STATE-OF-THE-ART REVIEW

Cancer Treatment-Related Cardiovascular Toxicity in Gynecologic Malignancies

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Improvements in early detection and treatment of gynecologic malignancies have led to an increasing number of survivors who are at risk of long-term cardiac complications from cancer treatment. Multimodality therapies for gynecologic malignancies, including conventional chemotherapy, targeted therapeutics, and hormonal agents, place patients at risk of cancer therapy-related cardiovascular toxicity during and following treatment. Although the cardiotoxicity associated with some female predominant cancers (eg, breast cancer) have been well recognized, there has been less recognition of the potential adverse cardiovascular effects of anticancer therapies used to treat gynecologic malignancies. In this review, the authors provide a comprehensive overview of the cancer therapeutic agents used in gynecologic malignancies, associated cardiovascular toxicities, risk factors for cardiotoxicity, cardiac imaging, and prevention strategies. (J Am Coll Cardiol CardioOnc 2023;5:159–173)
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Gynecologic cancers, predominantly carcinomas of the ovary, endometrium, and cervix, represent approximately 13% of all cancers in women. In the United States, in 2022, the estimated new cases for endometrial carcinoma was 65,950, ovarian carcinoma was 19,880, and cervical carcinoma was 14,100.[1] Ovarian cancer ranks fifth in cancer deaths among women, accounting for more

deaths than any other cancer of the female reproductive system, with 12,810 estimated deaths in 2022 in the United States.[2]

Although advanced and recurrent gynecologic cancers are associated with a poor prognosis, earlier detection, surgical intervention, chemotherapy, and emerging targeted therapies have led to improved clinical outcomes.[3,4] Modern cancer treatments, however, are associated with a variety of toxicities, including cancer therapy-related cardiovascular (CV) toxicity. Although cardiotoxicity in breast cancer has been well described in the literature,[5] there has been less recognition of the potential adverse CV impact of cancer therapies in gynecologic malignancies. Adverse CV effects range from asymptomatic left ventricular (LV) dysfunction to cardiogenic shock, microvascular, vasospastic, and thromboembolic vascular diseases, arrhythmias, valvular heart disease, and pericardial disease.[6] Women with gynecologic malignancies are also at risk of sex-specific consequences of cancer therapy, including premature (surgically or pharmacologically induced) menopause, reduced fertility, and adverse pregnancy outcomes.[7]

In this review, we provide a comprehensive overview of cancer therapies used in the treatment of gynecologic malignancies and associated CV toxicities, risk factors for cardiotoxicity, as well as cardiac surveillance and prevention strategies. In the absence of data specific to gynecologic cancers, we extrapolated information on cardiotoxicity from other malignancies, mainly breast cancer.

BURDEN OF GYNECOLOGIC MALIGNANCIES IN THE UNITED STATES

According to the American Cancer Society, there were an estimated 99,930 new cases and approximately 25,360 deaths from gynecologic cancers in the United States in 2022.[2] Although gynecologic cancers account for 12.5% of all estimated new cancer diagnoses in women, they account for 11.2% of all estimated female deaths—a high mortality relative to prevalence indicating the severity of these diseases.[8] Uterine cancer accounted for 3.4% of new female cancer cases in 2022, yet accounted for 2.1% of all cancer deaths in women. Ovarian cancer accounted for 1% of all female cancer cases, yet 2.1% of cancer deaths were due to ovarian cancer in 2022.[2]
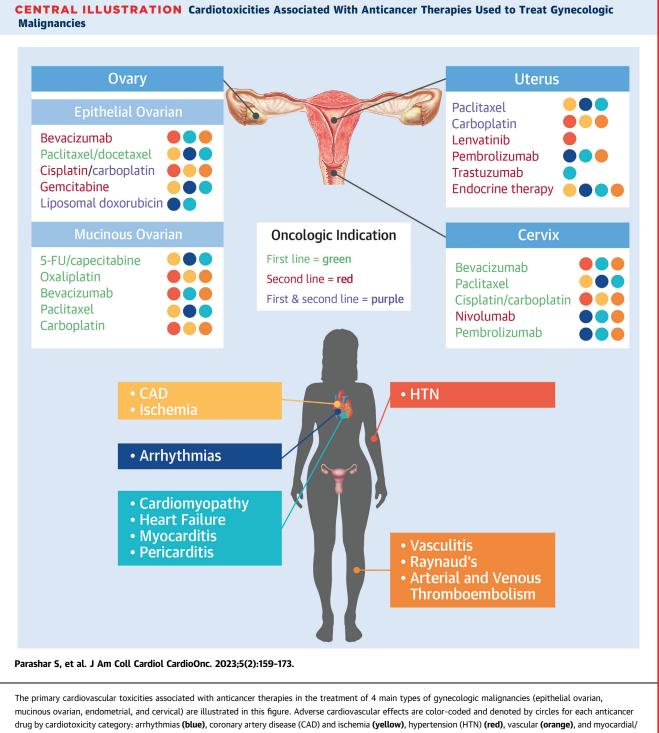
HIGHLIGHTS

- Cancer therapy is associated with CV toxicities in gynecologic cancers
- Risk stratification at baseline and management of CV risk factors/disease is key
- Prospective studies are needed on CV impact of cancer therapies in these patients

RISK FACTORS FOR CARDIOVASCULAR DISEASE AND CANCER

Women are at risk of both heart disease and cancer. Heart disease remains the primary cause of death in women over the age of 40 years. Increased age (>55 years) is associated with 78% of new cancer diagnoses in developed countries.[9] Gynecologic cancers and cardiovascular disease (CVD) share several modifiable and nonmodifiable risk factors.[10] Nonmodifiable risk factors include age, sex, family history, and ethnicity, whereas modifiable risk factors include smoking, lack of exercise, obesity, diabetes, hypertension, and hyperlipidemia. In addition, women diagnosed with gynecologic malignancies may already have underlying cardiac disease or risk factors for heart disease. For example, obesity, diabetes, and hypertension are primary risk factors for both endometrial cancer and heart disease.[10]

