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Letter to Editor

Levosimendan in Trastuzumab-induced cardiotoxicity: A mechanism-based perspective

Dear Editor

Trastuzumab is a cornerstone therapy in HER2-positive breast cancer, yet its association with cardiotoxicity remains a major limitation in clinical practice. Trastuzumab-induced cardiac dysfunction, although often considered non-necrotic and potentially reversible, frequently manifests as left ventricular ejection fraction decline and symptomatic heart failure, leading to treatment interruption and compromised oncologic outcomes (1, 2). These clinical challenges highlight the need for a proactive, mechanism-oriented strategy in managing trastuzumab-related cardiac adverse effects. Mechanistically, trastuzumab cardiotoxicity arises primarily from inhibition of HER2/ErbB2 signaling in cardiomyocytes, resulting in suppression of pro-survival pathways such as PI3K/Akt and increased susceptibility to oxidative and metabolic stress (1, 3). Recent transcriptomic and bioinformatics analyses further demonstrate dysregulation of genes involved in mitochondrial energy metabolism, calcium homeostasis, and apoptotic signaling, collectively impairing myocardial adaptive capacity (4). This molecular vulnerability explains why cardiac dysfunction may occur even in the absence of overt myocyte necrosis.

Current management strategies are largely reactive and rely on echocardiographic monitoring, neurohormonal blockade with angiotensin-converting enzyme inhibitors or beta-blockers, and temporary or permanent discontinuation of trastuzumab (1, 5). While these approaches may partially stabilize cardiac function, they do not directly target mitochondrial dysfunction or impaired intracellular signaling, and often fail to prevent treatment disruption or incomplete cardiac recovery. Levosimendan, a calcium sensitizer with mitochondrial K_ATP channel–opening properties, offers a biologically plausible and mechanism-driven therapeutic option in this setting. By enhancing myocardial contractility without increasing intracellular calcium concentration or myocardial oxygen consumption, levosimendan improves systolic performance while preserving energetic efficiency (6, 7). In addition, mitochondrial K_ATP channel activation confers cytoprotective effects through attenuation of oxidative stress, stabilization of mitochondrial membrane potential, and modulation of apoptotic pathways.

Recent systematic reviews and meta-analyses have demonstrated the safety and efficacy of levosimendan in advanced heart failure and cardiogenic shock, with favorable effects on hemodynamics, hospitalization rates, and functional recovery (6, 8, 9). Importantly, experimental and clinical studies suggest that levosimendan mitigates chemotherapy-induced cardiotoxicity by restoring PI3K/Akt signaling, preserving mitochondrial integrity, and reducing oxidative injury (10–12). These mechanisms closely overlap with those implicated in trastuzumab-induced myocardial dysfunction. Collectively, available evidence supports the concept that levosimendan may serve not only as a rescue inotrope, but also as part of a targeted, mechanism-based strategy for managing trastuzumab-related cardiotoxicity, particularly in high-risk patients or those exhibiting early ventricular impairment. Prospective clinical trials are warranted to evaluate its preventive and adjunctive role within integrated cardio-oncology care pathways, with the ultimate goal of preserving cardiac function while maintaining uninterrupted, effective anti-cancer therapy.

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