REVIEW ARTICLE

Chemotherapy-Induced Cardiotoxicity and the Pathways to Cardiac Arrest: Mechanisms, Epidemiology, and a Conceptual Framework for Risk-Aligned Surveillance

Khalid Omer Alfarouk, PhD

Professor of Molecular Pharmacology and Experimental Therapeutics
Zamzam University College, Khartoum, Sudan
Alfarouk Biomedical Research LLC, Valdosta, Georgia, USA
Correspondence: Khalid.alfarouk@alfaroukbiomed.com

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Abstract

Cardiac arrest complicating cancer chemotherapy is the most catastrophic endpoint of a broad spectrum of treatment-related cardiovascular injury. Although it is often the terminal expression of a mechanistically traceable pharmacological cascade, it is important to state at the outset that mechanistic traceability is not the same as individual clinical predictability: cardiac arrest in cancer patients is frequently multifactorial, compounded by sepsis, pulmonary embolism, electrolyte derangement, tumor-related inflammation, and pre-existing cardiovascular disease, and a substantial fraction of sudden cardiac deaths in this population has no single attributable drug cause. With that caveat, the principal mechanisms are increasingly well defined. Anthracyclines injure cardiomyocytes through topoisomerase IIβ poisoning and a constellation of iron-dependent oxidative pathways that now appears to include mitochondrial iron overload and ferroptosis alongside the classical reactive oxygen species paradigm. Fluoropyrimidines produce acute myocardial ischemia through mechanisms that probably combine coronary vasospasm with direct endothelial and mitochondrial toxicity, the relative contributions of which remain debated. HER2-targeted agents disrupt ErbB2/ErbB4 neuregulin-1 survival signaling, producing a typically reversible systolic dysfunction that becomes less reversible after anthracycline exposure. Tyrosine kinase inhibitors prolong repolarization through hERG channel blockade but, in practice, more commonly provoke atrial fibrillation and hypertension-mediated afterload stress than ventricular torsades. Immune checkpoint inhibitors trigger autoimmune myocarditis whose historical case-mortality of 25-50% has fallen substantially, to perhaps 10-15% in centers practicing systematic troponin surveillance with early corticosteroid treatment. High-dose alkylating agents cause direct hemorrhagic myocardial necrosis. Electrolyte dysregulation amplifies arrhythmic risk across all classes. This review maps each pathway from molecular target to arrest, provides comparative epidemiology of cardiac arrest and sudden cardiac death in oncology, and proposes a four-domain conceptual framework for risk-aligned surveillance, presented explicitly as a heuristic for organizing care rather than as a validated clinical risk model. We critically appraise the evidence for cardioprotective strategies, including the genuine clinical equipoise surrounding dexrazoxane, and address the practically important differential between treatment-related cardiogenic pulmonary edema and malignant lymphangitic disease.

1. Introduction

The cardiovascular system occupies a position of dual vulnerability in oncological pharmacology. The heart — a post-mitotic organ with limited regenerative capacity, high metabolic demand, and exquisite sensitivity to oxidative and immunological injury — is directly targeted by several of the most widely used chemotherapeutic classes. The vasculature, from the coronary arteries to the microcirculation, is subject to drug-induced vasospasm, endothelial dysfunction, thrombotic microangiopathy, and accelerated atherosclerosis. The electrical conduction system is vulnerable to ion channel toxicity and electrolyte imbalance.

Any of these injury pathways, alone or in combination, can culminate in cardiac arrest (1). Cardiac arrest — the abrupt cessation of effective cardiac mechanical activity — is the most severe endpoint of a continuous spectrum of chemotherapy-induced cardiovascular injury. This spectrum encompasses subclinical myocardial dysfunction detectable only by imaging, symptomatic cardiomyopathy, heart failure, life-threatening arrhythmia, and, at its extreme, sudden cardiac death and cardiac arrest (2). The emerging discipline of cardio- oncology has substantially advanced the recognition and management of this spectrum, yet the pharmacological mechanisms linking specific chemotherapeutic agents to their ultimate cardiac consequences remain underemphasized in clinical practice.

A central argument of this review is that chemotherapy- induced cardiac arrest is, in most cases, not a wholly unpredictable event but the terminal expression of a mechanistically intelligible cascade initiated by a defined drug-target interaction. This argument must, however, be stated carefully to avoid a reductionist overreach. Mechanistic traceability — understanding how doxorubicin damages the cardiomyocyte — is not equivalent to clinical predictability — knowing which patient will arrest, and when. In the polymorbid, polypharmacy reality of oncology, cardiac arrest is frequently multifactorial: it may be precipitated by sepsis, pulmonary embolism, tumor lysis, electrolyte derangement, or occult structural heart disease acting on a myocardium already sensitized by treatment, and a substantial proportion of sudden cardiac deaths in cancer patients has no single attributable drug etiology even at autopsy.

The claim advanced here is therefore the more modest one that mechanistic understanding identifies where injury is likely to arise and where to direct surveillance, not that it permits deterministic individual prediction. With that qualification, several pathways are well characterized: anthracycline cardiomyopathy develops through cumulative topoisomerase IIβ poisoning and iron-dependent oxidative injury detectable by imaging and biomarkers before symptoms emerge; immune checkpoint inhibitor myocarditis, though unpredictable in the individual, has defined warning signs and a known temporal window. The pharmacological specificity of each pathway suggests that monitoring tools and interventions are most

rational when matched to mechanism, while acknowledging that for several agents the mechanism-specific monitoring target is not yet clinically measurable (3). This review is organized by mechanism rather than by drug class, reflecting the conviction that it is the molecular pathway rather than the drug category that determines the appropriate clinical response.

We additionally address the practically important differential diagnosis between cardiogenic pulmonary edema (drug-induced or from disease progression-related pericardial effusion) and lymphangitic carcinomatosis — a distinction that determines whether the patient receives diuresis and cardiac support or oncological intervention, and which cannot be assumed from clinical appearance alone.

