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CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Cardiac Complications in the Adult Bone Marrow Transplant Patient

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Abstract

Purpose of Review Due to advancements in oncologic treatment strategies and techniques, the number of survivors who have undergone hematopoetic stem cell transplant (HCT) continues to increase in the United States; this number is projected to reach 502,000 by the year 2030. There is significant interest within the field of cardio-oncology to identify cardiotoxicity and cardiovascular disease in the HCT population. Epidemiologic studies analyzing both short- and long-term cardiovascular effects, risk stratification modeling, cardioprotective strategies, and expert consensus documents for cardiotoxicity surveillance recommendations are reviewed.

Recent Findings Patients who have undergone HCT are at increased risk of cardiovascular events and mortality compared to matched controls. The type of cardiotoxicity and the incidence rates vary based on specific therapeutic regimens and pre-existing cardiovascular risk factors. Life-threatening cardiotoxicity can present during HCT as acute heart failure, arrhythmias, pericardial tamponade, or cardiac arrest; or it can present late after treatment as cardiomyopathy, ischemic heart disease, vascular disease, stroke, or comorbid conditions, such as hypertension and diabetes mellitus that are associated with cardiac events.

Summary HCT is associated with excess cardiovascular risk partially due to exposure to cardiotoxic chemotherapy and radiation, as well as indirect and direct detrimental effects on cardiovascular reserve. This review discusses the epidemiology and the known cardiotoxic effects of historical chemoradiation agents in addition to newer targeted therapies. Recent expert consensus statements from cardiology and hematology/oncology societies are reviewed in regard to risk stratification of the cancer patient based on the type of treatments. Finally, gaps in knowledge are identified with proposed avenues of research that will allow for more accurate risk assessment, prediction, and potential treatment of the HCT patient in attenuating the risk of developing both short- and long-term cardiovascular comorbidities.

Keywords Hematopoietic stem cell transplant · Bone marrow transplant · Cancer survivor · Cardiotoxicity

Introduction

Hematopoietic stem cell transplant (HCT), also referred to as bone marrow transplant (BMT), is an important therapeutic option for certain hematologic and lymphoproliferative conditions in which long-term survival is the goal. The transplant involves initial ablation of the *marrow* and, then, reconstitution of *hematopoiesis* with either genetically identical marrow

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(such as patient's own or identical twin, also called autologous and syngeneic, respectively) or histocompatible marrow (such as from an allogeneic donor) [1]. The population of HCT survivors is expected to increase significantly by 2030. Currently, there are an estimated 108,900 transplant survivors in the US, including both allogeneic and autologous transplant recepients [2]. This number is expected to increase to 502,000 survivors by 2030 in the US based on data from the Center for International Blood and Marrow Transplant Registry (CIBMTR) [2].

Preparative regimens are an essential part of transplant because they provide immunosuppression to allow engraftment and help eradicate the underlying neoplastic disease. Preparative strategies consist of fully myeloablative, reduced intensity, or non-myeloablative conditioning regimens containing several combinations of chemotherapeutic regimens and/or radiation, some of which have known cardiotoxic effects. Different protocols are used depending on the recipient's comorbidities, risk of rejection, and the underlying disease, and they often include some combination of total body irradiation (TBI), busulfan, cytarabine, fludarabine, cyclophosphamide, idarubicin, thiotepa, and/or melphalan [3]. For allogeneic transplants, methotrexate and cyclosporine are used for prevention of graft versus host disease (GVHD). If GVHD does occur, corticosteroids are an important aspect of immunosuppressive therapy and are often required for extended periods of time. Acute and/or chronic GVHD can be treated with various immunosuppressive medications that may also have cardiotoxic effects.

A practitioner should be aware of chemotherapy and radiation exposure administered during prior treatments; these treatments will vary widely depending on each patient's diagnosis but can constitute significant risk factors for developing toxicity during and following HCT. One example includes anthracyclines that are commonly used for the treatment of hematologic malignancies and are known to cause significant cardiotoxicity that can manifest as ventricular dysfunction and HF.

Multiple studies have shown that HCT survivors have poorer long-term survival than expected due to multiple factors, including relapsed disease, infection, graft versus host disease, and cardiac events [4]. The literature on the incidence of cardiac events in patients who have undergone HCT, the treatment-related and patient-specific factors that impact risk of cardiotoxicity, as well as the current guidelines for cardiotoxicity surveillance both during and following HCT in cancer patients are reviewed.

Incidence of Cardiotoxicity During Hematopoietic Stem Cell Transplant

Studies have shown that the overall incidence of cardiotoxicity during HCT is moderate (range 0.9–8.9% depending on the study [5–8]) and includes serious and potentially fatal complications, such as congestive heart failure (CHF), arterial events, tamponade, and rhythm disturbances. There are often significant differences in the definition of cardiotoxicity between studies resulting in a wide range of reported cardiotoxicity rates. Several single-center studies [5–8] have evaluated the spectrum of cardiotoxicity across institutions and various preparative regimens in patients undergoing HCT.

A retrospective study of 2821 patients undergoing BMT at the University of Minnesota from 1977 to 1997 reported an incidence of major or fatal cardiotoxicity of 0.9%. Cardiotoxicity was defined as development of heart failure (HF), pericardial tamponade, ventricular fibrillation cardiac arrest, and cardiac arrhythmias [5]. In a single-center study of 170 BMT patients at the University of Ulm in Germany, incidence of cardiotoxicity was 4.7% overall and 1.8% for life-threatening cardiotoxicity, defined as pericardial effusion, HF, or sudden cardiac arrest [6]. The authors found that a reduction in left ventricular ejection fraction (LVEF) before transplant was a risk factor for minor cardiac events; however, it was not predictive of life-threatening cardiotoxicity [6]. Similarly, Fujimaki et al. reported that 3 of 80 (3.8%) HCT patients treated at the Kanagawa Cancer Center in Japan from 1994 to 1999 with a preparative regimen of thiotepa, cyclophosphamide, and TBI suffered severe cardiac toxicity. Severe cardiotoxicity was defined as grade III or IV cardiotoxicity with CHF, and all 3 patients subsequently died. Pre-existing reduction in LVEF, cumulative dose of anthracycline, and multiple chemotherapy regimens correlated with cardiac complications [8]. Kupari et al. specifically evaluated the incidence of CHF in 45 BMT patients one month after receiving cyclophosphamide and TBI and found that 4/45 (8.9%) patients were affected [7].

