Think cardiotoxicity is old news? Modern cancer therapy says otherwise

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> The expanding arsenal of cancer therapies, while extending lives, introduces a growing challenge: cardiotoxicity. Clinicians must balance oncologic efficacy with the imperative to preserve cardiac function, navigating complex decisions around monitoring, rechallenge, and toxicity management.

KEY TAKEAWAYS

- The Pivot: Cardiotoxicity is a class effect across many modern cancer therapies, requiring a proactive cardio-oncology approach.
- The Data: Immune checkpoint inhibitor myocarditis, though rare (0.06-1.14%), carries a high mortality rate (25-50%).
- The Action: Implement baseline cardiac assessment, vigilant monitoring for symptoms, and clear protocols for managing cardiotoxic events.

Cancer treatment has evolved dramatically, but the heart often bears the cost. From traditional chemotherapies to targeted agents and immunotherapies, nearly every class of antineoplastic drug carries a risk of cardiovascular complications. This necessitates a systematic approach to cardio-oncology, integrating cardiac risk assessment and management into the patient's overall cancer care plan.

Cardiotoxicity manifests in various forms, including left ventricular dysfunction, heart failure, arrhythmias, hypertension, and myocardial ischemia. The specific presentation depends on the agent, dose, duration of exposure, and individual patient risk factors. Identifying patients at high risk before treatment initiation is paramount, allowing for tailored monitoring strategies and prophylactic interventions where appropriate.

Immune Checkpoint Inhibitors and the Myocarditis Threat

Immune checkpoint inhibitors (ICIs), revolutionary for their ability to unleash the immune system against cancer, also carry the risk of immune-related adverse events (irAEs), including myocarditis. This is a rare but potentially fatal complication. The incidence of ICI-myocarditis ranges from 0.06% to 1.14% across various studies, but its mortality rate is alarmingly high, reported between 25% and 50%.1

Patients receiving ICIs require careful monitoring for cardiac symptoms such as dyspnea, chest pain, palpitations, or fatigue. Baseline electrocardiogram (ECG) and troponin levels are recommended, with repeat measurements during treatment, particularly if symptoms arise. Elevated troponin is a sensitive indicator of myocardial injury and warrants immediate investigation, including echocardiography and potentially cardiac magnetic resonance imaging (CMR).

Management of ICI-myocarditis typically involves high-dose corticosteroids, often methylprednisolone 1 g/day for 3-5

days, followed by a slow taper. In refractory cases, other immunosuppressants like infliximab or mycophenolate mofetil may be necessary. The decision to rechallenge with an ICI after myocarditis is complex and requires careful consideration of the cancer prognosis, the severity of the initial myocarditis, and the availability of alternative therapies. Generally, rechallenge is not recommended for severe myocarditis (grade 3-4).

5-Fluorouracil Toxicity: A Familiar Foe

5-Fluorouracil (5-FU) and its prodrug capecitabine remain cornerstones in the treatment of various solid tumors, including colorectal, breast, and gastric cancers. But 5-FU is notorious for its cardiotoxicity, which can manifest as angina, myocardial infarction, arrhythmias, and even sudden cardiac death. The incidence of 5-FU cardiotoxicity varies widely, from 1% to 18%, depending on the definition and patient population.2

The mechanism of 5-FU cardiotoxicity is multifactorial, involving coronary vasospasm, direct myocardial injury, and endothelial dysfunction. Symptoms typically appear within the first few days of treatment, often during the infusion. Clinicians should maintain a high index of suspicion for cardiac symptoms in patients receiving 5-FU, especially those with pre-existing coronary artery disease.

Management of 5-FU cardiotoxicity is primarily supportive. Discontinuation of the drug is usually necessary. Nitrates and calcium channel blockers can alleviate vasospasm. There is no specific antidote. For patients who experience significant cardiotoxicity, re-exposure to 5-FU is generally contraindicated. Alternative chemotherapy regimens should be explored. Genotyping for dihydropyrimidine dehydrogenase (DPD) deficiency, which leads to impaired 5-FU metabolism and increased toxicity, is increasingly recommended before initiating 5-FU therapy, particularly in patients with a history of severe adverse events or those at higher risk.

Anthracyclines and HER2-Targeted Therapies: Long-Term Surveillance

Anthracyclines, such as doxorubicin and epirubicin, are highly effective chemotherapeutic agents but are well-known for their dose-dependent cardiotoxicity, primarily leading to left ventricular dysfunction and heart failure. This can be acute, subacute, or chronic, with late-onset heart failure occurring years after treatment. The risk increases significantly with cumulative doses; for doxorubicin, the risk of heart failure is 5% at 400 mg/m2, rising to 26% at 550 mg/m2.3

HER2-targeted therapies, notably trastuzumab, also carry a risk of cardiotoxicity, typically manifesting as asymptomatic left ventricular ejection fraction (LVEF) decline. Unlike anthracycline-induced cardiotoxicity, trastuzumab-induced cardiac dysfunction is often reversible upon discontinuation of the drug. The incidence of symptomatic heart failure with trastuzumab monotherapy is around 2-4%, but it can be higher when combined with anthracyclines.4

For both anthracyclines and HER2-targeted agents, baseline and serial LVEF monitoring via echocardiography is crucial. Guidelines recommend LVEF assessment before treatment, at regular intervals during therapy, and for several years post-treatment, especially for anthracyclines. Cardioprotective strategies, such as liposomal formulations of doxorubicin, dexrazoxane, and concurrent use of beta-blockers or ACE inhibitors, can mitigate the risk in selected patients. The Oxford Handbook of Cardiology provides a concise guide to these complex management strategies.

