of multiple potential confounding factors are necessary to advance our understanding of the differences that exist and their ultimate impact on clinical care. With such an understanding, personalization of cardioprotective, risk-reducing and treatment strategies to optimize cardiovascular and oncologic care according to sex can be pursued.

Funding Sources:

JM is supported by the National Institutes of Health (R01HL141466, R01HL155990, and R01HL156021). SJR is supported in part by a grant from NIH NCATS 2KL2TR002547 PI: Dweik. JW is supported by the NIH (R01 HL123968, R01 HL141851, R01 HL150693) and AHA (17MERIT33610009 & Cardio-Oncology SFRN). SHA is supported by the NIH (R01 HL150069, R01 CA196854), Leukemia Lymphoma Society (Scholar Award 2315-17) and AHA (Cardio-Oncology SFRN). BK is supported by the NIH (R01 HL148272, R01 HL152707, R21 HL150723, R21 HL152148, R21 HL141802, R34 HL146927) and AHA (Cardio-Oncology SFRN). JWR is supported by the NIH (K08 HL148540) and the AHA (Career Development Award and Cardio-Oncology SFRN). MM is supported by the Stanford Propel Postdoctoral Scholar Award.

Abbreviations:

ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AI	Aromatase inhibitor
AR	Androgen receptor
CAR-T	Chimeric antigen receptor T cell
CTRCD	Cancer therapy-related cardiac dysfunction
CVD	Cardiovascular disease
GnRH	Gonadotropin-releasing hormone
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplant
HF	Heart failure
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
IRAE	Immune-related adverse event
LQTS	Long QT syndrome
LVSF	Left ventricular shortening fraction
NO	Nitric oxide
NSCLC	Non-small cell lung cancer
OR	Odds ratio
RR	Relative risk
SERM	Selective estrogen receptor modulator
SMR	Standardized mortality ratio

TdP	Torsades de Pointes
VTE	Venous thromboembolism

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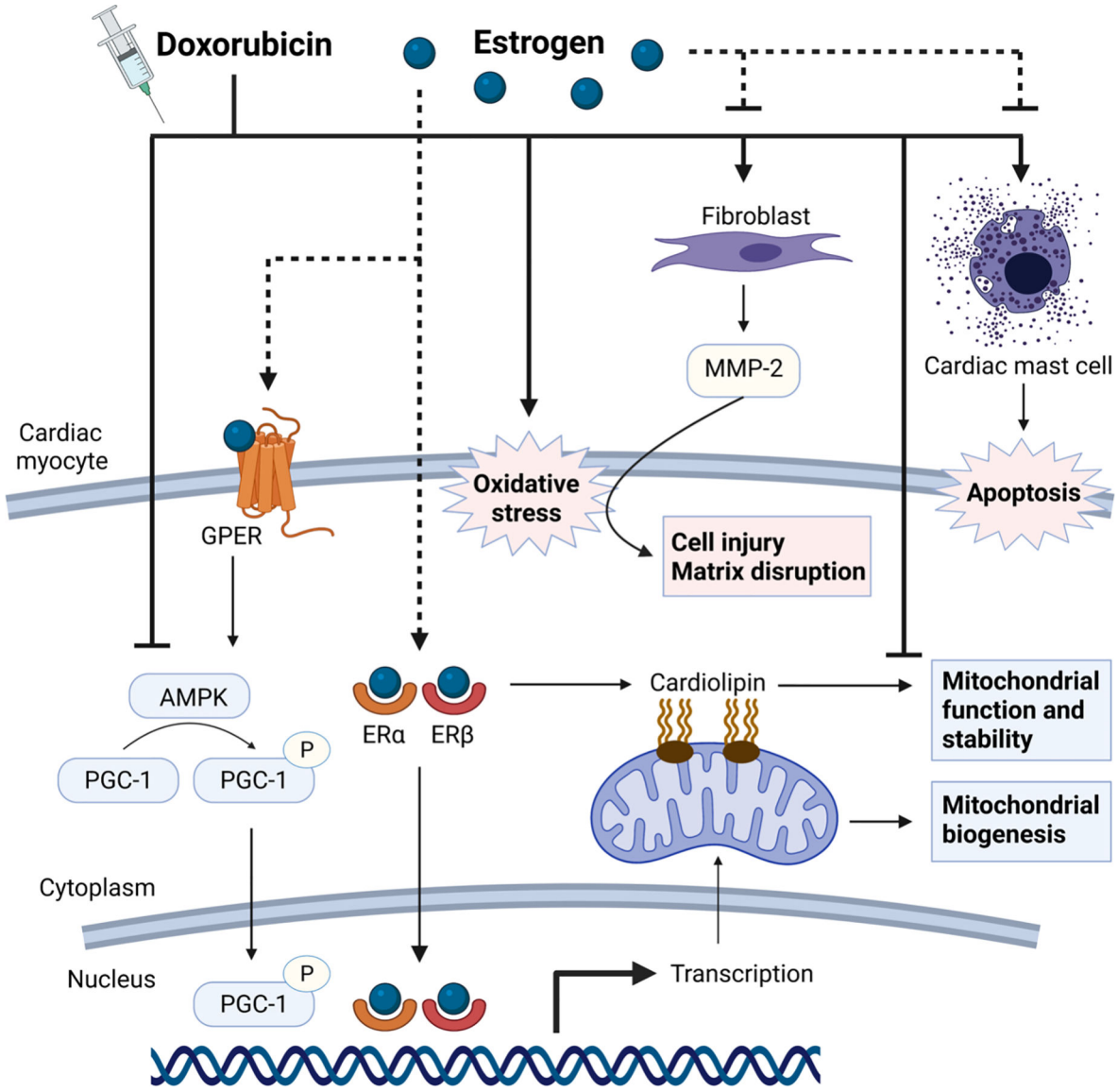