Among the more common cardiac complications seen during transplant are arrhythmias. One retrospective study reviewed 1177 adult patients receiving HCT over a ten-year period at the Memorial Sloan-Kettering Cancer Center and showed an incidence of 5.2% (61/1177) for developing an arrhythmia during or following transplant [9]. The most frequently encountered arrhythmias included atrial fibrillation, atrial flutter, and supraventricular tachycardia [9]. In this study, the authors found that developing post-transplant arrhythmias was predictive of longer hospitalization, increased likelihood of needing intensive care, and an increased risk of death (OR 3.5) at 1 year post-transplant [9].

Incidence of Late Cardiotoxicity in Hematopoietic Stem Cell Transplant Survivors

Late cardiotoxicity many years following HCT is well-described and appears to be more common than early cardiotoxicity. In a single-center retrospective cohort study of 1491 patients, patients

post-HCT (censored for relapse) had significantly increased risk of cardiovascular (CV) death (HR 2.7 95% CI [1.5–4.6]), ischemic heart disease (HR 1.4 95% CI [0.9–2.0]), cardiomyopathy/CHF (HR 2.5 95% CI [1.7–3.6]), stroke (HR 1.3 95% CI [0.7–2.6]), vascular disease (HR 2.2 95% CI [1.4–3.5]), rhythm disorder (HR 2.7 95% CI [2.0–3.7]), hypertension (HTN, HR 2.2 95% CI [1.8–2.7]), renal disease (HR 7.5 95% CI [5.1–11.0]), diabetes mellitus (DM, HR 2.3 95% [1.7–3.1]), and hyperlipidemia (HLD, HR 1.2 95% CI [0.9–1.8]) compared to matched controls in the general population [10].

Armenian et al. evaluated the incidence of CHF in patients at least one year post-HCT treated at the City of Hope National Medical Center in a case–control study. The authors found that the incidence of CHF was 11.7% with a median time of CHF onset of 3 years post-transplant [11]. Armenian et al. subsequently reported that the incidence of CHF among 1244 autologous HCT survivors treated at the City of Hope between 1988 and 2002 was 4.8% at 5 years and 9.1% at 15 years following transplant. Female lymphoma survivors had among the highest rate (14.5% at 15 years) of CHF, which may be due to the increased susceptibility to anthracycline-related cardiotoxicity in women compared to men [12]. Prior anthracycline therapy (OR 9.9) and other comorbidities (HTN + anthracycline OR 35.3; DM + anthracycline OR 26.8) significantly increased the risk of CHF [12].

Cardioprotective medications, such as angiotensin-converting enzyme inhibitors (Ace-I) and beta-blockers, may decrease the risk of LVEF reduction and HF; however, there is an overall lack of randomized clinical trials in the HCT population. Ninety patients with acute leukemia or hematologic malignancies undergoing autologous HCT were treated with either enalapril and carvedilol or control in a randomized controlled trial (OVERCOME) by Bosch et al. Compared to patients who did not receive either Ace-I or beta-blockers, patients treated with enalapril and carvedilol were less likely to suffer from a combined endpoint of death/HF/final LVEF < 45% (6.7% vs. 24.4%) [13••].

In addition to CHF, post-HCT patients are at risk of arterial events, such as coronary artery disease (CAD), cerebrovascular accidents (CVA or stroke), and peripheral artery disease (PAD). Compared to autologous HCT, allogeneic HCT survivors are more likely to experience cardiovascular events, including stroke, coronary artery disease, and peripheral artery disease (RR 6.92) [14]. In patients who have received an allogeneic HCT, the risk of arterial events, including CAD and CVA, is 10% at 15 years and > 20% at 20 years [14, 15]. A retrospective multicenter study of BMT survivors from the European Group of Blood and Marrow Transplantation reported a 3.6% incidence of cardiovascular events, including CAD and PAD, at a median age of 54 years (range 41–70 years) [16].

Cardiotoxicity has been identified as a significant cause of mortality in the HCT patient population as well. In 854 autologous HCT survivors who were registered in the Bone Marrow Transplant Survivor Study (BMTSS), cardiac events accounted for 2.4% of late death (≥ 2 years after transplant) [17]. In allogeneic HCT survivors, late cardiac deaths accounted for 3% of mortality [18].

Factors Impacting Incidence of Cardiotoxicity

Many factors influence the development of cardiotoxicity in patients undergoing HCT. First, any prior cardiotoxic treatments, such as anthracyclines and chest radiation, increase the risk of subsequent cardiotoxicity. In addition, development of comorbid conditions, such as HTN, DM, or HLD from HCT-related therapies or GVHD, is associated with subsequent long-term risk of CV disease. Many agents that are used prior to transplant for the treatment of the underlying primary hematologic malignancy, during HCT conditioning, and post-HCT for maintenance, have the potential to cause short- and long-term cardiotoxicity (Table 1). Chemoradiation therapy strategies and the evidence for their use in these malignancies are beyond the scope of this review.

Anthracyclines

Although anthracyclines are not typically used as part of the preparative regimen, they are commonly used to treat hematologic malignancies. The majority of patients with acute leukemia eligible for transplant will have received anthracyclines as part of the induction and/or consolidation portion of therapy. Those patients who have received anthracyclines prior to HCT are at significantly increased risk of cardiovascular death [69]. The cumulative anthracycline dose is predictive of cardiac complications post-transplant [70, 71]. In a nested case–control design of HCT survivors treated at City of Hope, receiving an anthracycline dose of ≥ 250 mg/m^2 was associated with late-onset CHF (OR 3.2) [11]. CPX-351, a liposomal formulation of daunorubicin and cytarabine, has shown a significant overall survival benefit compared to standard cytarabine and daunorubicin (7 + 3) chemotherapy in acute myeloid leukemia [47], allowing a once poor-risk group of AML patients to proceed to HCT. The long-term cardiac toxicities with the liposomal formulation of the anthracycline in CPX-351 with or without HCT have yet to be delineated.