Physical inactivity has been associated with an increased risk of CVD and cancer. In a meta-analysis of 33 studies, highly physically active women had a 20% lower risk of endometrial cancer compared with those with low levels of activity, although this association maybe indirect due to reduction in levels of obesity.[11,12] In a pooled analysis of 13 studies, combined exposure to smoking, overweight/obesity, and physical inactivity before a diagnosis of ovarian cancer was associated with a significantly increased risk of mortality compared with women who had never smoked, were active, and had a normal body mass index (HR: 1.37; 95% CI: 1.10-1.70).[13]

Women with endometrial cancer have a high risk of dying from CV causes 5 years from diagnosis.[11] A body mass index of >30 kg/m^2 is associated with an increased risk of endometrial and breast cancer, and a higher risk of cancer-related morbidity and mortality.[14] In the National Institutes of Health American Association of Retired Persons Diet and Health study, higher body mass index was associated with poorer cancer-specific and overall survival in patients with endometrial cancer.[15]

CENTRAL ILLUSTRATION Cardiotoxicities Associated With Anticancer Therapies Used to Treat Gynecologic Malignancies

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The primary cardiovascular toxicities associated with anticancer therapies in the treatment of 4 main types of gynecologic malignancies (epithelial ovarian, mucinous ovarian, endometrial, and cervical) are illustrated in this figure. Adverse cardiovascular effects are color-coded and denoted by circles for each anticancer drug by cardiotoxicity category: arrhythmias **(blue)**, coronary artery disease (CAD) and ischemia **(yellow)**, hypertension (HTN) **(red)**, vascular **(orange)**, and myocardial/pericardial **(turquoise)**. Treatment lines are indicated by color: first **(green)**, second **(red)**, and if given as either first/second **(purple)**. 5-FU = fluorouracil.

TABLE 1   Cardiovascular Toxicity of Cancer Agents in Gynecologic Malignancies

Anticancer Agents	Cancer Use	Type of Cardiotoxicity	Frequency
Doxorubicin	Endometrial	LVD	Common
		HF	Uncommon
		Arrhythmia	Uncommon
Pegylated liposomal doxorubicin	Endometrial	LVD	Common
	Epithelial ovarian	HF	Uncommon
		Arrhythmia	Rare
Angiogenesis inhibitors			
Bevacizumab	Cervical	HTN	Common
	Endometrial	LVD	Uncommon
	Epithelial ovarian	VTE	Common
	Mucinous ovarian	ATE	Uncommon
Antimetabolites			
5-Flurouracil/ capecitabine	Cervical	Coronary vasospasm	Uncommon
	Epithelial ovarian	Ischemia	Rare
	Mucinous ovarian	Arrhythmia	—
		LVD	—
		Myocarditis	—
Gemcitabine	Cervical	Edema	Common
	Endometrial	Capillary leak syndrome	Rare
		Arrhythmia	—
		HF	—
Immune checkpoint inhibitors			
Pembrolizumab	Cervical	Myocarditis	Rare
	Endometrial	Arrhythmia	Uncommon
	Mucinous ovarian	LVD	—
		SCD	—
		Vasculitis	Rare
		Pericarditis	Uncommon
Dostarlimab	Endometrial	Myocarditis	Rare
		Pericarditis	Rare
		Vasculitis	Rare
Avelumab	Endometrial	HTN	Common
		Edema	Common
		Myocarditis	Rare
		Pericarditis	Rare
		Vasculitis	Rare
Hormone therapy			
Tamoxifen	Endometrial	HTN	Common
	Epithelial ovarian	Edema	Common
		VTE	Uncommon
		QT prolongation	Rare
Aromatase inhibitors	Endometrial	Ischemia	Uncommon
	Epithelial ovarian	VTE	Uncommon
		Hyperlipidemia	Common
		HTN	Common
Gonadotropin-releasing hormone agonists	Epithelial ovarian	Ischemia	Common
		VTE	Uncommon
		CVA	—
		HF	Rare
		LVD	—
		QT prolongation	—
Megestrol acetate	Endometrial	HTN	Common
	Epithelial ovarian	LVD	Uncommon
Medroxyprogesterone	Endometrial	Edema	Uncommon
	Epithelial ovarian		

CANCER THERAPIES ASSOCIATED WITH CARDIOVASCULAR TOXICITIES

Several anticancer therapies used in the treatment of gynecologic malignancies are associated with CV toxicities that range in prevalence and severity (**Central Illustration, Table 1**).

Anthracyclines, such as doxorubicin and its pegylated liposomal form, are antitumor therapies that inhibit DNA and RNA by intercalating into base pair strands, inhibiting topoisomerase II, and producing free oxygen radicals. Anthracyclines remain an important line of treatment in advanced or recurrent ovarian and endometrial cancer.[16] Anthracyclines are well-recognized for dose-dependent cardiotoxicity, which is traditionally defined as a decline in left ventricular ejection fraction (LVEF) by >10% from baseline to a value <53%,[17] although this definition has not be universally adopted in clinical trials. In patients with advanced epithelial ovarian cancer, National Cancer Institute Common Terminology for Adverse Events (CTCAE) grade 1/2 cardiotoxicity defined as a decrease in LVEF of 5% to 20% and >20%, respectively, was observed in 46% patients who had received doxorubicin and 29% in epirubicin-treated patients.[18] In another small study, patients with stage III and IV epithelial ovarian cancer were prospectively randomized to receive 8 courses of cisplatin (60 mg/m²) plus either 75 mg/m² of epirubicin (n = 62) or 60 mg/m² of doxorubicin (n = 54). Cardiotoxicity, defined by a decrease in LVEF >10%, was observed in 49% of patients receiving doxorubicin, and 9% of patients receiving epirubicin.[19]

Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin that is encapsulated in a liposomal bilayer sphere with an outer layer of polyethylene glycol, which is used in the treatment of ovarian cancer (in association with carboplatin), endometrial cancer, and uterine sarcomas.[20] Due to the size of the liposomes, the drug is prevented from entering small capillary junctions in cardiac tissue and is therefore associated with less cardiotoxicity when compared with doxorubicin.[20] In a meta-analysis of patients with cancer, including ovarian cancer, PLD had lower rates of clinical cardiotoxicity (OR: 0.18; 95% CI: 0.08-0.38; $P < 0.001$; $I^2 = 0\%$) and subclinical cardiotoxicity (OR: 0.31; 95% CI: 0.20-0.48; $P < 0.01$; $I^2 = 48.5\%$) than doxorubicin, without compromising efficacy.[21] In a study in women with gynecologic cancers, high cumulative doses of liposomal doxorubicin $\geqq 400$ mg/m² were not associated with clinically evident cardiotoxicity.[22] In another study among women with gynecologic cancers who had both pre- and post-treatment cardiac testing, there was no significant difference in median LVEF ($P = 0.17$).[23] Although the risk for cardiotoxicity may be less than conventional doxorubicin, vigilance is still recommended in patients with multiple cardiac risk factors.[24]

Platinum-based chemotherapy regimens (eg, cisplatin), which cause DNA damage by creating intrastrand and interstrand crosslinks, are commonly used in the treatment of cervical, endometrial, and ovarian cancers.[25] Cisplatin-based chemotherapy is associated with thromboembolic events. A cancer cohort study with claims database analysis reported an 11% incidence of venous thromboembolic events (VTE) during the first 12 months after initiation of cisplatin-based chemotherapy in women with ovarian cancer (N = 1,880).[26] Platinum-based therapies can also increase the risk of arterial events such as coronary vasospasms and myocardial infarction, either during or following completion of treatment.[27] This mechanism is due to induced platelet activation and increased von Willebrand factor causing procoagulant effects. Other major (although uncommon) late CV consequences include vascular toxicity: early atherosclerosis, arterial thrombosis, hypertension, Raynaud's phenomenon, and dyslipidemia. Endothelial dysfunction is due to incomplete elimination and detectable levels of platinum found several years after treatment completion.[28] Cisplatin is also associated with sinus bradycardia, which starts during infusion and often resolves spontaneously. Frequent premature atrial and ventricular complexes are present in up to two-thirds of patients. Cases of supraventricular tachycardia and atrial fibrillation have also been reported. Carboplatin-induced cardiotoxicity is extremely rare but has been reported.[29]

Microtubule inhibitors (eg, paclitaxel and docetaxel) are frequently used in cervical, endometrial, and ovarian cancers.[30] Taxanes disrupt microtubule function thereby inhibiting cell division. Arrhythmias are the most commonly observed toxicity of taxanes. Paclitaxel has been associated with asymptomatic bradycardia in up to 29% of patients, which is often asymptomatic and self-limiting. Paclitaxel exposure decreases calcium amplitude and contraction in cardiac myocytes, which contributes to the bradycardia. In a phase II study of 140 women with ovarian cancer who were treated with maximally tolerated doses of taxol, transient asymptomatic bradycardia occurred in 29% of women.[31] More serious cardiotoxicity (atrioventricular conduction block, ventricular tachycardia, cardiac ischemia) was seen in 5% of patients.[31] The overall incidence of cardiac events in the National Cancer Institute database was low, and routine cardiac monitoring is not required for patients without risk factors.[32]

Antimetabolites are a class of drugs that are incorporated into DNA and inhibit thymidylate

TABLE 1 Continued			
Anticancer Agents	**Cancer Use**	**Type of Cardiotoxicity**	**Frequency**
Monoclonal antibodies (HER2)			
Trastuzumab	Endometrial	LVD	Common
		HF	Uncommon
Platinum agents			
Cisplatin	Cervical	Arrhythmia	Uncommon
	Endometrial	Ischemia	Rare
	Epithelial ovarian	VTE	Common
		HTN	—
		HL	—
		Raynaud's phenomenon	—
Carboplatin	Cervical	HTN	Rare
	Endometrial		
	Epithelial ovarian		
Oxaliplatin	Epithelial ovarian	Edema	Uncommon
		VTE	Uncommon
Taxanes			
Paclitaxel	Cervical	Edema	Common
	Endometrial	Bradyarrhythmia	Uncommon
	Epithelial ovarian		
Docetaxel	Cervical	Hypotension	Uncommon
	Endometrial	LVD	—
	Epithelial ovarian	Arrhythmia	—
Tyrosine kinase inhibitors			
Pazopanib	Endometrial	HTN	Common
		LVD	Common
		Bradyarrhythmia	Common
		Ischemia	Uncommon
		VTE	Uncommon
		QT prolongation	Uncommon
		HF	Rare
Lenvatinib	Endometrial	HTN	Common
		Edema	Common
		LVD	Uncommon
		HF	Uncommon
		ATE	Uncommon

The frequency of toxicity was graded as common ≥5% incidence, uncommon 1% to 5% incidence, or rare <1% incidence in clinical trials or observational studies. Undefined frequency is represented by a dash (—).