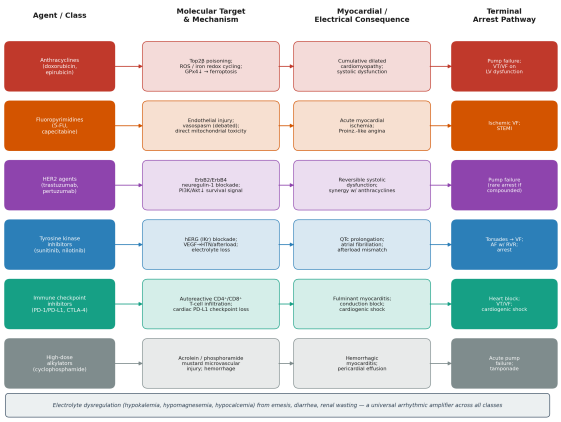

Figure 1. *Mechanistic pathways linking the principal chemotherapeutic classes to cardiac arrest. Each row traces the route from agent to molecular target, to the myocardial or electrical consequence, to the terminal arrest pathway. Electrolyte dysregulation (lower bar) acts as a universal arrhythmic amplifier across all classes.*

2. Defining Cardiac Arrest in the Oncological Context

Cardiac arrest, defined as the abrupt loss of effective cardiac output sufficient to sustain consciousness and tissue perfusion, encompasses several mechanistically distinct electrophysiological events. Ventricular fibrillation (VF) — chaotic, disorganized depolarization of the ventricular myocardium — is the most common initial rhythm in out-of- hospital cardiac arrest and may be precipitated by ischemia, cardiomyopathy, or electrolyte-mediated conduction instability. Pulseless ventricular tachycardia (VT), torsades de pointes (a polymorphic VT arising in the context of QT prolongation), and electromechanical dissociation (pulseless electrical activity, PEA) each represent distinct electrophysiological substrates with distinct pharmacological determinants (4). In cancer patients, the substrate for cardiac arrest is typically multifactorial.

A patient receiving anthracycline therapy may develop subclinical cardiomyopathy with reduced ejection fraction, reducing the threshold for VF in the setting of a subsequent ischemic event. A patient receiving a QT- prolonging tyrosine kinase inhibitor may have further QT prolongation from hypokalemia induced by chemotherapy- related diarrhea and vomiting, lowering the threshold for torsades de pointes. The multi-mechanistic nature of cardiac arrest risk in this population demands a diagnostic and preventive framework that evaluates the sum of contributing pharmacological and physiological factors rather than any single agent in isolation.

3. Epidemiology of Cardiac Arrest and Sudden Cardiac

Death in Cancer Patients Before examining individual mechanisms, it is important to situate cardiac arrest within the broader epidemiology of cardiovascular events in oncology, since arrest is a relatively uncommon endpoint relative to the spectrum of cardiotoxicity that precedes it. Cardiovascular disease is a major competing cause of mortality in cancer patients: in a large analysis of cancer survivors across many tumor types, a substantial minority of deaths were cardiovascular rather than oncological, with heart disease accounting for the majority of those cardiovascular deaths. Arrhythmias are common, occurring in an estimated 10-15% of cancer patients depending on tumor type and treatment, and the incidence of arrhythmia is several-fold higher than in matched non-cancer populations (5). The distribution of arrhythmia type is clinically instructive and, as discussed in the tyrosine kinase inhibitor section below, argues against an exclusive focus on ventricular repolarization.

Atrial fibrillation is the most common arrhythmia in cancer patients, with a reported incidence of approximately 5-16% depending on cancer type and risk profile, substantially exceeding that of the general population; ventricular arrhythmias are less frequent but more immediately life-threatening. Among cancer patients with implantable defibrillators, ventricular arrhythmia rates are high, and an ischemic substrate is identifiable in a large fraction of ventricular arrhythmic events, underscoring the multifactorial nature of the arrest substrate (6). Sudden cardiac death specifically is more common in advanced cancer than is generally appreciated, with reported incidences in advanced-cancer cohorts ranging from approximately 6% to 20% within the first six months of treatment. Critically for the thesis of this review, this frequency cannot be attributed solely to the direct cardiotoxic effects of chemotherapy or to metastatic cardiac involvement; it reflects the convergence of treatment toxicity with cancer- associated inflammation, prothrombotic state, autonomic dysfunction, electrolyte derangement, and pre-existing cardiovascular disease.

This epidemiological reality is itself the strongest argument for the multifactorial, integrative framing adopted here, and a caution against attributing any individual arrest to a single pharmacological mechanism. The sections that follow examine the drug-specific contributions to this aggregate risk, with Figure 2 summarizing their comparative incidence and severity, while keeping in view that in the individual patient these mechanisms rarely act alone (7).

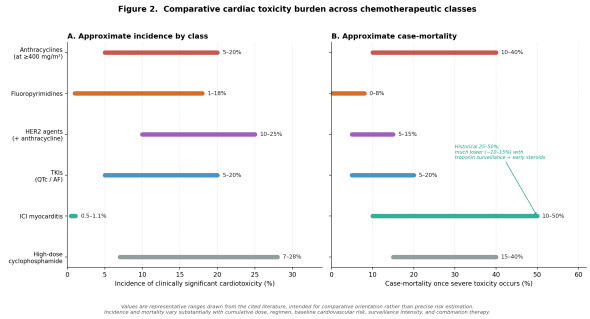

Figure 2. *Comparative cardiac toxicity burden across chemotherapeutic classes. Panel A shows the approximate incidence of clinically significant cardiotoxicity; Panel B shows approximate case-mortality once severe toxicity occurs. Values are representative ranges drawn from the cited literature for comparative orientation rather than precise risk estimation.*

4. Anthracycline Cardiotoxicity: The Prototypal

Cumulative Cardiomyopathy

4.1 Dual Mechanism: Topoisomerase IIβ Poisoning and

Redox Cycling Anthracyclines — doxorubicin, epirubicin, daunorubicin, and idarubicin — are among the most effective antineoplastic agents available and are central to the treatment of breast cancer, lymphoma, leukemia, and sarcoma. They are also the most extensively studied cardiotoxic chemotherapeutic class, and their cardiac injury mechanism is now understood to involve two distinct but interacting pathways (8). The first is inhibition of topoisomerase IIβ (Top2β), the cardiac isoform of the enzyme responsible for resolving DNA supercoiling during transcription. In cardiomyocytes, Top2β is essential for transcriptional programs that govern mitochondrial biogenesis, oxidative phosphorylation, and sarcomeric protein production.

Anthracycline-induced poisoning of the Top2β-DNA cleavage complex generates persistent DNA double-strand breaks in cardiomyocyte nuclei and mitochondria, activating p53-dependent transcriptional reprogramming that suppresses mitochondrial electron transport chain genes while upregulating proapoptotic and profibrotic targets (9). The resulting mitochondrial dysfunction impairs oxidative phosphorylation in the energy- demanding cardiomyocyte, producing an energetic deficit that underlies systolic dysfunction. Critically, this Top2β- mediated pathway is dose-dependent and cumulative: each anthracycline cycle inflicts additional DNA damage that, because cardiomyocytes are post-mitotic and cannot regenerate, is not repaired but accumulated. The second mechanism involves redox cycling of the anthracycline quinone moiety.