Chest Radiation

Chest radiation is a well-known cause of cardiovascular morbidity and mortality [72]. For example, a study of Hodgkin's lymphoma survivors with prior radiation therapy (48% of whom received ≥ 30 Gy) showed that coronary artery disease was present in 12 of 31 (39%) patients based on coronary CT

Table 1 A comprehensive summary of HCT induction and conditioning, GVHD prophylaxis and treatment, and post-HCT maintenance agents, including their mechanisms of action, mechanism of cardiotoxicity, cardiovascular effects, and the associated disease state

Drug class	Agent	Mechanism of action	Proposed mechanisms of toxicity/cardiovascular effects	Disease state
Alkylators	Cyclophosphamide	Binds to DNA resulting in DNA fragmentation, mutations, and cell death	Toxic vasculitis involving small arteries, direct endothelial injury and myocardial necrosis, lipid peroxidation resulting in oxidative damage, formation of intracapillary microemboli and coronary vasospasm, ifosfamide-induced glomerular injury that may decrease clearance of cardiotoxic metabolites, left ventricular dysfunction, acute cardiomyopathy not related to cumulative dose, hemorrhagic pericarditis [19–22]	B and T cell lymphoma, MM, GVHD
	Bendamustine			MM, lymphoma
	Carmustine			HCT conditioning
	Busulfan		Endocardial fibrosis [23]	HCT conditioning
	Melphalan		Supraventricular tachycardia, atrial fibrillation, ventricular arrhythmias [24]	HCT conditioning, MM
	Ifosfamide		Arrhythmias, ST-T wave changes on ECG, heart failure [25, 26]	B and T cell lymphoma, HCT conditioning
Anthracyclines	Daunorubicin Idarubicin Mitoxantrone	Intercalates into DNA resulting in cross-links and strand breaks	Free radical production, topoisomerase II inhibition, higher affinity of anthracyclines for cardiolipin, heart failure, hypertension, ischemia, cardiac arrhythmia [27]	AML, B and T cell ALL, MM, B and T cell lymphoma, HCT conditioning
	Doxorubicin			MM
Anti-thymocyte globulin (ATG)	–	Immunosuppression due to T cell depletion	Myocarditis, "cardiac irregularity," chest pain, hypertension, hypotension, tachycardia, bradycardia [28]	HCT conditioning, GVHD, aplastic anemia
Antibody–drug conjugates	Inotuzumab	Anti-CD22 monoclonal antibody conjugated to calicheamicin, which causes DNA breaks	QTc prolongation with other QT-prolonging agents (3%) [29]	B and T cell ALL
Anti-CD20 monoclonal antibody	Rituximab	Binds CD20 resulting in antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity	Myocardial infarction, ventricular fibrillation, cardiogenic shock [30, 31]; long-term toxicity not reported	B and T cell ALL
Antimetabolites	Cytarabine	Interferes with nucleic acid synthesis through disruption of DNA and RNA, resulting in cell death during S phase	Pericarditis, pericardial effusion, cardiac tamponade [32, 33]	AML, B and T cell lymphoma, HCT conditioning
	Clofarabine Fludarabine		Left ventricular dysfunction [34] Acute congestive heart failure when combined with melphalan [35, 36]	AML
	Methotrexate	Inhibits dihydrofolate reductase resulting in disruption of DNA synthesis	Supraventricular tachycardia, ventricular arrhythmias, myocardial infarction [37, 38]	B and T cell ALL
Bispecific T cell engager	Blinotumumab	Binds CD19 on B cells and CD3 on T cells to activate endogenous T cells to malignant B cells	Cytokine release syndrome leading to hypotension and cardiac arrhythmia [39]	B and T cell ALL
Btk inhibitor	Ibrutinib	Irreversible small molecule inhibitor of Btk	Btk inhibition in cardiac tissues, atrial fibrillation [40]	GVHD
Calcineurin inhibitors	Cyclosporine	Binds cyclophilin inhibiting T cell activation	Binds LDL receptor, hypertension, dyslipidemia [41, 42]	GVHD
	Tacrolimus	Binds FK-binding protein, blocking mTOR, causing cell cycle arrest	Hypertension, hypertrophic cardiomyopathy [43, 44]	
Corticosteroids	Dexamethasone	Effects gene transcription	Insulin resistance, increased hepatic secretion of VLDL, dyslipidemia [45, 46]	B and T cell ALL, MM

Table 1 (continued)

Drug class	Agent	Mechanism of action	Proposed mechanisms of toxicity/cardiovascular effects	Disease state
	Methylprednisolone			B and T cell lymphoma, GVHD
CPX-351	–	Liposomal combination of daunorubicin and cytarabine with fixed 1:5 molar ratio	Heart failure (incidence appears similar to standard 7 + 3 chemotherapy) [47]; long-term toxicity not yet available	AML
FLT3 inhibitor	Midostaurin	Tyrosine kinase inhibitor of wild-type and mutated FLT3	Ejection fraction reduction [48]	Post-HCT maintenance
Histone deacetylase inhibitor	Panobinostat	Inhibits histone deacetylase resulting in increased acetylation of histone proteins, which induces cell cycle arrest and/or apoptosis	Myocardial infarction, cerebrovascular accident, cardiac arrest, ECG changes (T wave abnormalities, ST depression, QT prolongation), cardiac arrhythmia [49]	MM
Hypomethylating agents	Azacitadine Decitabine	Inhibits DNA methyltransferase causing DNA hypomethylation, incorporates into RNA leading to disassembly of polyribosomes, hypomethylation of DNA restoring normal gene differentiation and proliferation, some direct toxicity in abnormal hematopoietic cells in the bone marrow	Pericarditis, myocarditis [50, 51]	AML, MDS/MPN
Immunomodulatory agents	Lenalidomide Thalidomide Pomalidomide	Immunomodulatory, antiangiogenic, and antineoplastic characteristics, inhibits secretion of proinflammatory cytokines (TNF-a)	Increased inflammation and TNF-a levels contributing to endothelial dysfunction and thrombosis; lenalidomide: venous thromboembolic event, arterial thromboembolic myocardial infarction, cerebral vascular events, deep vein thrombosis/pulmonary embolism [52]	MM
Janus-associated kinase (JAK) inhibitors	Ruxolitinib	JAK inhibitor which mediates signaling of cytokine and growth factors needed in hematopoiesis and immune function, JAK signaling recruits STATs to cytokine receptors leading to gene expression	Inhibition of JAK-STAT signaling pathway in the myocardium which is believed to be protective, edema, hypertension [53]	MDS/MPN
L-asparaginase	–	Reduces exogenous asparagine sources for leukemic cells	Thrombosis mainly in the central nervous system and in association with lines due to decreases in factors involved with fibrinolysis and coagulation, transient hypertriglyceridemia/combination of L-asparaginase and corticosteroids leads to abnormalities in lipid metabolism [54]	B and T cell ALL
Monoclonal antibodies	Daratumumab	Monoclonal antibody against CD38, which is a cell surface glycoprotein highly expressed on myeloma cells	Hypertension	MM
	Elotuzumab	Monoclonal antibody against signaling lymphocytic activation molecule family member 7 (SLAMF7) expressed on myeloma and natural killer cells	Tachycardia, bradycardia, changes in blood pressure, chest pain	MM
mTOR inhibitor	Sirolimus	Binds mTOR resulting in cell cycle arrest in G1	Hypertension, edema, chest pain, tachycardia [55]	GVHD
Nucleoside analog	Gemcitabine	Pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase	Congestive heart failure [56]	B and T cell lymphoma

