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Letter

Advances in Cardio-Oncology: The Emerging Role of Sglt2 Inhibitors in Cardioprotection

Tora Sadigova*

Department of Internal Medicine, Azerbaijan Medical University, Baku, Azerbaijan

Abstract

Background: The cardiotoxic effects of anti-tumor therapies represent a critical concern in oncology, as they compromise patient survival and quality of life by inducing cardiovascular diseases. With an increasing number of cancer patients undergoing treatments such as chemotherapy and radiation, the incidence of cardiotoxicity has surged. These adverse effects underscore the necessity of early detection, risk stratification, and preventive strategies tailored to mitigate cardiotoxicity and improve patient outcomes. *Objective:* This meta-analysis aims to systematically evaluate the effectiveness of various interventions designed to prevent or reduce cardiotoxicity associated with anti-tumor therapies. By synthesizing evidence from existing studies, we seek to identify the most effective measures, providing a comprehensive overview of the current landscape in cardioprotective strategies. *Methods:* We conducted a comprehensive literature search, including peer-reviewed studies that investigated preventive strategies for cardiotoxicity in patients undergoing anti-tumor therapy. Inclusion criteria were studies evaluating pharmacological and non-pharmacological interventions and their effects on cardiac function and patient outcomes. Data were extracted and analyzed to assess the impact of interventions on cardiotoxicity incidence, cardiac biomarkers, and clinical endpoints. *Main Findings:* Our analysis demonstrates a range of effective cardioprotective interventions, particularly focusing on beta-blockers, ACE inhibitors, and lifestyle modifications. Beta-blockers were found to reduce the incidence of left ventricular dysfunction, while ACE inhibitors showed promise in improving cardiac biomarkers. Additionally, lifestyle interventions, including exercise and dietary modifications, contributed to overall cardiovascular health, though further research is needed to define optimal protocols. *Conclusion:* Preventive strategies play a pivotal role in managing cardiotoxicity in cancer patients undergoing anti-tumor therapies. Pharmacological interventions, especially beta-blockers and ACE inhibitors, show significant potential in mitigating cardiac damage, while lifestyle interventions offer supplementary benefits. Our findings underscore the importance of an integrative approach, combining pharmacological and lifestyle modifications to protect cardiac function. Future research should focus on personalized cardioprotective protocols to optimize outcomes for cancer patients, ensuring that cardiovascular health is maintained alongside effective anti-tumor treatment.

Keywords

Cardiotoxicity, Anti-tumor Therapy, Cardioprotective Interventions, Cardiotoxicity Prevention, SGLTi

*Corresponding author: tsadiqova@amu.edu.az (Tora Sadigova)

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1. Introduction

Cardio-oncology, a rapidly evolving field, seeks to address the cardiovascular complications arising from cancer therapies. Traditional chemotherapies, targeted treatments, and immune checkpoint inhibitors have revolutionized cancer care but come with an increased risk of cardiotoxicity, posing significant challenges for patient management. In this context, Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors have emerged as promising agents in cardiovascular protection, extending their benefits beyond their primary use in managing type 2 diabetes and heart failure. This editorial explores the emerging role of SGLT2 inhibitors in cardio-oncology, highlighting recent findings from studies conducted between 2022 and 2024, all sourced from PubMed.

2. SGLT2 Inhibitors

Beyond Glycemic Control. Initially developed for glycemic control in diabetes, SGLT2 inhibitors have shown remarkable cardiovascular benefits, including reductions in heart failure hospitalizations and improved overall cardiac outcomes. Recent research indicates that their mechanisms of action, such as reducing myocardial inflammation, oxidative stress, and fibrosis - may also protect against chemotherapy-induced cardiotoxicity, a major concern in cancer treatment [1].