Figure 1. Sex Differences in Anthracyclines

Doxorubicin leads to oxidative stress, mitochondrial dysfunction, extracellular matrix disruption, and subsequent cardiomyocyte injury and death. Estrogen binds to the G-protein estrogen receptor (GPER) and nuclear estrogen receptors (ERα and ERβ). Estrogen may protect against doxorubicin-induced cardiomyocyte injury and death through multiple possible mechanisms. This includes (a) AMPK and peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC-1)-mediated upregulation of mitochondrial biogenesis genes, (b) inhibition of matrix metalloproteinase 2 (MMP-2) production by fibroblasts, (c) stabilization of cardiac mast cells and (d) preservation of mitochondrial cardiolipin. **Illustration credit: Ben Smith**.

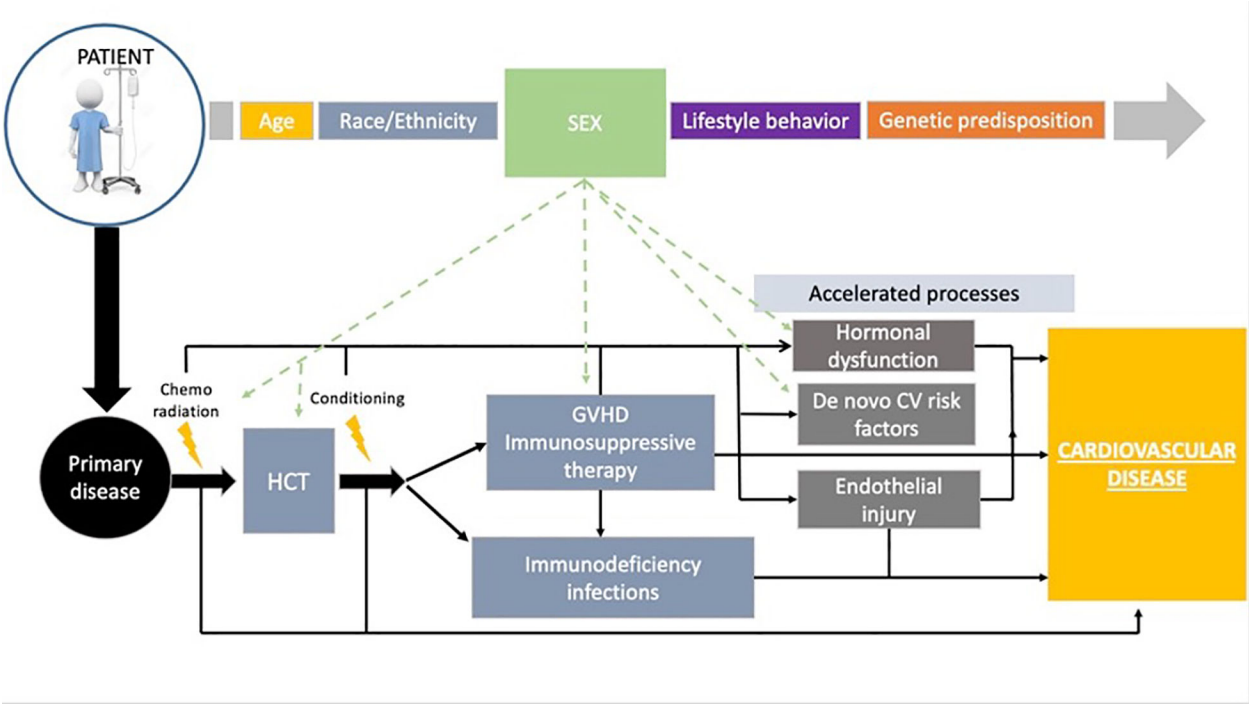

Figure 2. Sex Differences in Hematopoietic Cell Transplantation

The development of CVD in hematopoietic cell transplantation (HCT) patients involves the interplay of baseline cardiovascular risk factors, cardiac insults and the development of additional