Table 1 (continued)

Drug class	Agent	Mechanism of action	Proposed mechanisms of toxicity/cardiovascular effects	Disease state
Platinum-containing alkylators	Cisplatin Carboplatin	Inhibits DNA synthesis by formation of DNA cross-links	Supraventricular tachycardia, bradycardia, LBBB, and ST-T wave changes on ECG, myocardial infarction, ischemic cardiomyopathy, VTE; cisplatin: induces renal tubular defects resulting in hypomagnesemia, vascular toxicities [34, 57–59]	B and T cell lymphoma, MM HCT conditioning
Proteasome inhibitors	Bortezomib Carfilzomib Ixazomib	Activation of signaling cascades, cell cycle, arrest and apoptosis	Accumulation of intracellular proteins in cardiomyocytes, endothelial cell injury, changes in the endothelial nitric oxide synthase activity, plaque instability, hypertension, arrhythmia, heart failure/cardiomyopathy, ischemic heart disease [60, 61]	MM
Topoisomerase II inhibitor	Etoposide	Induces DNA strand breaks and inhibits mitochondrial transport	Vasospasm, myocardial ischemia/infarction	B and T cell lymphoma, MM, HCT conditioning
Tyrosine kinase inhibitors	Imatinib	Inhibits ABL1/2, PDGFRa/b, KIT	Congestive heart failure (rare) [62]	B and T cell ALL, CML, post-HCT maintenance
	Dasatinib	Inhibits ABL1/2, PDGFRa/b, KIT, Src family	Pulmonary arterial hypertension, QT prolongation, pericardial effusion, left ventricular dysfunction, heart failure, Src and Abl inhibition results in endoplasmic reticulum stress and cell death [63, 64]	
	Nilotinib	Inhibits ABL1/2, PDGFRa/b, KIT	QT prolongation, ischemic heart disease, peripheral artery disease, cerebrovascular disease [65]	
	Ponatinib	Pan-BCR-ABL tyrosine kinase inhibitor	Left ventricular dysfunction, congestive heart failure, arterial and venous thrombosis, supraventricular tachycardia [66]	
Vinca alkaloids	Vincristine	Inhibits microtubule formation	Myocardial infarction, hypertension, vaso-occlusive complications, microtubule stabilization/disarray [67, 68]	B and T cell ALL, B and T cell lymphoma

ALL, acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *GVHD*, graft versus host disease; *HCT*, hematopoietic stem cell transplant; *MM*, multiple myeloma; *MDS/MPN*, myelodysplastic and myeloproliferative neoplasms; CML, chronic myeloid leukemia

angiography [73]. In HCT survivors, chest radiation prior to transplant is associated with a 9.5-fold increase in CAD [74].

Cyclophosphamide

Cyclophosphamide is an alkylating agent commonly used in HCT preparative regimens to ablate the bone marrow. Cyclophosphamide is well-known to cause cardiotoxicity especially at higher doses > 100 mg/kg. Potential toxicity includes severe myocarditis, exudative pericarditis, myocardial depression, malignant arrhythmia, and CHF [75]. In a study of BMT patients from Brigham and Women's Hospital who were receiving either once daily lower-dose cyclophosphamide (mean total 87 ± mg/kg) or twice daily higher-dose of cyclophosphamide (mean total 174 ± 34 mg/kg), cardiotoxicity was noted in 5 of 44 (11%) patients [76]. The majority of patients who experienced cardiotoxicity received the higher-dose of cyclophosphamide. Cardiotoxicity included dyspnea/edema, chest pain, pericardial effusion, and atrial arrhythmia (flutter or fibrillation). Three of the five patients had received anthracyclines previously (range 250–720 mg/m^2). An LVEF < 50% prior to transplant was predictive of cardiotoxicity [76].

Graft Versus Host Disease

GVHD is a condition where immune cells from the donor's marrow attack healthy tissue of the recipient by recognizing those cells as being "non-self." GVHD is a common complication of allogeneic HCT where bone marrow or stem cells are

taken from a non-genetically identical donor; however, it is not seen with autologous HCT. Development of GVHD may be one factor explaining the higher rate of cardiotoxicity observed in patients undergoing allogeneic HCT compared to autologous HCT [15]. There are several explanations for why GVHD may predispose patients to cardiovascular events. First, a history of grade II–IV acute GVHD is associated with development of established cardiovascular risk factors, such as DM (RR 5.8), HTN (RR 9.1), and HLD (RR 3.2) [69]. Development of these comorbidities is likely related to side effects of steroids and calcineurin inhibitors which are commonly used for the treatment of GVHD [69]. Additionally, ibrutinib, which was recently approved for the treatment of chronic GVHD, is associated with atrial fibrillation [40]. Ruxolitinib, in the off-label treatment of steroid-refractory GVHD, has also been added to the GVHD treatment armamentarium with known increased incidence of hyperlipidemia [77]. Lastly, GVHD may also affect the vascular endothelium itself, causing injury and inflammation that can predispose to arterial events [78]. If it affects serosal tissue, it can present similarly to autoimmune diseases, such as systemic lupus erythematosus, with development of pericardial effusion or tamponade [79].