3. Emerging Evidence from Recent Studies

Recent studies published between 2022 and 2024 have highlighted the potential of SGLT2 inhibitors as cardioprotective agents in the oncology setting:

3.1. Heart Failure and Cardioprotective Effects

A study by Osataphan et al. (2024) [2] demonstrated that SGLT2 inhibitors may offer cardioprotective benefits in cancer patients undergoing chemotherapy, particularly with anthracyclines. These studies indicate a reduction in heart failure incidence, cardiomyopathy, hospitalizations, and overall mortality among patients treated with SGLT2i compared to controls. However, the evidence is limited by potential confounding factors, as these studies are primarily conducted in diabetic patients, and randomized controlled trials (RCTs) are needed to validate these findings. The EMPACT trial [3] is a key RCT currently investigating the efficacy of empagliflozin in preventing chemotherapy-related cardiotoxicity in patients receiving high-dose anthracyclines. This double-blinded, placebo-controlled study aims to assess the impact of empagliflozin on cardiac function, structural myocardial changes, and cardiovascular outcomes, with results eagerly awaited to confirm the potential of SGLT2 inhibitors as a preventive strategy in cardio-oncology.

3.2. Reduction of Myocardial Injury

Recent data suggest that SGLT2 inhibitors may attenuate subclinical myocardial injury in patients undergoing chemotherapy. Study of Manhas et al. (2024) [4] highlighted advancements in human induced pluripotent stem cell (hiPSC) technology, which aids in modeling drug-induced cardiotoxicity and offers personalized approaches to mitigate heart damage during cancer therapy. Despite progress, challenges remain in replicating adult heart tissue accurately and ensuring reproducibility in clinical models. Continued research is essential for developing patient-specific therapies that balance effective cancer treatment with cardiovascular safety. Also, they showed that the use of SGLT2 inhibitors was associated with lower levels of cardiac biomarkers, such as troponins, compared to standard care, suggesting a protective effect at the myocardial level.

3.3. Synergistic Effects with Traditional Cardioprotective Agents

The study by Carlos A. Gongora et al. (2022) [5] examined the role of SGLT2 inhibitors in reducing cardiotoxicity among cancer patients with diabetes treated with anthracyclines. A retrospective cohort of 128 patients was analyzed, comparing those on SGLT2 inhibitors during anthracycline therapy to those who were not. Key findings included a significantly lower rate of cardiac events, heart failure admissions, and overall mortality in the SGLT2 inhibitor group, supporting the need for randomized clinical trials to validate these findings. While observational data support the use of SGLT2 inhibitors, ongoing randomized trials aim to provide robust evidence on their efficacy and safety in preventing cardiotoxicity during cancer therapy, particularly focusing on their role in high-risk patients.

3.4. Improvement in Cardiac Remodeling

The EMPACARD-PILOT [6] trial was a prospective case-control study evaluating the impact of empagliflozin on preventing cardiac dysfunction in breast cancer patients undergoing anthracycline-based chemotherapy. The study included 76 patients with diabetes or stable heart failure with preserved ejection fraction (HFpEF), who were identified as high-risk using the HFA/ICOS risk score. Patients were assigned to either empagliflozin (10 mg/day) starting seven days before chemotherapy or to a control group. The primary endpoint was cancer therapy-related cardiac dysfunction (CTRCD), defined by significant declines in left ventricular ejection fraction (LVEF) or global longitudinal strain (GLS). Secondary endpoints included mortality and heart failure

hospitalization rates. The study drug was administered during a six-month period, with regular assessments of cardiac function, biomarkers, and safety outcomes. Empagliflozin significantly reduced the incidence of CTRCD compared to controls (6.5% vs. 35.5%). There was also significant preservation of LVEF and GLS in the empagliflozin group. No significant differences were observed in secondary outcomes like heart failure, NT-proBNP levels, or clinical heart failure. Empagliflozin may offer cardioprotective benefits in patients at high risk of anthracycline-induced cardiotoxicity, supporting further research into SGLT2 inhibitors for cardio-oncology applications. These findings highlight the potential of SGLT2 inhibitors as an effective strategy for mitigating cardiotoxicity during cancer therapy, particularly in high-risk populations.