risk factors during and soon after HCT, as well as accelerating processes occurring in long-term survivors. Sex, in addition to several other factors, may impact cardiovascular risk factors before, during and after HCT.

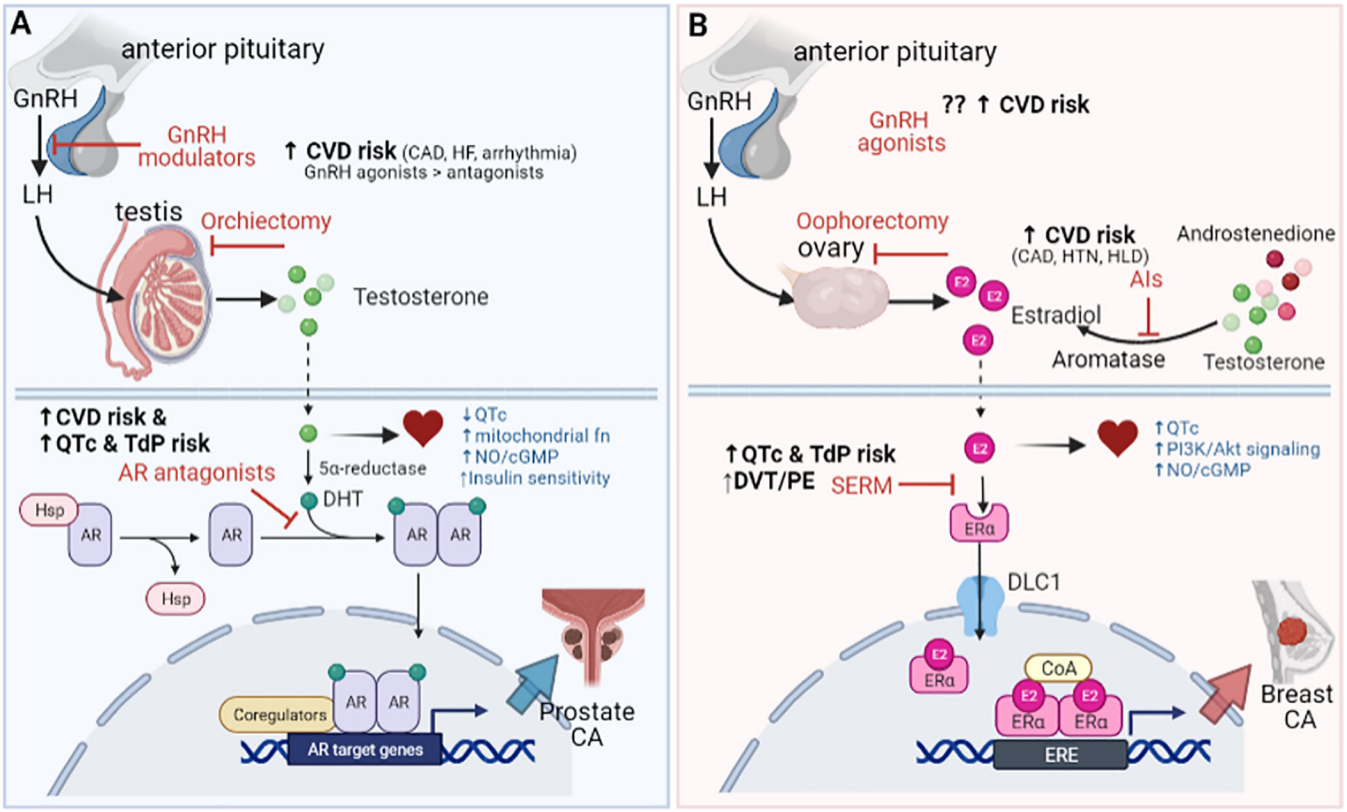

Figure 3. Sex Differences in Hormone Therapy

Sex hormones, testosterone, and estradiol are essential in cardiovascular health, and drugs to antagonize their effects have been linked to increased rates of adverse cardiovascular risk. **A**. Androgen deprivation therapies (Gonadotropin-releasing hormone (GnRH) agonists/antagonists and androgen receptor (AR) antagonists) have been shown to increase the risk of cardiovascular diseases including coronary artery disease, heart failure, and arrhythmia. **B**. Aromatase inhibitors (AIs) have been found to increase the risk of cardiovascular diseases while selective estrogen receptor modulator (SERM) increases the risk of drug-induced QT prolongation, torsades de pointes (TdP), and thromboembolism. **Illustration credit: Ben Smith**.