Comorbidities/Cardiovascular Risk Factors

HCT survivors have increased risk of developing medical comorbidities. TBI which is typically done as part of the preparative regimen is associated with an increased risk of DM (OR 3.4) [80] and HLD [69]. Presence of multiple comorbidities portends a higher risk of cardiac complications during and after HCT. In autologous HCT survivors, presence of HTN (OR 35.3) and DM (OR 26.3) is associated with a risk of CHF [12]. This was also shown in a study by Armenian et al. where two or more comorbidities (including HTN, chronic renal insufficiency, chronic lung disease, DM) were associated with development of late CHF (OR 4.3) in both autologous HCT and allogeneic HCT [11]. Tichelli et al. [16] defined a high global cardiovascular risk score as having ≥ 50% of the following risk factors: arterial HTN, DM, dyslipidemia, elevated body mass index, physical inactivity, or smoking. They found that in allogeneic HCT survivors, a high global cardiovascular risk score was associated with a relative risk of 9.81 for suffering an arterial vascular event post-transplant [16].

Risk Prediction Model

Armenian et al. [81••] developed a model for predicting risk of cardiovascular disease based on the outcomes of 1828 patients who received HCT at the City of Hope and survived at least 1 year post-transplant (Fig. 1). Variables, including age, anthracycline dose, chest radiation exposure, hypertension, diabetes, and smoking, were included as predictors of heart failure and coronary artery disease 10 years after the index date (defined as 1 year post-HCT). Patients with ≤ 3 risk factors (low risk), 4–5 risk factors (intermediate risk), or ≥ 6 risk factors (high risk) have a 10-year risk of cardiovascular disease of 3.7, 9.9, or 26.2%, respectively (Table 1) [81••].

Surveillance Guideline Recommendations

Major recommendations for the management of cancer patients receiving cardiotoxic treatment from five different groups are reviewed (Table 2). Of the five guidelines, only one [4] is specific to HCT survivors. The remaining societies provide recommendations for cancer patients based on the cardiotoxic therapy, with some being specific to childhood-onset cancer [84, 85••, 87••] and others intended for adult patients/adult-onset cancer survivors [82••, 83•, 86••]. All of the guideline statements highlight that chest radiation and anthracycline exposure are significant contributors of cancer therapy-related cardiotoxicity.

American Society of Echocardiography/European Association of Cardiovascular Imaging

The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) released a joint expert consensus statement in 2014 proposing cardiotoxicity imaging surveillance algorithms based on the chemotherapy regimen. While these guidelines do not specifically address HCT survivors, they do provide surveillance guidelines for anthracycline agents that are commonly used for the treatment of many hematologic malignancies. Anthracyclines are considered "type I" agents which refer to chemotherapeutic agents known to cause irreversible cardiac injury due to cardiomyocyte necrosis, although this classification is oversimplified and not likely accurately reflective of the complex mechanisms contributing to cardiotoxicity with various chemotherapeutic agents [82••].

Patients who receive anthracyclines should have an assessment of cardiac function, including LVEF prior to anthracycline initiation, at the end of treatment, and again 6 months after completion of therapy (do you have a reference for this?) [82••]. Echocardiography is the preferred first-line imaging modality for assessment of cardiac function and structure. For anthracycline doses > 240 mg/m^2, an echocardiogram for ventricular function should be repeated prior to each additional dose of 50 mg/m^2. Cardiac assessment with 3D echocardiography is preferable; however, if 2D echocardiography is used, then additional evaluation with contrast for more precise endocardial enhancement, and global longitudinal strain (GLS) and checking serial troponin level should be considered. Cardiology consultation is appropriate for patients with abnormal LVEF (< 53%), abnormal GLS, or positive troponin level [82••].