Rechallenge Decisions: Balancing Risk and Benefit

The decision to rechallenge a patient with a cancer therapy after a cardiotoxic event is one of the most challenging in cardio-oncology. It requires a multidisciplinary discussion involving oncologists, cardiologists, and the patient. Factors to consider include the severity and reversibility of the initial cardiotoxicity, the availability of alternative effective cancer

treatments, the prognosis of the cancer, and the patient's overall health status and preferences.

For mild, reversible cardiotoxicity, such as asymptomatic LVEF decline with trastuzumab, rechallenge may be considered after cardiac function has recovered, often with closer monitoring and potentially concurrent cardioprotective medications. But for severe events, like symptomatic heart failure or high-grade arrhythmias, rechallenge is generally contraindicated due to the unacceptable risk of recurrence and worsening cardiac damage.

The lack of robust prospective data on rechallenge strategies for many cardiotoxic agents is an obvious caveat. Most recommendations stem from expert consensus and retrospective analyses. This gap matters, as it leaves clinicians to navigate these high-stakes decisions with limited empirical guidance. Future trials need to address specific rechallenge protocols and their long-term cardiac and oncologic outcomes.

The Role of Biomarkers and Imaging

Biomarkers like troponin and natriuretic peptides (BNP/NT-proBNP) play an increasingly important role in the early detection of cardiotoxicity. Elevated troponin levels, even in the absence of symptoms, can signal myocardial injury and prompt further cardiac evaluation. BNP/NT-proBNP levels can indicate cardiac strain and predict the development of heart failure.

Echocardiography remains the cornerstone for assessing LVEF and cardiac structure. Newer echocardiographic techniques, such as global longitudinal strain (GLS), offer more sensitive detection of subclinical myocardial dysfunction, often preceding changes in LVEF. CMR provides detailed anatomical and functional information, particularly useful for diagnosing myocarditis or diffuse myocardial fibrosis. These tools, when used systematically, can help identify cardiotoxicity early, allowing for timely intervention and potentially preventing irreversible cardiac damage.

The integration of these diagnostic modalities into routine cardio-oncology practice is essential. Standardized protocols for monitoring, tailored to the specific cardiotoxic agent and patient risk profile, can improve outcomes. For example, patients on anthracyclines might benefit from baseline and serial echocardiograms with GLS, while those on ICIs require vigilant symptom monitoring and troponin checks. The Oxford Handbook of Oncology offers practical guidance on these monitoring schedules.

Preventive Strategies and Future Directions

Preventive strategies are a critical component of cardio-oncology. These include optimizing cardiovascular risk factors before initiating cancer therapy, using less cardiotoxic alternatives when available, and employing cardioprotective agents. For example, beta-blockers and ACE inhibitors have shown promise in preventing or mitigating anthracycline-induced cardiotoxicity in some studies.

Still, the field needs more dedicated research. Prospective trials are needed to define optimal monitoring strategies, validate novel biomarkers, and evaluate the efficacy of cardioprotective interventions across different cancer therapies. Establishing clear, evidence-based guidelines for managing cardiotoxicity and making rechallenge decisions will be crucial for improving patient outcomes. The unanswered question remains: how do we best balance aggressive cancer treatment with long-term cardiac health, especially as cancer survivors live longer?

CLINICAL IMPLICATIONS

> The era of precision oncology demands precision cardio-oncology. Clinicians can no longer treat cancer without a keen eye on the heart. The increasing complexity of cardiotoxicity, particularly with immune checkpoint inhibitors, means a reactive approach is simply inadequate; early detection and proactive management are not optional extras, they are fundamental to patient safety.
> The high mortality associated with ICI-myocarditis, despite its rarity, should drive a low threshold for investigation. Any new cardiac symptom in an ICI-treated patient warrants immediate troponin and ECG. The consequences of missing it are too severe to equivocate. Similarly, the familiar threat of 5-FU cardiotoxicity necessitates careful patient selection and vigilance, especially in those with pre-existing cardiac risk factors.
> Guideline bodies like ESMO and ASCO have begun to issue recommendations, but their implementation in routine practice remains inconsistent. Integrating cardio-oncology services, even if virtual, can bridge the knowledge gap for general practitioners and specialists. This is not about adding another layer of bureaucracy; it is about ensuring that the hard-won gains in cancer survival are not undermined by preventable cardiac events.
> Ultimately, the goal is not just to support management of / may help patients with cancer, but to ensure a good quality of life for survivors. That means preserving cardiac function. The onus is on us to read the full paper, understand the nuances of each agent's cardiotoxicity, and integrate this knowledge into every treatment decision.

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