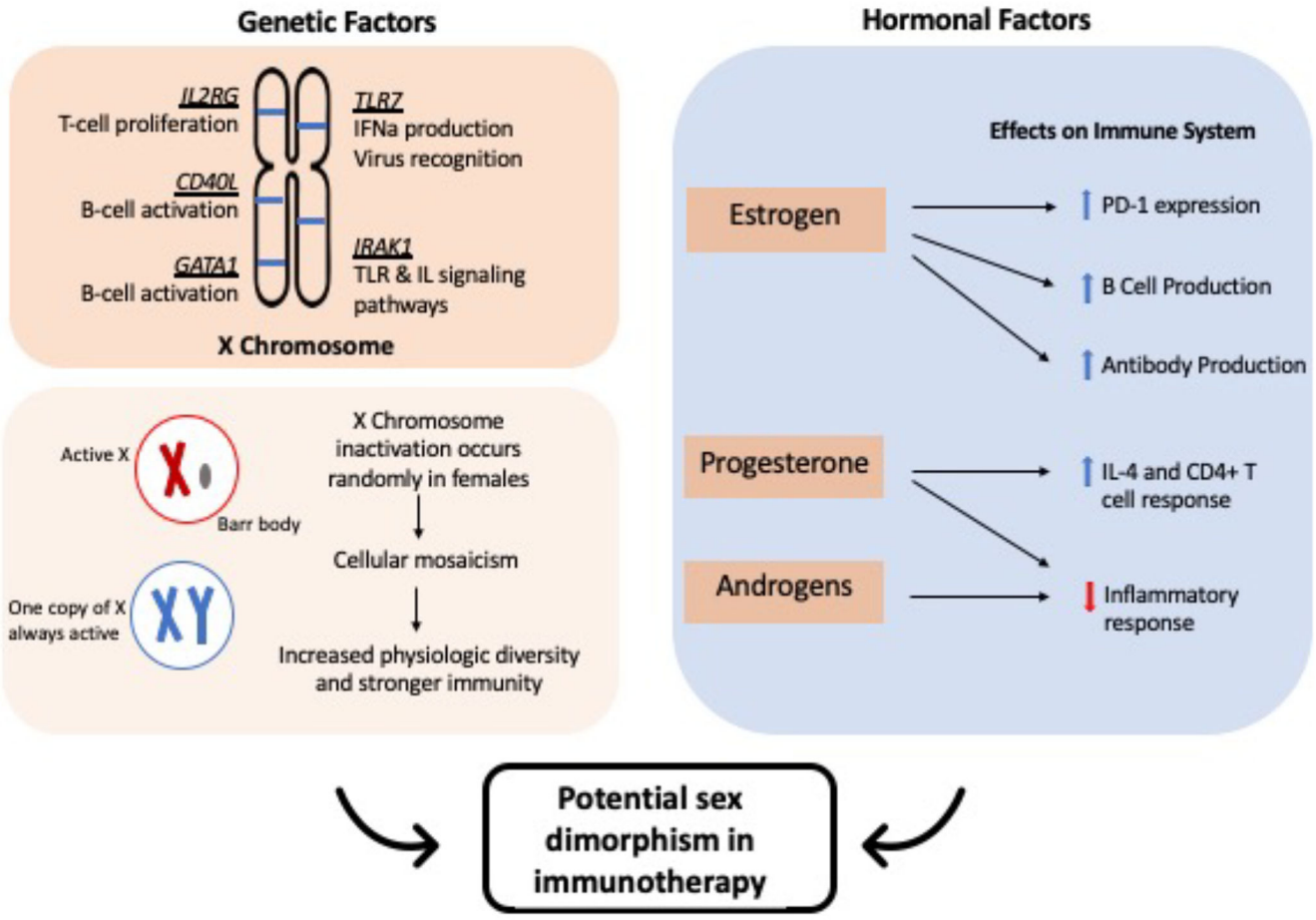

Figure 4. Sex Differences in Immunotherapy

Both genetic and hormonal factors contribute to sex differences in immune response, leading to possible sex dimorphism in immunotherapy. Genetically, X chromosome encodes many immune function genes. Random X chromosome inactivation that occurs in females results in added physiologic diversity and stronger immunity. Hormonally, different sex hormones have various effects on the immune system. *IL2RG,* Interleukin-2 receptor-gamma; *CD40LG*, CD40 ligand; *GATA1*, GATA binding protein 1; *TLR7,* Toll-like receptor 7; *IRAK1,* Interleukin 1 Receptor Associated Kinase 1; PD-1, Programmed cell death protein 1