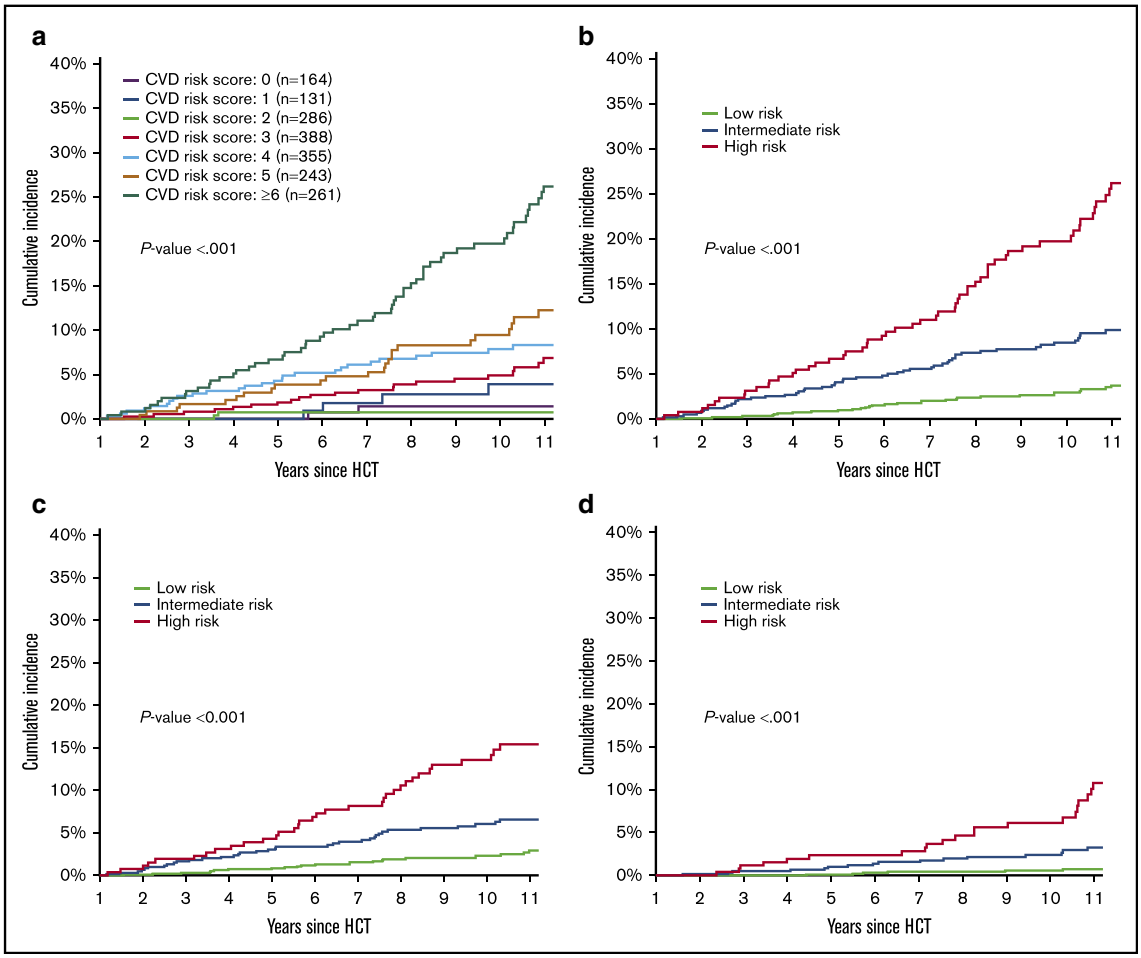

Fig. 1 Ten-year cumulative incidence of cardiovascular disease. By integer risk score (**a**) and by risk groups (**b**). Cumulative incidence of heart failure (**c**) and coronary artery disease (**d**) by risk groups. Curves start at index date (1 year from HCT). Reproduced from [81••], with permission from the American Society of Hematology

The ASE/EACVI released separate guidelines for patients with prior radiation therapy in 2013 [83•]. Patients with prior radiation exposure are at risk for multiple cardiac complications, including coronary artery disease, restrictive cardiomyopathy, valvular dysfunction, and constrictive pericarditis. Given the potential for numerous complications, patients exposed to radiation therapy should have an annual clinical assessment with a thorough evaluation of cardiovascular system symptoms. For asymptomatic patients, a screening echocardiogram is recommended 5 or 10 years following treatment depending on risk factors. Patients with history of anterior or left sided chest radiation with any one of the following are considered high risk: > 30 Gy of radiation, < 50 years at time of exposure, > 2 Gy/day of radiation, lack of shielding, tumor in or next to the heart, receiving concomitant chemotherapy with known high risk of cardiotoxicity, pre-existing cardiovascular disease, or multiple cardiovascular risk factors. Evaluation for coronary artery disease with a functional non-invasive stress test should also be considered for high risk patients 5–10 years post-exposure [83•].

Children's Oncology Group Long-Term Follow-Up

The Children's Oncology Group (COG) Long-Term Follow-up guidelines provide surveillance recommendations for organ toxicity for patients who are ≥ 2 years post-transplant based on their exposure history. They emphasize pre-transplant treatments, such as anthracycline and radiation therapy, which both heavily impact cardiac toxicity risk. Patients with a history of anthracycline/anthraquinone chemotherapy or chest radiation should have an annual history and physical with a thorough assessment of cardiac symptoms. Aggressive cardiovascular risk factor treatment is recommended for all bone marrow transplant survivors. Assessment of cardiac function should be done every 1–5 years depending on the individual's exposure type, cumulative dose, and age at time of exposure. Patients who have received cranial radiation should also be screened for development of neurologic symptoms which may be a sign of cerebrovascular disease [84, 85••].

Table 2 Summary of surveillance recommendations for patients with prior anthracycline exposure, chest radiation, and/or hematopoietic stem cell transplant

Group/society	Recommendation	Timing	Comments
ASE/EACVI [82••, 83•]	Clinical assessment with evaluation of cardiovascular symptoms	Annually	For patients with prior radiation exposure
	LVEF assessment	At baseline, end of treatment, and 6 months post-treatment	For patients receiving anthracyclines; use 3D echocardiogram or 2D echocardiogram with consideration of contrast for endocardial enhancement, and GLS and troponin level
	Echocardiogram[a] for anthracycline doses > 240 mg/m^2	Prior to each additional 50 mg/m^2	
	Cardiology consultation if: 1) LVEF < 53%	–	–
	2) Abnormal GLS		
	3) Positive troponin		
	Echocardiogram[a] for high-risk patients	5–10 years post-treatment	High risk: > 30 Gy of radiation, < 50 years at time of exposure, > 2 Gy/day of radiation, lack of shielding, tumor in or next to the heart, receiving concomitant chemotherapy with known high risk of cardiotoxicity, pre-existing cardiovascular disease, or multiple cardiovascular risk factors
	Non-invasive stress test for high-risk patients		
COG long-term follow-up [84, 85]	Clinical assessment with evaluation of cardiovascular symptoms	Annually	For patients with prior radiation or anthracycline exposure (include assessment of neurologic signs and symptoms for patients with prior cranial radiation)
	Screening with lipid panel and fasting glucose or hgba1c	Every 2 years	For any patient with prior radiation exposure
	ECG	At entry to long-term monitoring, then as clinically indicated	For patients with prior radiation or anthracycline exposure
	Echocardiogram[a]	At entry to long-term monitoring, then every 1–5 years depending on exposure type, dose, and age at time of exposure	
	Provide counseling regarding maintaining appropriate weight, blood pressure, and heart-healthy diet	–	Aerobic exercise is generally safe and encouraged while intensive isometric activity should be avoided
	Provide counseling regarding endocarditis prophylaxis counseling for those at highest risk	–	Based on AHA recommendations
	Consider cardiology consultation if: 1) Any subclinical abnormalities noted on screening	–	–
	2) 5–10 years after chest radiation of ≥ 40 Gy alone or ≥ 30 Gy with prior anthracycline exposure		
	3) ≥ 300 mg/m^2 or < 300 mg/m^2 and chest radiation in patients who are pregnant or planning pregnancy		

Table 2 (continued)

