Letter to the Editor

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Ivabradine for anthracycline-induced cardiotoxicity: emerging promise and current evidence

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Dear Editor,

Anthracycline-based chemotherapy (including doxorubicin, epirubicin) remains foundational in the management of many types of cancers, including breast cancers, lymphomas, sarcomas, and other malignancies. However, its cumulative dose-dependent cardiotoxicity, manifesting from subclinical left-ventricular dysfunction to overt heart failure, limits optimal therapy. Emerging strategies are focussing on early detection and prevention of cardiotoxicity instead of waiting for symptomatic heart failure.

The pharmacologic rationale for ivabradine as a prophylactic approach in this regard is plausible. Ivabradine selectively inhibits the I_f ("funny") current in the sino-atrial node, reducing heart rate without adverse effects on myocardial contractility or systemic blood pressure. Lower heart rate reduces myocardial oxygen consumption, extends diastolic perfusion time and may enhance myocardial reserve under stress. Preclinical work in rat models of doxorubicin (DXR) cardiotoxicity showed that ivabradine attenuated cardiac troponin-I release and reduced malondialdehyde (MDA) levels compared to control, suggesting that ivabradine could be effective in mitigating DXR-induced cardiotoxicity[1].

Early clinical trials also suggested possible benefits. A 2023 open-label randomized trial in breast cancer patients reported that ivabradine reduced the incidence of troponin elevation (four-fold lower) compared to controls during anthracycline therapy[2]. Another randomized trial discussed the feasibility of ivabradine in patients with breast cancer undergoing anthracycline chemotherapy[3]. It found significant differences in the left ventricular global longitudinal strain in the earlier months of observation ($P < 0.05$), but after 12 months the groups were comparable in longitudinal strain values.

However, the evidence is not yet definitive. A recent triple-blind, placebo-controlled trial (IPAC) assessing ivabradine, given 5 mg twice daily, in patients receiving anthracyclines found no major differences in global longitudinal strain decline or biomarker release[4]. Importantly, this trial excluded breast cancer patients, leaving ivabradine's utility in cancer patients uncertain. Furthermore, a network meta-analysis of 128 trials in 10 431 cancer patients found that while agents such as beta-blockers and dexrazoxane showed benefit, ivabradine was not among the high-ranked agents for preventing cardiotoxicity[5].

Ivabradine represents an innovative concept in cardio-oncology prophylaxis, offering selective heart rate reduction without the hemodynamic penalties of beta-blockade. However, despite a strong mechanistic rationale and encouraging biomarker and strain data from early-phase studies, the most recent randomized controlled evidence indicates no consistent benefit in preventing anthracycline-induced left ventricular dysfunction or biomarker elevation at conventional dosing. These mixed results suggest that the cardioprotective efficacy of ivabradine may depend on the type of cancer, optimal dosing, and timing relative to anthracycline administration. Its benefit may also be limited to specific clinical contexts, such as in those with high resting heart rates, concomitant tachyarrhythmias, or where standard cardioprotective drugs are contraindicated. Importantly, ivabradine has not yet demonstrated superiority or additive benefit over established prophylactic regimens based on beta-blockers, ACE inhibitors, or dexrazoxane.

The cumulative evidence, though supports its safety, questions its efficacy as a stand-alone cardioprotective agent. Large, adequately powered trials with stratified patient populations, optimized dosing/timing and modern imaging/biomarker endpoints are needed to further explore ivabradine's role as a prophylactic in this regard. Oncology and cardio-oncology teams should monitor emerging data closely and consider ivabradine in selected high-risk cases within clinical-trial frameworks. Combination therapies of ivabradine with other established prophylactics may also be explored in future trials to investigate possible benefits over current regimens. This letter followed the transparency in the reporting of artificial intelligence (TITAN) guidelines 2025[6].

Ethics approval and consent to participate

Not needed as this study uses already published, publicly available data.

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