ATE = arterial thromboembolism; CVA = cerebral vascular accident; HF = heart failure; HL = hyperlipidemia; HTN = hypertension; LVD = left ventricular dysfunction; SCD = sudden cardiac death; VTE = venous thromboembolism.

synthase, thus interfering with the DNA and RNA growth. Fluorouracil (5-FU) is a commonly used antimetabolite therapy in cervical, epithelial, and mucinous ovarian cancer. Although there is a paucity of data in the literature specific to gynecologic malignancies, in solid organ tumors, 5-FU has an incidence of cardiotoxicity ranging from 1% to 7.6%.[33] 5-FU is associated with a wide-spectrum of cardiotoxicities, including arrhythmias and heart failure; the most commonly described cardiac effects are myocardial ischemia, angina, chest pain, and electrocardiogram (ECG) changes (ST-segment changes and T-wave abnormalities).[33,34] Coronary thrombosis or coronary arterial vasospasm are possible mechanisms for the chest pain and ischemia. The incidence of ischemia related to 5-FU is higher in patients with underlying coronary artery disease (4.5%) compared

with patients without known disease (1.1%), emphasizing the need for aggressive management of coronary artery disease.[34] A prospective study of 25 patients using continuous ambulatory electrocardiogram monitoring peri-infusion of 5-FU found that 24% of patients had ECG changes, more commonly seen in those with known coronary artery disease.[35] Cardiac events typically occur early (during the first to third dose) and are more common after higher doses and continuous infusions.[36] Generally, a rechallenge of 5-FU reproduces the ischemic syndrome/symptoms. Although 68% of symptomatic patients responded to conservative antianginal therapy, mortality rate was high (8%), and even higher in those who were rechallenged (13%).[37]

Antiangiogenic agents such as bevacizumab and pazopanib are used to treat cervical, epithelial, and mucinous ovarian cancers, and leiomyosarcoma. Vascular endothelial growth factor (VEGF) signaling pathway inhibitors include small molecule tyrosine kinase inhibitors and monoclonal antibodies. VEGF, which induces the proliferation and migration of endothelial cell survival and increases vascular permeability, is a primary mediator of tumor angiogenesis. As of January 2020, there were 12 completed phase III trials assessing the efficacy and safety of antiangiogenetic agents for gynecologic cancers, especially in ovarian cancer.[3] Bevacizumab, a humanized anti-VEGF monoclonal antibody used in the treatment of ovarian and cervical cancer, has significant CV morbidity, including hypertension, arterial and VTE, and heart failure.[38] The rate of ≥NCI CTCAE grade 3 hypertension varies from 2% to 23% in ovarian cancer studies with grade ≥2 hypertension occurring in 20% of patients in the AURELIA trial (bevacizumab with chemotherapy) in platinum resistant ovarian cancer.[39] Bevacizumab-related cardiotoxicity frequently manifests within the first cycle of therapy, and appears to be dose-dependent.[40] VEGF inhibition also promotes microvascular injury and potentiates thrombosis. VEGF-targeted therapies are associated with a 3-fold increase in risk for arterial thromboembolic events (stroke, transient ischemic attacks, myocardial infarction, angina, and other arterial events), but LV dysfunction is not common.[41] Similarly, pazopanib, which has shown clinical benefit in the treatment of advanced ovarian cancer and gynecologic leiomyosarcomas,[42,43] is associated with the development of hypertension,[44,45] cardiomyopathy, LV dysfunction, heart failure, QT prolongation, and myocardial ischemia.[43,46] A phase III randomized clinical trial (PALETTE [Pazopanib Versus Placebo in Patients With Soft Tissue Sarcoma Whose Disease Has Progressed During or Following Prior Therapy]) of pazopanib vs placebo in patients with soft tissue tumors that included leiomyosarcoma, whose disease had progressed during or following prior therapy, found that 5% of patients on placebo had a decrease in LVEF compared with 11% of patients on pazopanib.[43] The hypertensive response of pazopanib is rapid, and its incidence correlates with pre-existing hypertension.[47] There remains a critical gap in data pertaining to pazopanib in patients with gynecologic cancers.

Lenvatinib, a small molecule inhibitor of multiple receptor tyrosine kinases, targets VEGF receptor 1 to 3, fibroblast growth factor receptor 1 to 4, platelet-derived growth factor receptor α, stem cell factor receptor, and rearranged during transfection—all receptors responsible for tumor angiogenesis, as well as proliferation of cancer cells.[48] The combination of lenvatinib and pembrolizumab is approved for treatment of endometrial cancer due to demonstrated response in more than one-third of patients, even in those lacking microsatellite instability. Hypertension occurred in 73% of patients, with 44% of patients experiencing grade 3/4 blood pressure elevation (CTCAE version 4.08) in a recent open-label phase III trial in advanced endometrial cancer.[49] Blood pressure control before medication initiation along with close monitoring of blood pressure every 1 to 2 weeks during treatment for the first 2 months and at least monthly thereafter is recommended.

Immune checkpoint inhibitors are anticancer drugs that work by disinhibiting T-cell activity by interfering with checkpoint molecules and thus result in T-cell activation and enhanced antitumor immune response. Although several trials of checkpoint inhibitors in ovarian cancer have failed to show significant response rates and were overall disappointing, there are ongoing trials exploring the role of these agents in combination.[50,51] Immune checkpoint inhibitors have been approved for the treatment of uterine and cervical cancer. Pembrolizumab (anti-PD1) is currently Food and Drug Administration approved for the treatment of unresectable or metastatic endometrial cancer and PD-L1-positive recurrent or metastatic cervical cancer. Dostarlimab (anti-PD-1) received accelerated Food and Drug Administration approval in 2021 for the treatment of recurrent or advanced endometrial cancer in the presence of a biomarker for deficient mismatch repair.[52] Fatal cardiac complications of immune checkpoint inhibitors such as myocarditis and acute myocardial infarction are rare (0.1%-1.4%) but may occur. Conduction system disease, ventricular arrhythmias, and noninflammatory cardiomyopathies have also been reported.[53]

Human epidermal growth factor receptor-2 (HER2) agents are a class of drugs that specifically target and inhibit HER2/*neu* receptors. Trastuzumab, a humanized monoclonal antibody against HER2, is indicated for HER2-overexpressing uterine cancers, which comprise about 30% of serous papillary tumors.[54] However, trastuzumab has been associated with treatment-related CV dysfunction, ranging from asymptomatic declines in LVEF (25%) to clinical heart failure (3%-4%).[55,56] Although the majority of the literature pertains to the breast cancer population, it is reasonable to extrapolate these data to determine the risk of CV toxicity in patients with gynecologic malignancies. There is a greater risk for LV dysfunction for patients >50 years of age and those with underlying CVD. Anthracycline-based chemotherapy given before, or in combination, with HER2 targeted agents is associated with a greater risk of LV dysfunction, with the later associated with the greatest risk.[57] LV dysfunction has most commonly been reported within 1 year after initiation of HER2 targeted therapy; however, some studies have reported this risk persists up to 5 years after completing trastuzumab.[55]