Group/society	Recommendation	Timing	Comments
Consensus Statement from Seven International Bone Marrow Transplant Societies [4]	Clinical assessment with evaluation of cardiovascular risk factors	One year following transplant and then annually	Fasting lipid panel and fasting glucose
	Early treatment of cardiovascular risk factors, including hypertension, hyperlipidemia, and diabetes	–	–
	Provide counseling regarding regular exercise, healthy weight and diet, and no smoking	–	–
	Endocarditis prophylaxis	–	Based on AHA recommendations
	ECG for patients at risk or symptomatic	–	Patients with Hodgkin's lymphoma who have received mediastinal radiation therapy, patients with amyloidosis, and patients with pre-existing cardiac and vascular abnormalities
	Echocardiogram for patients at risk or symptomatic	–	
ASCO clinical practice guidelines [86••]	Clinical assessment with evaluation and treatment of cardiovascular risk factor	Prior to, during, and after treatment	All patients receiving potentially cardiotoxic treatment. High risk: high dose anthracyclines (doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2), high-dose radiation therapy involving the heart (≥ 30 Gy), low-dose anthracycline in combination with radiation therapy, low-dose anthracyclines or trastuzumab with multiple cardiovascular risk factors, older age, or compromised cardiac function, or sequential therapy with anthracycline and trastuzumab
	Echocardiogram[a]	Prior to treatment, with any signs or symptoms of cardiac dysfunction, 6–12 months after treatment. Additional surveillance for patients at high risk or with metastatic breast cancer on indefinite trastuzumab can be offered.	
	Cardiac biomarkers or echocardiography-derived strain	At time of signs or symptoms of cardiac dysfunction	
	Cardiology consultation based on diagnostic findings	–	
International Late Effects of Childhood Cancer Guideline Harmonization Group [87••]	Echocardiogram[a]	No later than 2 years after completion of therapy, 5 years post-diagnosis and every 5 years thereafter. More frequent can be considered for high-risk survivors.	High risk: ≥ 250 mg/m^2 of anthracyclines, ≥ 35 Gy of chest radiation, ≥ 100 mg/m^2 of anthracyclines and ≥ 16 Gy of chest radiation
	Regular exercise	–	Patients treated with anthracyclines and/or chest radiation who have normal left ventricular systolic function
	Cardiology consultation for asymptomatic cardiomyopathy	–	–
	Screening for cardiovascular risk factors	–	Patients with prior anthracycline exposure or chest radiation
	Cardiac biomarkers	–	May be reasonable if symptomatic cardiomyopathy is strongly suspected or an individuals has borderline cardiac function during primary surveillance

[a] If an echocardiogram is not feasible or optimal, other imaging modalities include cardiac MRI and multi-gated acquisition scan (MUGA). In general, cardiac MRI is preferred over MUGA

GLS, global longitudinal strain; *LVEF*, left ventricular ejection fraction; *ECG*, electrocardiogram; *AHA*, American Heart Association; *COG*, Children's Oncology Group; *ASE/EACVI*, American Society of Echocardiography/European Association of Cardiovascular Imaging; *ASCO*, American Society of Clinical Oncology

Consensus Statement from Seven International Bone Marrow Transplant Societies

A special report from the Center for International Blood and Marrow Transplant Research (CIBMTR), the American Society of Blood and Marrow Transplantation (ASBMT), the European Group for Blood and Marrow Transplantation (EBMT), the Asia-Pacific Blood and Marrow Transplantation Group (APBMT), the Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), the East Mediterranean Blood and Marrow Transplantation Group (EMBMT), and the Sociedade Brasileira de Transplante de Medula Ossea (SBTMO) outlines system-based recommendations for long-term surveillance of BMT survivors who are at least 6 months post-transplant. Recognizing that there is a general lack of clinical trials that address the specific prevention and treatment needs of transplant survivors, most of the recommendations are based on retrospective studies and expert/consensus opinion. All BMT survivors should undergo a full clinical assessment for cardiovascular risk factors at one year following transplant and annually thereafter. Clinical assessment includes screening with fasting lipid panel and fasting glucose. Patients with prior exposure to anthracyclines should have precise monitoring of the cumulative dose and a screening echocardiogram when appropriate. Early recognition and aggressive management of cardiovascular risk factors, such as diabetes mellitus, hypertension, or hyperlipidemia, is recommended. BMT survivors should also receive counseling and education regarding heart healthy lifestyles, including healthy diet and exercise. For patients with radiation exposure and valvular disease, endocarditis prophylaxis should be administered according to the American Heart Association guidelines [4].

American Society of Clinical Oncology Clinical Practice Guidelines

The American Society of Clinical Oncology (ASCO) published clinical practice guidelines for the prevention and monitoring of survivors of adult-onset cancer in 2017 [86••]. The authors define patients who have received any of the following as high risk for developing cardio-toxicity: exposure to high-dose anthracyclines (doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2), high-dose radiation therapy involving the heart (≥ 30 Gy), low-dose anthracycline in combination with radiation therapy, low-dose anthracyclines or trastuzumab with multiple cardiovascular risk factors, older age, or compromised cardiac function, or sequential therapy with anthracyclines and trastuzumab. Patients receiving treatment with potential for cardiotoxicity should undergo a comprehensive evaluation, including a history, physical, cardiovascular risk factor screening and an echocardiogram prior to initiation of treatment. Modifiable cardiovascular risk factors should be treated. A clinical assessment should be repeated during and after completion of any cardiotoxic treatment. Patients with symptoms or signs of cardiac dysfunction during or after treatment should have a diagnostic evaluation, including an echocardiogram, cardiac biomarkers, and echo-derived strain. Cardiology consultation may be needed depending on the findings. After completion of potentially cardiotoxic therapy, an echocardiogram can be considered 6 to 12 months following treatment in asymptomatic but high-risk patients. No recommendations for screening are made past 12 months for asymptomatic individuals with no evidence of cardiac dysfunction on their 6- to 12-month study [86••].

International Late Effects of Childhood Cancer Guideline Harmonization Group

The International Late Effects of Childhood Cancer Guideline Harmonization Group [87••] published guidelines for cardiomyopathy surveillance in survivors of childhood cancers. Childhood cancer survivors who received prior treatment with high-dose (≥ 250 mg/m^2) anthracyclines, high-dose (≥ 35 Gy) chest radiation, or ≥ 100 mg/m^2 anthracyclines and ≥ 15 Gy chest radiation were deemed high risk for developing cardiomyopathy and should undergo surveillance with an echocardiography. Surveillance should begin no later than 2 years after completion of potentially cardiotoxic treatment and should be repeated 5 years after the initial diagnosis and every 5 years thereafter. Cardiology consultation is recommended for patients with asymptomatic cardiomyopathy. Screening for modifiable cardiovascular risk factors is recommended for all survivors. Regular exercise is recommended for survivors with prior anthracycline exposure and/or chest radiation with normal LV systolic function [87••].