Doxorubicin accepts a single electron from mitochondrial complex I of the electron transport chain to form a semiquinone radical, which in the presence of oxygen undergoes back-oxidation to the quinone, regenerating superoxide anion and hydrogen peroxide in a catalytic cycle (10). This continuous ROS generation is amplified by iron chelation: the doxorubicin-iron(III) complex reacts with hydrogen peroxide through a Fenton reaction to generate the highly reactive hydroxyl radical. The cardiomyocyte is particularly susceptible to this oxidative assault because of its relatively low catalase and glutathione peroxidase activity compared with other tissues, and because the proximity of the electron transport chain to the mitochondrial DNA maximizes oxidative DNA damage per ROS molecule generated. Progressive oxidative injury to lipids, proteins, and nucleic acids in the cardiomyocyte contributes to a phenotype of cardiomyocyte loss and replacement fibrosis.

The classical topoisomerase-and-ROS account, while well established, is no longer regarded as a complete description of anthracycline cardiotoxicity, and a rigorous treatment must acknowledge the substantial body of more recent mechanistic work. Foremost among newer pathways is ferroptosis, an iron-dependent form of regulated cell death driven by glutathione peroxidase 4 (GPx4) inhibition and the accumulation of lethal lipid peroxides. Doxorubicin downregulates GPx4 and, by intercalating into mitochondrial DNA and disrupting heme synthesis, promotes mitochondrial iron accumulation that drives lipid peroxidation through a doxorubicin-Fe(II) complex; preclinical evidence now identifies mitochondria-dependent ferroptosis as a major mechanism of doxorubicin cardiotoxicity, and ferroptosis inhibition is cardioprotective in animal models (31). This ferroptotic mechanism is mechanistically continuous with the iron biology that underlies dexrazoxane's protective effect and may help explain why iron-directed strategies are cardioprotective.

Beyond ferroptosis, contemporary work implicates additional, partly overlapping pathways: dysregulated autophagy and mitophagy, disturbances of mitochondrial dynamics (fusion-fission imbalance), calcium- handling abnormalities promoting arrhythmogenicity, and inflammatory and innate-immune signaling (32). The practical implication is that anthracycline cardiotoxicity is best understood as a convergence of several iron- and mitochondrion-centered death pathways rather than a single linear cascade, and that this mechanistic plurality is itself an argument against overconfident single-pathway reasoning. The clinical consequence is a dose-dependent, progressive cardiomyopathy with a cumulative incidence of clinically significant cardiac dysfunction of approximately 5% at a lifetime doxorubicin dose of 400 mg/m², rising steeply to over 20% at 700 mg/m² (11). However, subclinical systolic dysfunction, detectable by echocardiographic strain imaging, occurs at substantially lower cumulative doses and may progress to overt heart failure years after treatment completion — a long-term risk of particular importance in pediatric and young adult survivors.

4.2 Cardioprotective Strategies: Dexrazoxane and Beyond

Dexrazoxane, a cyclic bis-anhydride of EDTA, is the only pharmacological agent specifically approved for the prevention of anthracycline cardiotoxicity. It is hydrolyzed intracellularly to a ring-opened form that chelates intracellular iron, preventing formation of the anthracycline- iron-ROS complex and thereby reducing oxidative cardiomyocyte injury (12). Randomized trial evidence demonstrates that dexrazoxane administered concurrently with anthracyclines reduces the incidence of cardiac events without compromising antitumor efficacy in most settings. Despite this evidence, dexrazoxane remains underused, but it would be inaccurate to attribute this solely to clinical inertia.

The historical reluctance reflected a genuine safety concern rather than mere bureaucratic caution: earlier data raised the possibility of an increased incidence of second malignancies, particularly myelodysplastic syndrome and acute myeloid leukemia, in pediatric and breast cancer populations, and although subsequent meta-analyses have substantially tempered this signal, real clinical equipoise persists among oncologists, especially in curative settings such as Hodgkin lymphoma where long-term survival makes any leukemogenic risk weighty. A balanced position is that dexrazoxane is most clearly indicated when high cumulative anthracycline exposure is anticipated or in patients at elevated baseline cardiac risk, where the absolute cardioprotective benefit is greatest; its value at lower cumulative doses, where the absolute risk of cardiomyopathy is more modest, is correspondingly less compelling and must be weighed against the residual safety question. Contemporary cardio-oncology guidance increasingly supports its use at cumulative doses in the region of 250-300 mg/m² doxorubicin-equivalent and above, but the decision remains a genuine risk-benefit judgment rather than a settled default. Beyond dexrazoxane, cumulative dose limitation — maintaining lifetime doxorubicin equivalent doses below 400-450 mg/m² where oncologically feasible — and substitution with liposomal doxorubicin, whose polyethylene glycol coating reduces myocardial uptake relative to free drug, provide meaningful cardioprotection.

Renin-angiotensin system blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and beta-adrenoceptor antagonism, have demonstrated benefit in attenuating anthracycline-related left ventricular dysfunction in several clinical trials, consistent with their established role in non-ischemic cardiomyopathy of other etiologies (13). These agents are most beneficial when initiated at the time of cardiomyopathy detection rather than universally prophylactically, though prophylactic use in high-risk patients is supported by some guidelines.

5. Fluoropyrimidines: Coronary Vasospasm and Acute

Myocardial Ischemia Fluoropyrimidines — 5-fluorouracil (5-FU) and its oral prodrug capecitabine — are widely used in colorectal, gastric, esophageal, and breast malignancies. They produce a distinctive pattern of cardiac toxicity characterized by coronary vasospasm, with an incidence of clinically symptomatic cardiac events of approximately 1-18% depending on infusion schedule, with continuous infusion carrying higher risk than bolus dosing (14). The mechanism is multifactorial and remains incompletely defined. The most widely held hypothesis is coronary vasospasm arising from 5-FU-induced endothelial injury, with proposed mediators including endothelin-1 and reduced nitric oxide-dependent vasodilation, alongside a possible endothelial-independent component of primary vascular smooth muscle dysfunction; direct mitochondrial myocardial toxicity and a procoagulant state have also been implicated.

It should be acknowledged that the vasospasm hypothesis is not universally supported — vasospasm has not been reproducibly provoked during cardiac catheterization in all studies — and the relative contribution of each proposed mechanism remains an area of active investigation. The net clinical effect is episodic myocardial ischemia, often clinically resembling Prinzmetal angina, that may precipitate acute ST-elevation myocardial infarction, ventricular arrhythmia, and cardiac arrest (15). Fluorouracil cardiotoxicity is notable for its temporal predictability: symptoms typically develop during or immediately after drug infusion, with the first or second cycle carrying the highest risk for first presentation. This temporal signature, when recognized, allows appropriate monitoring during infusion and prompt intervention with vasodilators — sublingual nitrates or calcium channel blockers — if vasospasm is suspected.