Endocrine therapy involves reducing the levels of hormones or inhibiting their biological activity thereby stopping/slowing or preventing cancer growth. Tamoxifen is frequently used in the treatment of cervical, ovarian, and uterine/endometrial cancer and vulvar/vaginal cancer.[56] Tamoxifen, a selective estrogen receptor modulator, is a competitive inhibitor of estrogen binding to the estrogen receptor. Tamoxifen has an estrogen-agonistic effect on the CV system and has a favorable effect on the lipid profile, with reductions in total serum cholesterol (in the range of 10% to 15%) and low-density lipoprotein cholesterol (reductions ranging from 15% to 22%), but no significant changes in high-density lipoprotein cholesterol.[5,58] However, favorable effects on the lipid profile have not translated into clinically relevant benefit in terms of prevention of CV death in clinical trials.[59] Due to the estrogen-agonistic action, tamoxifen increases the risk of venous thromboembolism, including deep venous thrombosis, pulmonary embolism, and long-term sequelae such as pulmonary hypertension and stroke resulting in mortality and significant morbidity.[60]

CV IMPACT OF EARLY MENOPAUSE

Early menopause can be gradual or rapid depending on baseline ovarian reserve, gonadotoxicity, and duration of exposure to cancer agents (cancer therapy and/or endocrine therapy).[61] Premature menopause (age <40 years) not only confers risk of coronary artery disease in women after adjustment for conventional risk factors, but also predicts worse outcomes in coronary artery disease patients including worse angina and higher mortality.[62] Bilateral oophorectomy before the age of 50 years increased the risk of CVD (relative risk [RR]: 4.55; 95% CI: 2.56-8.01), heart failure, and stroke.[63] The higher risk associated with early menopause is due to longstanding deprivation of endogenous estrogen, which may influence CV risk through a variety of effects on metabolism and vascular function including reduced glucose tolerance, abnormal lipids, higher blood pressure, and endothelial dysfunction.[63] Premature menopause was identified as a CVD risk-enhancing factor in the 2018 cholesterol guidelines.[64] Aggressive monitoring and treatment of blood pressure, cholesterol, diabetes, and weight reduction is recommended for patients with early menopause.

STRATEGIES TO MINIMIZE CARDIOTOXICITY RISK

PRETREATMENT RISK ASSESSMENT. Patients with baseline LV dysfunction and/ or history of prior heart failure are at highest risk for developing cardiac dysfunction or worsening heart failure during cancer treatment.[28,65] Depending on the severity of LV dysfunction and/or presence of clinical heart failure, doxorubicin-based regimens should generally be avoided in patients with LVEF <40%. Those with LVEF 40% to 50% can be considered for anthracycline-based regimens based on tumor burden and if the benefits outweigh risks of cardiac dysfunction. The recently published European Society of Cardiology (ESC) guidelines provide excellent guidance on the definition, diagnostic criteria, prevention, and treatment of cardiotoxicity.[66] All patients, including those with gynecologic cancers, should be assessed for risk of developing cardiotoxicity before initiating cancer treatment. The ESC guideline endorses the use of proformas, developed by the Heart Failure Association of the ESC and the International Cardio-Oncology Society, to calculate a baseline CV risk score, although they acknowledge the risk score has not been prospectively validated.[67] The risk score is based on several factors, including: age, cancer treatment, CV history, underlying CV risk factors (prior cardiac history, diabetes, family history, renal disease, hypertension, hyperlipidemia), and lifestyle factors (eg, obesity). Depending on the baseline CV risk (eg, low/medium vs high/very high)

the ESC guidelines provide recommendations for type and frequency of cardiac monitoring before and during cancer therapy. For example, a 66-year-old postmenopausal women with advanced epithelial ovarian cancer is scheduled to received bevacizumab in combination with carboplatin and paclitaxel. She has a history of type II diabetes mellitus, hyperlipidemia, obesity (body mass index >30 kg/m²), and is a smoker. Based on the baseline risk proforma for "VEGF inhibitors," this patient is at high risk of developing cardiotoxicity. She should have baseline cardiac imaging (ECG and echocardiogram) performed and ideally be referred to a specialist cardio-oncology service to optimize management of their pre-existing CVD and modifiable CV risk factors, and provide a personalized management plan for surveillance during cancer treatment. A similar approach can be used for assessment of baseline CV risk with immune checkpoint inhibitors (cervical, uterine cancer) endocrine therapy (uterine cancer), and HER2 targeted agents (uterine cancer).

Surgical interventions in patients with gynecologic malignancies are important when considering CV risk. Patients requiring a hysterectomy, with or without oophorectomy, are at greater risk of coronary artery disease and stroke, especially in younger women (age <50 years).[68] Surgically induced menopause (ie, bilateral oophorectomy) before age 40 years increases the risk of CVD.[69] Therefore, discussion of increased CV risk is essential for women considering bilateral oophorectomy.[69] Treating underlying CV risk factors aggressively before surgery should be considered in all patients.