Table 1 –

Summary of Sex-Specific Cardiovascular Risks of Cancer and Its Therapies

Oncologic Therapy	Key Clinical Findings Regarding Sex Differences	Ongoing Research to Define Sex Differences	Research Priorities to Advance Our Understanding
Anthracycline	**Relative to males**: • Pre-pubertal women are at increased risk of cardiotoxicity [4–6] • Pre-menopausal women are at decreased risk of cardiotoxicity [7–10] • Post-menopausal women are not clearly at increased risk of cardiotoxicity [11]	• Sex-Specific Differences in the Development of Anthracycline Cardiotoxicity (R21HL148748)	• Preclinical studies elucidating and targeting pathways responsible for estrogen's cardioprotective effects • Preclinical studies investigating the sexual dimorphism of anthracycline pharmacokinetics • Clinical studies of cancer patients and survivors that account for the age of onset of anthracycline cardiotoxicity in describing sex-related differences • Sex-specific strategies to mitigate cardiotoxicity risk
Hematopoietic Cell Transplantation (HCT)	• **Autologous**: - Late heart failure rates are higher in females in lymphoma cohort and may be associated with anthracycline exposure [71, 72] • **Allogeneic:** - No clear sex differences in CV risk [48] • **Chemotherapy conditioning:** - Thiotepa: higher acute heart failure rates in females [73]	• Pilot Study on Gender Differences in Hematopoietic Cell Transplantation Outcomes in the Pediatric Population (Retrospective Observational Cohort Study, NCT04580576)	• **Autologous**: - Studies analyzing cardiac outcomes in autologous HCT by sex, adjusting for anthracycline exposure - Murine models of autologous HCT with and without anthracycline exposure, and variable sex hormone exposure • **Allogeneic**: - Clinical and preclinical investigation of mechanisms of sex-based differences in CV outcomes, including impact of chronic GVHD and hormone status - Evaluation of risk of VTE and impact of sex-based differences - Impact of sex on metabolism of chemotherapy agents, specifically cyclophosphamide given increasing use in the allogeneic setting
Hormone Therapy	• **GnRH modulators (antagonists and agonists)** - Increased rates of cardiovascular events (antagonists > agonists), most notably in men [99, 124] • **AR antagonists (male)** - QT prolongation [110, 113, 114] - Increased risk of ventricular arrythmia [110, 113, 114] • **Selective estrogen receptor modulators (female)** - Increased risk of VTE [101] - QT prolongation [115, 116] • **Aromatase inhibitors (female)** - Increased risk of adverse cardiovascular events including dyslipidemia [101]	• To authors' knowledge, no studies directly comparing risk of therapies in males versus females; this may be because therapies are used for sex-specific cancers	• **GnRH modulators (antagonists and agonists)** - Mechanism of GnRH agonist-mediated plaque destabilization and rupture - Epidemiology of cardiotoxicity and risk predictors of cardiotoxicity and how this differs according to sex and host factors, particularly in the long term - Cardioprotective strategies • **AR antagonists (male) and Selective estrogen receptor modulators (female)** - Epidemiology of cardiotoxicity - Mechanisms of cardiotoxicity • **Aromatase inhibitors (female)** - Sex differences in QTc prolongation - Effects of sex hormones in lipid homeostasis, vascular health, and cardiac metabolism
Immunotherapy	• Low representation of female patients in trials may limit the accurate assessment of sex dimorphism in ICI • Meta-analyses of recent clinical trials do not demonstrate differences in efficacy and outcomes based on sex [147] • Sex differences in irAEs are largely speculative with mixed results based on retrospective studies [148–151] • Female sex is associated with a higher risk for ICI-myocarditis in one retrospective study [153] and preclinical mouse models [157]	• G-DEFINER: multicenter prospective observational study on gender difference in irAEs [152] • JOCARDITE (JOint use of database to identify risk factors of CARDiovascular toxicity induced by Immune Checkpoint Inhibitors (NCT04294771) [142]	• Multi-center prospective studies on sex differences in ICI outcomes, irAEs, and efficacy. Analyses should incorporate the denominator (i.e., male patients being treated) • Preclinical mouse models of ICI-cardiotoxicity to better understand mechanisms