Patients who develop fluoropyrimidine-induced cardiotoxicity face the clinical dilemma of rechallenge, which carries a substantial risk of recurrence. Empiric prophylaxis with calcium channel blockers and/or nitrates is sometimes used to permit continuation of this important chemotherapy, but the evidence for its efficacy is mixed — several reports indicate that prophylactic vasodilators do not reliably prevent recurrent chest pain — so rechallenge decisions must be individualized, undertaken with cardiology involvement and monitoring. Conversion to alternative regimens, including bolus rather than infusional 5-FU or substitution with raltitrexed, should be considered where oncologically feasible. Preexisting coronary artery disease may modify the risk profile, and traditional cardiovascular risk factors and concurrent or prior chest irradiation are recognized contributors.

6. HER2-Targeted Agents: Reversible Systolic

Dysfunction and Synergistic Cardiotoxicity Trastuzumab, pertuzumab, and lapatinib — agents targeting the HER2 (ErbB2) receptor tyrosine kinase — have transformed outcomes in HER2-positive breast cancer, but produce a clinically important cardiomyopathy through disruption of ErbB2/ErbB4 signaling in cardiomyocytes. Neuregulin-1, released by cardiac endothelial cells and fibroblasts, binds ErbB4 which heterodimerizes with ErbB2 to activate downstream PI3K/Akt/mTOR and Ras/MAPK survival signaling in cardiomyocytes, promoting myocyte survival, sarcomeric organization, and adaptive hypertrophy in response to hemodynamic stress (16). Pharmacological blockade of ErbB2 by trastuzumab deprives cardiomyocytes of this survival signal, reducing their tolerance of oxidative and hemodynamic stress — the mechanistic basis of the synergistic cardiotoxicity observed when trastuzumab is combined with or follows anthracycline therapy. Unlike anthracycline cardiomyopathy, which is dose- dependent and largely irreversible due to cumulative cardiomyocyte loss, trastuzumab-related cardiac dysfunction is typically reversible upon drug discontinuation, reflecting a functional rather than structural injury — impaired survival signaling rather than cardiomyocyte death (17).

Left ventricular ejection fraction (LVEF) recovers in the majority of patients after trastuzumab withdrawal, and rechallenge is often feasible after cardiac function normalizes. However, the distinction between reversible and irreversible dysfunction becomes less reliable when trastuzumab is used after anthracyclines, as the structural cardiomyocyte loss from anthracycline therapy removes the regenerative buffer that underlies reversibility. This mechanistic understanding has directly informed clinical practice: serial LVEF monitoring by echocardiography or multigated acquisition (MUGA) scanning is mandated during HER2-targeted therapy to enable early detection and drug modification before irreversible dysfunction develops.

7. Tyrosine Kinase Inhibitors: Arrhythmogenesis Beyond

QT Prolongation Small-molecule tyrosine kinase inhibitors (TKIs) — including sunitinib, sorafenib, nilotinib, dasatinib, vandetanib, and others — produce QT interval prolongation through off-target blockade of the human ether-à-go-go- related gene (hERG) potassium channel (KCNH2), which encodes the rapidly activating delayed rectifier potassium current (IKr) responsible for phase 3 ventricular repolarization (18). Reduction of IKr slows repolarization, prolonging the QT interval and creating a vulnerable window during which early afterdepolarizations (EADs) may arise and trigger polymorphic ventricular tachycardia — particularly torsades de pointes — that can degenerate into ventricular fibrillation and cardiac arrest. The QT prolongation risk of individual TKIs varies considerably: vandetanib carries the highest risk and requires restricted distribution with mandatory QT monitoring, while imatinib poses comparatively low risk. However, the clinical context in which TKIs are administered substantially amplifies the arrhythmic risk beyond the drug effect alone.

Chemotherapy-induced vomiting and diarrhea produce hypokalemia and hypomagnesemia, both of which independently reduce IKr by reducing the potassium gradient driving channel conductance and by blocking Mg-dependent channel gating, thereby prolonging the QT independently of direct channel blockade (19). The combination of TKI- mediated IKr blockade and electrolyte-mediated IKr reduction can produce QT prolongation far exceeding that predicted by either factor alone. Concurrent administration of other QT-prolonging drugs — antiemetics (ondansetron, haloperidol), antibiotics (fluoroquinolones, azithromycin), and antifungals (fluconazole, voriconazole, which additionally inhibit TKI metabolism through CYP3A4) — further compounds this risk. It would, however, be a

mistake to let the focus on QT prolongation eclipse what is, in aggregate, a more common arrhythmic consequence of several tyrosine kinase inhibitors: atrial fibrillation.

QTc prolongation is, moreover, an imperfect surrogate for arrhythmic risk — many patients with a QTc above 500 ms never develop torsades, while some with lesser prolongation do, and measures of repolarization heterogeneity such as the T-peak-to-T-end interval may predict risk better than QTc alone. Clinically, agents such as ibrutinib are strongly associated with atrial fibrillation, and vascular endothelial growth factor pathway inhibitors (sunitinib, sorafenib) produce severe hypertension and afterload mismatch that promote atrial fibrillation and, in susceptible patients, heart failure decompensation. Rapid atrial fibrillation with a poorly controlled ventricular response can itself precipitate hemodynamic collapse and arrest, particularly on a background of anthracycline-related left ventricular dysfunction. A balanced account of tyrosine kinase inhibitor arrhythmogenicity therefore weighs atrial fibrillation and afterload-mediated decompensation alongside, and often above, the more frequently emphasized risk of QT-dependent ventricular arrhythmia.

Pharmacological management centers on maintaining electrolyte homeostasis — targeting serum potassium above 4.0 mEq/L and magnesium above 0.8 mmol/L — conducting baseline and periodic ECG monitoring with defined thresholds for dose modification (QTc > 500 ms or increase > 60 ms from baseline prompting review), and auditing concurrent QT-prolonging medications at each visit. The risk of torsades de pointes from QT prolongation is not linearly related to QTc: the risk increases steeply above QTc 500 ms, and the combination of multiple risk factors (female sex, bradycardia, hypokalemia, structural heart disease, high QT- prolonging drug burden) is more predictive than QTc alone.