STRATEGIES TO MINIMIZE CARDIOTOXICITY RISK BEFORE CANCER THERAPY. Cancer therapy strategies to prevent cardiotoxicity.
Several strategies have been studied to prevent cardiotoxicity. Based on the baseline CV risk profile of the patient, avoidance of cardiotoxic therapy, exploration of alternative therapies, and plan for surveillance before initiation of treatment should be discussed with a multidisciplinary team. For patients receiving doxorubicin, adjustments to infusion schedule, reducing frequency of treatment, switching to a continuous infusion, the use of dexrazoxane, or liposomal formulations are potential strategies.[65,70,71] PLD is commonly used as part of standard cardioprotective regimens for ovarian cancer and has been discussed in the previous section on anthracyclines. 5FU-associated cardiotoxicity can be reduced with dose reduction or a change from continuous to bolus infusion schedule. A dose reduction to 50% to 70% with or without an antianginal medication has been shown to reduce subsequent cardiotoxicity.[72] In a small case series, 5-FU cardiotoxicity was ameliorated by switching from continuous to bolus infusion.[73] Symptomatic patients with 5FU-associated chest pain responded to prophylactic antianginal administration with transepidermal nitroglycerin or sublingual nitroglycerin.[72,74] Rechallenging patients with cardiotoxicity should be considered with caution if alternative therapy does not exist, and in a closely monitored setting.[37,75] Currently, there are no established cancer therapy strategies (beyond holding or discontinuation of drug) to prevent cardiotoxicity for other classes of drugs utilized in gynecologic malignancies.

CV strategies to prevent cardiotoxicity.
CV risk factors (hypertension, diabetes, hyperlipidemia) should be evaluated and managed before cancer therapy using a multidisciplinary approach with the goal to reduce the risk of developing cardiotoxicity.[65] Cancer and CVD share modifiable and nonmodifiable risk factors as they both relate to a proinflammatory/prothrombotic disease process. Patients at high or very high risk of cardiotoxicity should be considered for primary prevention strategies with neurohormonal agents.

The American College of Cardiology/American Heart Association and the American Cancer Society recommend 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week for adult cancer patients.[76] In a large prospective study of nonmetastatic breast cancer survivors, exercise (>9 MET-h/week) was associated with an adjusted 23% decrease in risk of CV events.[76]

The ESC guidelines and the American Heart Association recommend developing cardio-oncology rehabilitation programs to provide structured exercise services for cancer patients and survivors.[66,76] Exercise is felt to target the modifiable risk factors that cancer and CVD have in common. Current data support high-intensity interval training before, during, and after cancer treatment. An actual rehabilitation center could allow for patient-specific exercise avoiding areas of pain and frailty.

Neurohormonal therapies.
Several smaller single-center studies have investigated the use of prophylactic angiotensin-converting enzyme (ACE) inhibitors and/or β-blockers for the prevention of anthracycline-mediated cardiomyopathy (with or without trastuzumab), mainly in the breast cancer population; with

mixed results.[77-80] The American Society of Clinical Oncology guidelines recommend cardioprotective measures for high-risk patients; however, there is no recommendation for a neurohormonal inhibition strategy to prevent cardiotoxicity.[65] More recent studies have demonstrated a modest benefit from prophylactic neurohormonal inhibition. The European Society of Medical Oncology Consensus recommends prophylactic use of ACE inhibitors or angiotensin receptor blockers and/or selected β-blockers to reduce the risk of cardiotoxicity in patients with normal LVEF and CV risk factors undergoing cardiotoxic therapy.[28] The ESC guideline recommends consideration of prophylactic use of neurohormonal agents in patients deemed to be at high or very high risk of cardiotoxicity.[66]

Dexrazoxane. Dexrazoxane is a potent intracellular iron chelating agent used in conjunction with anthracyclines. In a meta-analysis of 9 studies including 2,177 patients, dexrazoxane reduced the risk of clinical heart failure and cardiac events in breast cancer patients undergoing doxorubicin-based chemotherapy.[81] In a recent small case series of 5 patients, concomitant administration of dexrazoxane in patients with pre-existing cardiomyopathy permitted successful delivery of doxorubicin-based chemotherapy without cardiac decompensation.[82]

SURVEILLANCE STRATEGIES TO MINIMIZE CARDIOTOXICITY BEFORE, DURING, AND AFTER CANCER THERAPY. Surveillance of patients, particularly those with comorbid CV risk factors and pre-existing CVD, is critical around the time of treatment as cardiotoxicity can appear years after completion of cancer therapy.[5] A multidisciplinary team should collaborate to form a comprehensive care plan for patients and survivors to optimize CV health.

Frequent blood pressure monitoring is recommended during the first cycle of VEGF inhibitors (eg, bevacizumab), especially in high-risk patients with pre-existing hypertension and increased CV risk. Once blood pressure is stable, routine monitoring every 2 weeks is recommended for the duration of treatment.[28] According to expert recommendations on the management of hypertension in patients with ovarian and cervical cancer receiving bevacizumab in the United Kingdom, bevacizumab can be infused in all patients with clinic blood pressure <160/100 mm Hg. If blood pressure is ≥160/100 mm Hg, bevacizumab should not be administered until the blood pressure is better controlled. Amlodipine is considered a safe and effective treatment for bevacizumab-associated hypertension. Patients who are already receiving antihypertensive treatment should have their treatment modified if needed in accordance with standard antihypertensive guidelines. Underlying causes of secondary hypertension should be excluded. Discontinuation or dose reduction of bevacizumab may be necessary to control hypertension in some patients. De-escalation of antihypertensive therapy can be undertaken after discontinuation of bevacizumab.[83]

Patients receiving treatment with tyrosine kinase inhibitors, specifically patients prescribed pazopanib should be monitored closely for prolonged QTc (>500 ms) and torsade de points although this is uncommon (incidence <2%). It should be used with caution in patients with a history of prolonged QTc and in patients on antiarrhythmic therapy or other medications that may prolong the QTc. Electrolyte levels (potassium/magnesium) should be optimized before starting treatment. An ECG should be obtained at baseline and at 1 month with additional monitoring as clinically indicated (eg, dose changes, electrolyte disturbances).[46]