Future Avenues and Strategies

Preventive and therapeutic strategies for cardiovascular complications in the HCT population are poorly studied. To our knowledge, there has only been one randomized controlled trial (OVERCOME trial) evaluating the benefit of cardioprotective strategies in patients undergoing HCT; however, this study only looked at autologous HCT patients with short-term follow-up of 6 months. The authors reported that Ace-I and beta-blockers might prevent against LVEF reduction in patients with hematologic malignancies receiving intensive chemotherapy. Given these results, initiation of cardioprotective medications may also be helpful to patients undergoing allogeneic transplant who have an even higher incidence of cardiovascular events overall; however, this needs to be studied further.

Cancer patients often suffer from generalized fatigue and have reduction in their exercise capacity during and after treatment [88•]. HCT survivors have low peak oxygen uptake, a measure of cardiopulmonary fitness, which are on average 22% less than age- and sex-predicted values [89]. A single-center study of allogeneic BMT patients showed that an 8-week outpatient and home-based exercise and education program instituted after transplant can improve exercise capacity and quality of life [90]. Similarly, a study of children undergoing HCT transplant showed that supervised exercise during HCT can improve functional performance, mobility, and strength [91]. There is now increasing interest in implementing exercise programs prior to transplant (termed prehabilitation) in order to potentially prevent transplant-related cardiovascular complications based in part on encouraging results from animal studies which show that exercise can reduce anthracycline-related cardiotoxicity [88•]. Randomized research studies are needed to understand the possible benefit of exercise in functional capacity, quality of life, as well as cardiovascular outcomes. Multiple on-going studies will hopefully provide many answers regarding the safety and benefit of exercise including the following: the Feasibility of Pre Transplant Exercise (pre-habilitation) for Multiple Myeloma Patients Awaiting Autologous Stem Cell Transplantation (PREeMPT) study [92], the EXercise to prevent AnthrCycline-based Cardio-Toxicity (EXACT) in individuals with breast or hematological cancers' study [93], and the rationale and design of the multidisciplinary team IntervenTion in cArdio-oNcology study (TITAN) [94].

While there are screening recommendations for patients with exposure to anthracyclines or radiation, guidelines targeted to HCT patients who receive a wide spectrum of cardiotoxic medications are lacking and mainly provide recommendations for management during survivorship. Defining high-risk patients prior to transplant who may benefit from early cardiology evaluation, pre-transplant ischemia evaluation, initiation of cardioprotective agents, and/or closer monitoring during treatment is critical to ensuring optimal care for cancer patients. For example, initiation of statin therapy for patients with elevated calcium scores on chest CT scans, which are routinely done as part of cancer staging, can be considered for prevention of coronary events. Pharmacogenetic testing for susceptibility to anthracycline-induced cardiotoxicity that is already recommended in children with cancer can also be studied in adult cancer patients in an effort to identify those who are most vulnerable [95]. While the agent dexrazoxane has been studied in the pediatric and advanced breast cancer population with demonstrated cardioprotective effects [96, 97], its use and efficacy in the adult hematologic population is less clear. It may be of interest to study the use of dexrazoxane in adult patients with significant cardiac risk factors and/or preexisting cardiomyopathy entering transplantation who would benefit from anthracycline treatments for their hematologic condition. The goal going forward should be to focus on both prevention as well as surveillance and treatment.

Cancer and cardiovascular disease share overlapping risk factors, including behaviors, such as tobacco use and sedentary lifestyle, comorbidities, such as hypertension and diabetes, and processes, such as infection and inflammation [98]. The recent CANTOS trial, which investigated an anti-inflammatory monoclonal antibody—canakinumab—which targets interleukin-1β, demonstrated both a reduction in cardiovascular events and a reduction in lung cancer-related mortality; these preliminary findings suggest that inflammation is a potentially significant contributor to development of both cardiac and oncologic disease states [99]. Understanding and identifying mechanistic overlap in pathogenesis opens the door to smarter drug development for both conditions and can improve the ability to both anticipate and treat cardiotoxicity. Non-clinical models of cardiomyocytes, including in vivo, in vitro, and in silico models, are essential for pushing our understanding of the mechanism of cardiotoxicity across various agents at the basic level. They also offer an opportunity for advancing personalized medicine for cancer patients through the use of patient-derived somatic cells [100].

Recent efforts to uncover genetic causes of hematologic malignancies have revealed an unexpected link to atherosclerotic disease. An age-related disorder defined by an expansion of hematopoietic clones with recurrent somatic mutations (particularly loss-of-function alleles in the genes DNMT3A, TET2, and ASXL1 that are mutations found in myelodysplastic syndrome and acute myeloid leukemia) was more common in older people and was defined as clonal hematopoiesis of indeterminate potential (CHIP) without having any active underlying malignancy [101]. An exploratory analysis revealed that people with CHIP had an increased risk of hematologic cancers as well as an increased risk of death from any cause [102]; subsequent case–control analyses revealed that the incidence of coronary heart disease and myocardial infarction was 1.9 and 4.0 times greater than in non-carriers, respectively. CHIP carriers with the above-mentioned mutations along with JAK2 also had increased coronary artery calcification [103•]. These overlapping links provide the grounds to potentially investigate if patients who develop hematologic malignancies with these mutations may be prone to cardiotoxicity or cardiovascular events with treatment in the short- and long-term.

The transition from active cancer treatment to long-term survivorship is a vulnerable time for the increasing number of cancer survivors. While there has been progress in patient education regarding the potential long-term cardiotoxic effects of cancer treatments, more awareness and education for physicians is also essential. Many cancer survivors return to the care of general medicine providers for whom it is nearly

impossible to keep up with the increasing quantity of treatments and all of their potential complications. The rise of the cardio-oncologist, who focuses on the specific cardiac needs of cancer patients, is one step that can hopefully improve long-term care of cancer patients. Cardio-oncologists can also serve as a valuable partner in recognizing and reporting complications from new therapies as they arise alongside oncologists. In addition, creating large nationwide registries to track cardiovascular complications is essential especially in light of an ever-growing number of novel targeted oncologic therapies in use with uncertain real-life cardiotoxicity profiles.

Compliance with Ethical Standards

Conflict of Interest Mirela Tuzovic, Monica Mead, Patricia A. Young, Gary Schiller, and Eric H. Yang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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