8. Immune Checkpoint Inhibitor Myocarditis: The Most

Lethal Immune-Related Adverse Event Immune checkpoint inhibitor (ICI)-associated myocarditis, though occurring in only approximately 1% of ICI-treated patients, carries a case fatality rate approaching 25-50% and represents the most lethal immune-related adverse event in oncological practice (20). It exemplifies a mechanism in which restoration of T-lymphocyte effector function against tumor antigens results in simultaneous autoreactive attack on cardiac myocytes sharing antigenic epitopes with tumor cells. Postmortem and biopsy studies demonstrate dense infiltration of the myocardium by CD4 and CD8 T-lymphocytes, with the latter showing clonal expansion patterns suggesting antigen-driven activation against shared tumor-myocyte targets rather than non-specific bystander inflammation (21). The mechanistic basis reflects the normal physiological role of PD-1/PD-L1 signaling in maintaining cardiac immune tolerance.

The heart expresses PD-L1 on cardiomyocytes and endothelial cells, and PD-1 signaling on infiltrating T-cells normally suppresses autoreactive myocardial inflammation. Pharmacological PD-1 or PD-L1 blockade removes this cardiac immune checkpoint, permitting autoreactive T-cells — presumably held in check in the normal state — to infiltrate and injure the myocardium (22). CTLA-4 blockade, which operates at the initial T-cell activation stage rather than the effector stage, compounds this risk when combined with PD-1 inhibition, and combination ICI regimens carry substantially higher myocarditis risk than monotherapy. The clinical presentation of ICI myocarditis is notable for its variety and its mimicry of other conditions.

Patients may present with chest pain, dyspnea, palpitations, syncope, or new conduction abnormalities on electrocardiography — patterns that individually overlap with a wide differential. Fulminant presentations with complete heart block, ventricular arrhythmia, or cardiogenic shock may develop rapidly from a seemingly mild prodrome, and the interval from symptom onset to hemodynamic collapse can be measured in hours (23). Troponin elevation is the most sensitive serological marker, present in over 90% of confirmed cases; BNP or NT-proBNP elevation indicates hemodynamic compromise; ECG changes including ST- segment abnormalities, conduction block, and QRS prolongation reflect the extent of myocardial and conduction system involvement. Management of confirmed or suspected grade 3-4 ICI myocarditis constitutes one of the most urgent therapeutic challenges in oncological practice.

Immediate ICI discontinuation is mandatory. High-dose corticosteroids — intravenous methylprednisolone at 1000 mg/day for 3-5 days (pulse dosing) in fulminant cases, with transition to oral prednisone at 1-2 mg/kg/day upon stabilization — constitute first-line immunosuppression (24). The mechanism is NF-κB-mediated suppression of pro-inflammatory cytokine transcription and reduction of T-cell effector activity. Steroid- refractory cases, which occur in a substantial proportion, have been managed with additional immunosuppression: mycophenolate mofetil (inhibiting de novo purine synthesis in proliferating lymphocytes), abatacept (CTLA-4 immunoglobulin fusion protein that competitively blocks T- cell co-stimulation), and anti-thymocyte globulin for the most severe refractory presentations.

Hemodynamic support with vasopressors and mechanical circulatory support (intra-aortic balloon pump, extracorporeal membrane oxygenation) is essential in cardiogenic shock. Temporary pacing may be required for complete heart block. Implantable cardioverter-defibrillator placement may be considered in survivors with residual ventricular dysfunction. Notably, emerging data from centers employing systematic troponin surveillance with prompt corticosteroid treatment upon biomarker rise report substantially lower myocarditis mortality than the historical 25-50% range, reinforcing the central thesis of this review: mechanism-aligned early detection and intervention can meaningfully alter outcomes in treatment-related cardiac toxicity.

9. Alkylating Agents: Direct Myocardial Necrosis

High-dose cyclophosphamide, used in hematopoietic stem cell transplantation conditioning regimens, produces a dose- related hemorrhagic myocarditis through direct cardiomyocyte injury mediated by its metabolites phosphoramide mustard and acrolein. At the doses employed in conditioning (typically 60-200 mg/kg over 2-4 days), these metabolites cause diffuse endothelial injury to the microvasculature of the myocardium, producing capillary leak, interstitial hemorrhage, and edema within the myocardial wall (25). The clinical consequence ranges from subclinical troponin elevation to a fulminant syndrome of pericardial effusion, hemodynamic compromise, and cardiogenic shock — the last carrying a mortality rate approaching 40% in some series. The onset is characteristically rapid, within 1-10 days of cyclophosphamide administration, and unlike anthracycline cardiomyopathy is not preceded by a detectable subclinical phase, making prevention through dose reduction the principal risk-mitigation strategy.

Ifosfamide similarly produces myocardial injury through chloroacetaldehyde-mediated mitochondrial dysfunction in

cardiomyocytes, though at clinical doses cardiac manifestations are less prominent than the renal tubulopathy described in the accompanying article in this series. Platinum-based agents contribute to cardiac risk through electrolyte wasting (hypomagnesemia, hypokalemia), endothelial injury predisposing to thrombotic cardiovascular events, and autonomic neuropathy impairing heart rate variability — each increasing arrhythmic susceptibility without producing direct cardiomyopathy.

10. Electrolyte Dysregulation as a Universal Arrhythmic

Risk Amplifier Electrolyte disturbances represent a ubiquitous and frequently underweighted contributor to cardiac arrhythmia risk across all chemotherapeutic classes. The mechanistic link between electrolyte dysregulation and arrhythmogenesis is well established at the level of cardiac ion channel physiology. Hypokalemia reduces the electrochemical gradient for IKr, prolongs phase 3 repolarization, and increases the propensity for early afterdepolarizations and triggered activity. Hypomagnesemia, which commonly accompanies hypokalemia and is directly caused by platinum agents and high-dose chemotherapy-associated vomiting, reduces the magnesium-dependent gating of the KATP channel and the sodium-potassium ATPase, impairing cellular repolarization and predisposing to both atrial and ventricular arrhythmia (26).

Hypocalcemia — produced by tumor lysis syndrome, cisplatin renal wasting, and bisphosphonate therapy — prolongs the cardiac action potential plateau by extending the window during which L-type calcium channels drive the membrane potential, producing QT prolongation that is additive to drug-mediated QT effects. Hyponatremia, common in cancer patients receiving nephrotoxic agents, thiazide diuretics for blood pressure management, or experiencing the syndrome of inappropriate antidiuretic hormone secretion from tumor or drug effects, may precipitate cardiac conduction abnormalities at severe concentrations. The clinical implication is that electrolyte screening and correction constitute a basic but genuinely arrhythmia-preventive pharmacological intervention — not merely a supportive measure — and should be integrated into the monitoring framework for any patient receiving QT- prolonging, cardiotoxic, or emetogenic chemotherapy. Table 1.