Imaging surveillance. Surveillance for cardiotoxicity is recommended for several anticancer agents used in gynecologic malignancies. Oncology and cardiology societies currently recommend that patients receiving cancer drugs associated with increased risk of LV dysfunction undergo a noninvasive assessment of cardiac function before initiation of treatment.[17,28] Most centers use echocardiography as a noninvasive method (without ionizing radiation) to serially assess LVEF, which also allows assessment of diastolic function, as well as valvular and pericardial involvement. Furthermore, there is robust literature demonstrating the prognostic value of global longitudinal strain (GLS) in patients treated with anthracyclines. Preclinical changes in cardiac mechanics can be detected by GLS, before and during anthracycline-based chemotherapy.[17,84-86] Subclinical LV dysfunction associated with cancer therapy is defined as a change in GLS >12% to 15% from baseline before development of overt cardiotoxicity.[17,28] A GLS <16% or a decrease of 15% after treatment is considered a marker of increased cardiac risk.[66,87] However, there are no specific studies in patients with gynecologic malignancies. Overall, cardiac imaging with echocardiography is recommended for determination of LVEF and GLS measurement at baseline before potentially cardiotoxic cancer therapy (such as anthracyclines), and depending on risk level, after every 2 cycles beyond 250 mg/m², and within a year of the end of treatment if patients have received >250 mg/m² doxorubicin cumulative dose or its equivalent anthracycline.[28,66] Optimization of all risk

factors, closer surveillance, and consideration of cardioprotective medications in these patients is recommended.[87]

Cardiac magnetic resonance imaging (CMR) has excellent sensitivity and specificity in the assessment of cardiac structure and function, and in patients with poor transthoracic echocardiography image quality or when transthoracic echocardiography is not diagnostic, CMR should be considered. Furthermore, CMR can be used to exclude other etiologies of cardiomyopathy such as myocarditis.[66,88] The role of late gadolinium enhancement as a prognosticator in patients with myocarditis (immune checkpoint associated or secondary to other agents) is controversial.[89] Multigated acquisition nuclear scans are considered third-line in assessing LVEF[66] and, during the COVID19 pandemic, had the advantage of lower exposure of health care providers compared with echocardiograms.

There is limited guidance regarding imaging protocols for nonanthracycline cancer agents, other than trastuzumab, in gynecologic malignancies. The imaging surveillance proposed for trastuzumab includes baseline and serial LVEF assessments every 3 months while on therapy; although this frequency of imaging is now debated.[90]

In a study of 40 patients treated with VEGF inhibitors for metastatic colorectal and renal cell carcinomas, serial assessment of GLS during VEGF therapy showed that 30% of patients developed a clinically significant decrease in GLS, whereas only 8% developed asymptomatic cardiotoxicity.[91] All patients treated with a VEGF inhibitor should have a baseline CV risk assessment including clinical exam, blood pressure measurement, and an ECG with baseline QTc measurement. A baseline echocardiogram is recommended for high- and very-high-risk patients.[28,66] Patients with impaired LV function and/or patients at high or very high risk of developing heart failure should be referred to a cardiologist before starting VEGF therapy.[55]

Other commonly used therapies, such as cisplatin and 5-FU, can induce ischemia, especially in patients with pre-existing coronary artery disease.[34] Diagnosis of coronary artery disease before treatment using stress imaging or computed tomography may be warranted in patients at high risk of ischemia.

Uterine and ovarian malignancies are associated with some of the highest rates of VTE compared with other cancers.[92] There is currently no role for routine surveillance recommendations for vascular complication in these patients. However, if VTE is suspected due to unexplained unilateral lower extremity swelling or dyspnea, then imaging with a comprehensive duplex ultrasound protocol from thigh to ankle and computed tomography pulmonary angiography should be considered. An evaluation for coronary artery disease with stress testing/coronary computed tomography imaging and cardiac catheterization should be considered in symptomatic patients.

Biomarker surveillance. The routine use of biomarkers such as troponin (Tn), high-sensitivity Tn assays (hs-Tn), and B-type natriuretic peptide in the surveillance of CV toxicity in patients receiving anticancer therapy continues to evolve. The majority of studies have evaluated women with breast cancer and have demonstrated that increases in troponin occurring with doxorubicin are associated with cardiotoxicity.[93,94] There are also data for the use of biomarkers during treatment with trastuzumab, although the data are generally less robust for their use to monitor for trastuzumab-related cardiotoxicity. The largest study examining this was a subanalysis of the Herceptin Adjuvant trial, in which 533 patients with breast cancer who were receiving trastuzumab had serial measurements of hs-TnI and hs-TnT.[95] In this study, elevated pretreatment Tn was associated with a 4-fold increase in cardiotoxicity. Tn may also have a role in monitoring cardiac function during cancer therapy. Several observational studies have demonstrated that abnormal levels of TnI, ultra-sensitivity TnI, hs-TnI, TnT, and hs-TnT are associated with a decrease in LVEF after anthracycline and/or trastuzumab treatment.[96] For gynecologic malignancies, 1 small study reported increased hs-Tn in 25 patients with untreated ovarian malignancy, underlining the difficulty in analyzing biomarkers in patients with cancer.[97]

The ESC guidelines recommend baseline biomarkers for patients treated with anthracyclines and HER2 targeted therapies who are considered at high or very high risk of cardiotoxicity (Class I recommendation). Baseline biomarkers may be useful in patients treated with VEGF inhibitors at high risk (Class IIa recommendation) or those considered at low/moderate risk of cardiotoxicity related to anthracyclines (Class IIa recommendation) or HER2 targeted therapy (Class IIb recommendation). This is in contrast to immune checkpoint inhibitors where a baseline troponin is recommended for all patients. Baseline troponin values can be helpful as a comparator to later values if there are new signs or symptoms concerning for myocarditis.[66]

SPECIAL CONSIDERATIONS

TAKOTSUBO SYNDROME. Takotsubo syndrome, or stress-induced cardiomyopathy, represents an acute

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TABLE 2 Recommendations for Cardiac Monitoring in Pregnancy for Patients With Cardiotoxicity

LVEF <30%—Pregnancy is contraindicated

LVEF 30%-50% or high-risk features listed above

- Baseline echo, BNP, and clinical exam
- Echo and BNP every trimester
- Clinical exam every 4-8 wk
- Consider echocardiogram 1 mo after delivery

LVEF >50% and no high-risk features

- Baseline echo, BNP, and clinical exam
- Repeat echo and BNP if change in symptoms
- Clinical evaluation every trimester and with change in symptoms
- Consider echocardiogram in third trimester and 1 mo after delivery

Left ventricular ejection fraction (LVEF) cutoff used by the modified World Health Organization and other organizations where "pregnancy is contraindicated" is 30%.[107,111]

BNP = B-type natriuretic peptide.

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heart failure syndrome, is usually precipitated by an emotional or physical stressor, and is commonly seen among postmenopausal women.[98] The underlying pathophysiological mechanisms for this condition remain poorly understood. Excessive catecholamine secretion, coronary artery vasospasm, and coronary endothelial dysfunction have been postulated as possible mechanisms.

Cancer is a chronic inflammatory condition and is associated with significant physical and emotional stress.[99] Some data have suggested that cancer therapy, rather than the cancer itself, is a more significant predictor of takotsubo. Several chemotherapeutic agents which are used in the treatment of gynecologic malignancies have been linked with takotsubo syndrome in cases reports and case series (eg, 5-FU, capecitabine, bevacizumab).[100] It is postulated that the coronary vasospasm and coronary endothelial dysfunction with these anticancer agents could be the precipitating factor for takotsubo. In the largest multicenter prospective registry, International Takotsubo Registry, malignancy was observed in ~17% of 1,604 patients,[101] and the majority of the patients were women (~88%). In the cohort of malignancy patients, physical triggers were observed in 48%, emotional triggers in 18%, and both physical and emotional triggers in 10%. Takotsubo cardiomyopathy in the context of malignancy appeared to have a similar 30-day mortality compared with takotsubo without malignancy, but worse mortality during 5-year follow-up.[101] Data regarding the management of takotsubo in the context of malignancy (including gynecologic malignancies) are limited. Based on available retrospective studies, ACE inhibitor and β-blockers are recommended if tolerated.[98]

CORONARY MICROVASCULAR DYSFUNCTION. Coronary microvascular dysfunction is characterized by reduced coronary flow reserve and abnormal epicardial coronary endothelium dilation. It most commonly affects women (~70%), and is associated with other traditional CV risk factors such as hypertension, diabetes, and obesity.[102] Patients with coronary microvascular dysfunction usually present with stable angina and have nonobstructive coronary disease.[103] The diagnosis is usually confirmed by demonstrating a reduction in the coronary flow reserve on noninvasive imaging or invasive angiography.

Endothelial cells normally produce VEGF to maintain normal vascular function, and endothelial dysfunction has been implicated in the pathogenesis of coronary microvascular dysfunction.[104] Certain cancer agents such as bevacizumab and tyrosine kinase inhibitors, which are used in patients with metastatic and advanced cervical cancer, inhibit the signaling of VEGF and have been linked to coronary microvascular disease.[105] Treatment for coronary microvascular disease includes angina relief with β-blockers, ACE inhibitor, aspirin, and high-dose statins for concomitant nonobstructive coronary artery disease.[102]

CARDIOVASCULAR CONSIDERATIONS DURING PREGNANCY AFTER GYNECOLOGIC MALIGNANCY TREATMENT. Cancer therapy, in particular alkylating agents, and radiation can affect the ovaries, affecting fertility and possibly inducing early menopause. The American Society of Clinical Oncology recommends that all women of reproductive age with cancer discuss the risk of infertility and fertility preservation options with their physicians before treatment begins.[106]

The management of cardiotoxicity during pregnancy is challenging and often determined by the severity of CVD. Some data are available regarding CV outcomes in women following anthracycline therapy for childhood cancers.[7,107-109] Women who have had prepregnancy cardiotoxicity appear to be at highest risk of developing LV dysfunction or heart failure during pregnancy (28% risk; OR: 47).[110] Major risk factors for adverse CV events during pregnancy appear to be a longer time between cardiotoxic cancer therapy and pregnancy (>15 years) and a higher total anthracycline dose (>250 mg/m²).[7] Recommendations for cardiac surveillance in pregnancy are summarized in **Table 2**.[107] Although there should be shared decision-making and communication with patients about risk of pregnancy with any degree of cardiomyopathy, the current LVEF cutoff

recommended by the modified World Health Organization and other professional societies, where pregnancy is contraindicated, is 30%.[111,112]

All patients with cardiotoxicity should be followed throughout pregnancy with a multidisciplinary cardio-obstetrics team.[6,110,113,114] Prepregnancy assessment should include a discussion of the risks to mother and fetus, and adjustment of heart failure medications to reduce the risk of fetal harm.[113] Postpartum, there is a rapid rise in afterload in the first 2 weeks after delivery, which can precipitate clinical heart failure.[115] Therefore, patients should be monitored closely in the early postpartum period. Finally, CV medications should be adjusted for lactation if desired by the patient, and multidisciplinary contraception planning should be discussed.

CONCLUSIONS

Cytotoxic and targeted cancer therapies used in the treatment of gynecologic malignancies are associated with an increased risk of cardiotoxicity and should be addressed by a multidisciplinary team to ensure the best cancer outcomes, without compromising CV health. Optimal preventive efforts should start with risk stratification and careful selection of cancer regimens combined with management of underlying CV risk factors. It is critical to consider prevention strategies and provide optimal management and surveillance of cardiotoxicity during treatment of gynecologic malignancies. Larger and more comprehensive prospective studies are needed to solidify guidelines on appropriate monitoring, prevention, and treatment of cardiotoxicity in patients with gynecologic malignancies.

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