Chemotherapy agents, primary mechanisms of cardiac injury, and arrhythmic or arrest pathways Agent / Class Primary Cardiac Clinical Syndrome Pathway to Cardiac Arrest Mechanism Anthracyclines Top2β poisoning; ROS via Dilated cardiomyopathy; Progressive HF → low-output state; quinone redox cycling; systolic dysfunction arrhythmia on background of LV Fe(III) complex dysfunction 5-FU / capecitabine Endothelin-1 upregulation; Angina; STEMI; arrhythmia Vasospasm → acute ischemia → VF; eNOS inhibition; coronary during infusion highest risk during continuous infusion vasospasm Trastuzumab / HER2 ErbB2/ErbB4 neuregulin-1 Reversible systolic HF progression; irreversible with prior agents signaling disruption; PI3K/ dysfunction; synergistic with anthracycline exposure Akt suppression anthracyclines TKIs (sunitinib, hERG (IKr) channel QTc prolongation; torsades Torsades → VF; compounded by nilotinib, blockade; QT prolongation de pointes hypokalemia and concurrent QT- vandetanib) prolonging drugs Immune checkpoint CD4 /CD8 autoreactive T- Fulminant myocarditis; Arrhythmia; heart block; cardiogenic inhibitors cell myocardial infiltration; complete heart block; shock; case fatality ~25-50% PD-L1 cardiac checkpoint cardiogenic shock loss High-dose Phosphoramide mustard/ Hemorrhagic myocarditis; Rapid-onset cardiogenic shock within cyclophosphamide acrolein myocardial pericardial effusion; shock 1-10 days of conditioning microvascular injury Platinum agents Electrolyte wasting (Mg^{2} , Arrhythmia; thrombotic Electrolyte-mediated arrhythmia; K); endothelial injury; cardiovascular events thrombotic MI autonomic neuropathy Abbreviations: Top2β, topoisomerase II beta; ROS, reactive oxygen species; eNOS, endothelial nitric oxide synthase; 5-FU, 5-fluorouracil; STEMI, ST-elevation myocardial infarction; VF, ventricular fibrillation; HF, heart failure; LV, left ventricular; ErbB2/4, epidermal growth factor receptor 2/4; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; TKI, tyrosine kinase inhibitor; hERG, human ether-a-go-go-related gene; IKr, rapidly activating delayed rectifier potassium current; ICI, immune checkpoint inhibitor; PD-L1, programmed death ligand-1.

11. The Critical Differential: Cardiogenic Pulmonary

Edema Versus Lymphangitic Carcinomatosis Among the most clinically consequential diagnostic challenges in cardio-oncology is the distinction between pulmonary edema of cardiogenic origin — resulting from chemotherapy-induced cardiomyopathy, acute myocarditis, or drug-induced heart failure — and pulmonary infiltration from malignant disease, principally lymphangitic carcinomatosis or malignant pleural effusion. The distinction is therapeutically critical: cardiogenic edema is treated with diuresis, afterload reduction, and cardiac support, while lymphangitic disease requires oncological intervention; administering diuretics to a patient with predominantly lymphangitic disease risks hemodynamic deterioration and acute kidney injury, while withholding diuresis from a patient in cardiogenic pulmonary edema risks respiratory arrest (27). This differential is included not because it outweighs the arrhythmic and pump- failure pathways to arrest discussed in Sections 3 through 10 — it does not — but because it is a recurrent bedside dilemma in patients receiving cardiotoxic therapy and because misclassification carries immediate, bidirectional harm. An important caveat, frequently neglected in didactic treatments of this distinction, is that the two processes commonly coexist: a patient with established lymphangitic spread who then develops anthracycline cardiomyopathy will have a mixed picture, and the clinical task is often to estimate the relative contribution of each rather than to choose between them.

Several clinical features provide initial orientation. Cardiogenic edema typically produces bilateral symmetric basal infiltrates, elevated jugular venous pressure, peripheral pitting edema, a third heart sound (S3 gallop), and a clinical history consistent with recent exposure to a cardiotoxic agent or prior cardiomyopathy. Lymphangitic carcinomatosis, by contrast, produces a characteristic radiographic pattern of nodular or irregular (beaded) interlobular septal thickening on high-resolution computed tomography, reflecting malignant infiltration of the pulmonary lymphatics — a pattern distinct from the smooth septal thickening of cardiogenic edema. Lymphangitic disease may be asymmetric or unilateral, may be accompanied by mediastinal lymphadenopathy, and typically fails to respond to diuresis.

Biomarker differentiation provides the most pharmacologically grounded discrimination. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT- proBNP) are synthesized and released by ventricular cardiomyocytes in response to wall stress, volume overload, and neurohormonal activation of the failing heart. Markedly elevated values — BNP above 400 pg/mL or NT-proBNP above age-adjusted thresholds — strongly support a cardiogenic origin of dyspnea with high sensitivity and moderate specificity (28).

A normal or minimally elevated BNP in a dyspneic cancer patient makes cardiogenic edema considerably less likely, directing the differential toward malignant, infectious, or inflammatory pulmonary disease.

Importantly, BNP may be modestly elevated in the absence of heart failure in cancer patients due to right ventricular strain from pulmonary hypertension, sepsis, or renal dysfunction, and interpretation requires integration with clinical and imaging findings. Echocardiography provides definitive assessment of ventricular function and is the most important single investigation in this differential. Reduced LVEF, elevated filling pressures (estimated by transmitral Doppler and tissue Doppler imaging), right ventricular dilation, pericardial effusion, and regional wall motion abnormalities each provide mechanistic information about the cardiac contribution to dyspnea. A preserved LVEF with normal filling pressures in a patient with bilateral pulmonary infiltrates significantly lowers the probability of cardiogenic edema and increases suspicion for parenchymal malignant or inflammatory disease.

High-resolution CT of the chest characterizes the distribution, morphology, and associated lymphadenopathy that distinguish smooth cardiogenic septal thickening from nodular lymphangitic infiltration. A practical approach incorporates the therapeutic trial: a patient with intermediate clinical probability for cardiogenic edema who shows symptomatic improvement and radiographic clearance with cautious diuresis (monitored for hemodynamic response) supports a cardiogenic diagnosis, while failure to respond to diuresis with preserved hemodynamics shifts the diagnosis toward malignant infiltration. Biomarker trends over 24-48 hours — BNP falling with diuresis in cardiogenic edema — provide additional diagnostic information without requiring invasive measurement. Table 2.

Differential diagnosis of pulmonary infiltrates in the chemotherapy-treated patient: cardiogenic edema versus lymphangitic carcinomatosis Feature Cardiogenic Pulmonary Edema Lymphangitic Carcinomatosis Radiographic pattern Bilateral symmetric basal infiltrates; smooth Nodular (beaded) septal thickening; may be interlobular septal thickening; cardiomegaly; asymmetric or unilateral; mediastinal bilateral pleural effusions lymphadenopathy; normal or enlarged cardiac silhouette BNP / NT-proBNP Markedly elevated; falls with effective Normal or mildly elevated (from RV strain or diuresis renal failure) Echocardiography Reduced LVEF; elevated filling pressures; Preserved LVEF and filling pressures; may regional WMA; pericardial effusion possible show RV dilation from PH Jugular venous pressure Elevated Usually normal Peripheral edema Pitting, bilateral, dependent Absent or lymphedematous (non-pitting) Cardiac auscultation S3 gallop; mitral regurgitation murmur may Normal heart sounds be present Response to diuresis Symptomatic and radiographic improvement; No improvement; risk of hemodynamic BNP falls deterioration with aggressive diuresis Relevant drug history Anthracyclines; trastuzumab; Disease progression on any regimen; new cyclophosphamide; recent TKI sites of spread on imaging Troponin May be elevated (myocarditis, ischemia) Usually normal unless coincident cardiac event Abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; LVEF, left ventricular ejection fraction; WMA, wall motion abnormalities; RV, right ventricular; PH, pulmonary hypertension; TKI, tyrosine kinase inhibitor.

12. A Conceptual Framework for Cardiotoxicity Risk

Stratification The mechanistic diversity of chemotherapy-related cardiac injury motivates a structured, prospective approach to surveillance. We present the following four-domain framework explicitly as a conceptual organizing heuristic rather than a validated clinical risk model: it has not been prospectively tested, carries no derived scoring coefficients, and has not been compared head-to-head against established tools such as the HFA-ICOS risk stratification, which should remain the validated instrument of choice in practice. Its purpose is pedagogical and organizational — to make explicit how mechanism, baseline risk, monitoring, and intervention relate — and we make no claim that following it would, by itself, prevent additional cardiac arrests relative to current ESC or ASCO guideline-based care; that question would require prospective validation that does not yet exist. With that limitation stated plainly, the four domains are as follows.

The first domain, baseline cardiovascular assessment, quantifies the functional cardiac reserve and identifies pre- existing vulnerabilities. Echocardiography with LVEF and global longitudinal strain (GLS) before anthracycline or HER2-targeted therapy establishes a baseline against which treatment-related decline can be benchmarked; GLS, a measure of myocardial deformation, detects subclinical dysfunction before LVEF falls and may guide earlier intervention. Baseline ECG with QTc measurement is essential before any QT-prolonging TKI. Baseline troponin and BNP characterize myocardial stress before ICI therapy in higher-risk patients.

The second domain, cardiotoxicity risk scoring, integrates patient-level and drug-level risk factors. Established cardiac risk scores such as the Heart Failure Association/International Cardio-Oncology Society (HFA-ICOS) risk stratification tool weight prior cardiovascular disease, age, hypertension, diabetes, prior chest irradiation, prior anthracycline exposure, and planned regimen to define low, medium, high, and very- high cardiac risk — with surveillance intensity calibrated accordingly (29). Pharmacogenomic factors including Top2β polymorphisms modulating anthracycline cardiac sensitivity, and KCNH2 variants affecting baseline QT duration, represent emerging individualization tools not yet in routine practice. The third domain, mechanism-aligned monitoring, matches surveillance modality and interval to the expected injury pathway.

Serial echocardiography (with GLS) at defined cumulative anthracycline dose thresholds and every 3 months during HER2-targeted therapy detects cardiomyopathy early. ECG and electrolyte monitoring before each TKI cycle enables QT risk assessment and correction of hypokalemia and hypomagnesemia before drug administration. Troponin and ECG monitoring during ICI therapy, with immediate cardiology referral for any new elevation, provides the earliest available signal for myocarditis. Troponin monitoring during and immediately after high-dose cyclophosphamide conditioning enables early detection of hemorrhagic myocarditis.

The fourth domain, cardioprotective interventions, encompasses the pharmacological and procedural measures that reduce incident cardiac injury or mitigate established toxicity. Dexrazoxane remains the best-evidenced pharmacological cardioprotectant for anthracycline therapy and is underused relative to its evidence base. Beta-blocker and ACE inhibitor therapy for detected cardiomyopathy follows established heart failure pharmacology; it is worth being candid that these agents are symptom- and physiology- directed rather than mechanism-specific — they are the same drugs used for heart failure of other etiologies, and truly mechanism-targeted

cardioprotection (for example, Top2β- sparing anthracycline analogues or selective ferroptosis inhibitors) remains largely investigational or unrealized, with several mitochondrial antioxidant strategies having failed in late-phase trials. Empiric vasodilator therapy (nitrates or calcium channel blockers) for fluoropyrimidine cardiotoxicity, recognizing that its preventive efficacy on rechallenge is not firmly established.

Electrolyte replacement protocols targeting potassium above 4.0 mEq/L and magnesium above 0.8 mmol/L throughout TKI therapy. Prompt high-dose corticosteroid initiation within hours of suspected ICI myocarditis, given the steep mortality associated with delayed treatment. Table 3. Risk stratification and monitoring framework for chemotherapy-related cardiac events Drug / Class High-Risk Features Monitoring Strategy Cardioprotective Intervention Anthracyclines Prior cardiac disease; Echo + GLS before, at 300 mg/m², Dexrazoxane; liposomal cumulative dose >300 mg/ and post-treatment; troponin formulation; dose capping; ACEi/ m²; mediastinal RT; age optional at high dose BB for detected LVD extremes 5-FU / capecitabine Prior CAD; high-dose Cardiac monitoring during first Empiric CCB/nitrate for continuous infusion; prior infusion(s); ECG if chest cardiotoxicity (efficacy on chest RT symptoms rechallenge not firmly established); consider bolus instead of infusional, or raltitrexed Trastuzumab / HER2 Prior anthracycline Echo q3 months during therapy; ACEi/BB for LVD; usually agents exposure; baseline LVEF hold if LVEF drops ≥10% to below reversible on drug hold; <55%; hypertension 50% rechallenge feasible if recovery TKIs (QT- Baseline QTc >450 ms; ECG and electrolytes at baseline, Electrolyte repletion (K >4.0, prolonging) hypokalemia; day 14, and each cycle; dose-hold Mg² >0.8); audit concurrent QT- hypomagnesemia; if QTc >500 ms prolonging drugs; dose modify per concurrent QT drugs; protocol female sex Immune checkpoint Combination ICI; prior Troponin and ECG at baseline and Immediate ICI hold + high-dose inhibitors cardiac disease; elevated with each cycle; echo if troponin methylprednisolone; MMF/ baseline troponin rises abatacept if refractory; hemodynamic support High-dose Conditioning doses; pre- Troponin daily during Dose limitation; no established cyclophosphamide existing cardiac conditioning; echo if troponin rises pharmacological prevention; dysfunction; prior or symptoms develop supportive care for established anthracyclines myocarditis Abbreviations: Echo, echocardiography; GLS, global longitudinal strain; RT, radiotherapy; ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blocker; LVD, left ventricular dysfunction; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; 5-FU, 5-fluorouracil; TKI, tyrosine kinase inhibitor; QTc, corrected QT interval; ICI, immune checkpoint inhibitor; MMF, mycophenolate mofetil.

13. Special Populations

Pediatric and young adult cancer survivors treated with anthracyclines carry a lifetime risk of cardiomyopathy that exceeds that of adults treated at equivalent cumulative doses, reflecting both the longer window of post-treatment life over which subclinical dysfunction may progress and the greater per-dose cardiac sensitivity in the developing heart. The Children's Oncology Group long-term follow-up guidelines recommend echocardiographic surveillance extending decades after anthracycline exposure in this population (30). This long surveillance horizon is an argument for reducing cumulative anthracycline dose wherever oncologically feasible in young patients and for maximizing dexrazoxane use when high cumulative doses cannot be avoided. Patients with pre-existing cardiovascular disease — coronary artery disease, prior heart failure, uncontrolled hypertension, or significant arrhythmia — carry substantially elevated baseline cardiac risk that is compounded by each cardiotoxic treatment element.

Multidisciplinary cardio-oncology assessment before initiation of cardiotoxic therapy is recommended in this group, with individualized risk-benefit analysis determining regimen selection, monitoring intensity, and whether cardioprotective medications should be initiated prophylactically. The concept of a lifetime cardiovascular risk budget — the total tolerable cardiac insult across all treatment lines — is a practical framework for such discussions. Elderly patients present compounding vulnerabilities through age-related reductions in cardiac reserve, higher prevalence of baseline coronary artery disease and hypertension, reduced tolerance of QT-prolonging drugs due to baseline autonomic changes in repolarization, and polypharmacy producing greater drug-drug interaction burden. The same principles of baseline assessment, mechanism-aligned monitoring, and cardioprotective intervention apply, with dosing and monitoring thresholds adjusted for age-related pharmacokinetic changes in drug clearance.

14. Conclusions and Future Directions

Chemotherapy-induced cardiac arrest is, in most cases, the terminal expression of a mechanistically defined pharmacological cascade that begins with a specific drug- target interaction and traverses cardiomyocyte energy failure, coronary vasospasm, ion channel toxicity, or fulminant autoimmune myocardial destruction on its way to loss of effective cardiac output. The pharmacological specificity of each pathway suggests that monitoring and intervention are most rationally matched to mechanism where the means to do so exist. This aspiration must, however, be tempered by two honest concessions developed throughout this review. First, for several agents the mechanism-specific monitoring target is not clinically measurable — there is no routine assay for endothelin-mediated vasospasm or for Top2β engagement — so that in practice surveillance often relies on general tools (troponin, natriuretic peptides, strain echocardiography, the electrocardiogram and electrolytes) rather than mechanism- specific ones.

Second, the therapies that demonstrably alter outcome — renin-angiotensin and beta-adrenergic blockade for cardiomyopathy, corticosteroids for myocarditis, electrolyte correction, and drug cessation — are largely physiology- and symptom-directed rather than molecularly bespoke. The honest synthesis is therefore not that mechanism-specific care has been shown superior to good general cardio-oncology care, but that mechanistic understanding sharpens where to look, when to act, and which patients warrant the most intensive application of the supportive tools that are already known to help. Several research priorities emerge. First, global longitudinal strain imaging and high-sensitivity troponin have substantially advanced early detection of subclinical anthracycline cardiomyopathy, but validated biomarker- triggered intervention protocols that demonstrably improve long-term cardiac outcomes are still needed.

Second, the mechanism of ICI myocarditis — autoreactive T-cell clonal expansion against shared tumor-myocardial antigens — suggests that tumor antigen profiling could identify patients at elevated myocarditis risk before ICI initiation, though this remains exploratory. Third, the pharmacological development of agents that selectively protect Top2β in cardiomyocytes without compromising Top2α-mediated antitumor activity represents a mechanistically rational extension of the dexrazoxane principle. Fourth, the

cardio-oncology model — multidisciplinary integration of cardiology and oncology expertise before, during, and after cancer treatment — is the most impactful organizational innovation available with current tools and should be the standard of care for patients receiving cardiotoxic therapy. The principle that unifies this review and its companions in this series on respiratory and renal arrest is that organ- threatening toxicity in cancer treatment is, for most agents, mechanistically intelligible and therefore pharmacologically actionable.

The distance between current mechanistic understanding and reliable clinical prevention varies by organ and by drug, and intellectual honesty demands that this distance be acknowledged rather than minimized. What mechanistic understanding reliably provides — in the cardiac domain as in the renal and respiratory — is the map: a molecular roadmap from drug exposure to organ failure, along which surveillance can be placed, interventions can be targeted, and care can be rationalized for the benefit of patients. Disclosure Statement The author declares no conflicts of interest, financial or otherwise, related to the subject matter of this manuscript, and has no financial or commercial relationship with Anthropic, the developer of the artificial intelligence tool referenced in the declaration below. Declaration of Generative AI and AI-Assisted Technologies in the Writing Process During the preparation of this manuscript, the author used Claude (Anthropic; Claude Opus model family) as a generative artificial intelligence (AI) assistant to support structural organization, editorial drafting, language refinement, and the preparation of summary tables and figure drafts.

The AI tool was not used to generate primary scientific data, to design or interpret original experiments, or to formulate the scientific hypotheses, which originate with the author. After using this tool, the author reviewed and edited the content as needed, independently verified all factual statements and confirmed that every cited reference is genuine, accurately represented, and correctly attributed, and takes full responsibility for the accuracy, originality, and integrity of the published work. In accordance with the recommendations of the International Committee of Medical Journal Editors (ICMJE) and the Committee on Publication Ethics (COPE), the AI tool is not listed as an author and does not meet authorship criteria, because accountability for the work, approval of its final version, and agreement to its submission can be borne only by the human author. The author affirms that the manuscript contains no plagiarized text or images, including content that may have been produced with AI assistance, and that the intellectual contributions, critical judgments, and conclusions are the author's own.

Should the target journal specify an alternative format or location for AI disclosure, the author will adapt this declaration to the journal's instructions, recognizing that Annual Reviews advises authors to confirm AI-use requirements with their Production Editor. References

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