3.5. Patient-Centric Outcomes

There is another systematic review and meta-analysis held by Tabowei G. et al. aimed to evaluate the cardioprotective effects of Sodium-Glucose Cotransporter 2 inhibitors in patients undergoing anthracycline-based cancer therapy. [9] Anthracyclines, while effective against various cancers, are associated with a high risk of cardiotoxicity, including heart failure. This comprehensive search was conducted across multiple databases, including PubMed, Embase, and Cochrane Library, using keywords related to SGLT2 inhibitors and anthracycline-induced heart failure. Studies were selected based on predefined criteria, including observational studies and randomized controlled trials involving adult patients receiving anthracycline-based therapy. Four observational studies involving 5,590 patients met the inclusion criteria. Data extraction and quality assessment were independently performed by two reviewers. Statistical analysis was conducted using RevMan software to calculate risk ratios for heart failure incidence, heart failure hospitalization, and all-cause mortality. As a result of this meta-analysis we can conclude that the SGLT2i were associated with a non-significant reduction in heart failure risk (RR = 0.67; 95% CI: 0.40-1.41); hospitalization rates were lower in the SGLT2i group, though not statistically significant (RR = 0.46; 95% CI: 0.15-1.42); mortality rates in SGLT2i groups were significantly reduced the risk of all-cause mortality (RR = 0.55; 95% CI: 0.39-0.77). This meta-analysis suggests that SGLT2 inhibitors may offer a protective effect against heart failure and reduce mortality in anthracycline-treated patients, although the reduction in heart failure risk was not statistically significant. The findings highlight the potential of SGLT2i as a cardioprotective strategy, warranting further research through large-scale clinical trials to confirm these results and explore the underlying mechanisms. Despite the limitations, such as the small number of studies and inherent biases of observational research, this study provides promising insights into the potential benefits of SGLT2 inhibitors in a high-risk oncology population.

4. Attenuating Trastuzumab-Induced Cardiotoxicity

Jie Min et al. [7] investigated the cardioprotective effects of Empagliflozin on Trastuzumab (TZM)-induced cardiotoxicity in HER2-positive breast cancer therapy. TZM is effective but often leads to cardiotoxicity through mechanisms involving DNA damage and ferroptosis. Adult C57BL/6 mice were administered TZM weekly for six weeks, with some receiving concurrent Empagliflozin treatment. Cardiac function, mitochondrial integrity, and levels of oxidative stress and cell death markers were assessed. TZM significantly increased serum biomarkers of cardiac injury, promoted adverse myocardial remodeling, and induced oxidative stress, apoptosis, and ferroptosis. Empagliflozin treatment mitigated these effects, improving mitochondrial integrity and reducing cardiac dysfunction. Empagliflozin offers cardioprotection against TZM-induced damage, likely by suppressing DNA damage and ferroptosis, suggesting it as a potential adjunct in managing cardiotoxicity during cancer treatment.

5. Anti-Inflammatory and Antioxidative Benefits

Mahmoud Refaie et al. [8] in their comprehensive research studied the cardioprotective effects of dapagliflozin (DAP) on cyclophosphamide (CP)-induced cardiotoxicity. The focus was on the modulation of the hypoxia-inducible factor α (HIF1α)/vascular endothelial growth factor (VEGF)/endothelial nitric oxide synthase (eNOS) signaling pathway, known to play a key role in cardiovascular health. 40 male Wistar albino rats were used, divided into four groups: a control group, a CP group, a CP group treated with DAP, and a CP group treated with both DAP and a nitric oxide synthase inhibitor (L-NNA). Rats received treatments for five days, with CP administered on days four and five to induce cardiotoxicity. Biochemical analyses were conducted, including measurements of cardiac enzymes, oxidative stress markers, and proteins related to apoptosis, inflammation, and signaling pathways. Biochemical parameters such as malondialdehyde (MDA), reduced glutathione (GSH), total antioxidant capacity (TAC), and cardiac enzymes (troponin I, CK-MB, and LDH) were measured. Histopathological and immunohistochemical analyses assessed the structural and molecular changes in cardiac tissue. Interesting results were obtained:

1. Biochemical Findings: CP significantly increased cardiac enzymes, oxidative stress markers, and inflammatory proteins, indicating severe cardiac injury. DAP treatment significantly ameliorated these changes, demonstrating antioxidant, anti-inflammatory, and anti-apoptotic properties.
2. Histopathological Findings: CP caused significant cardiac damage, including cellular infiltration, edema,

and disrupted muscle architecture. Co-administration of DAP restored normal cardiac structure and reduced signs of injury.

3. Molecular Pathway Modulation: CP-induced cardiotoxicity involved the activation of HIF1α, suppression of VEGF, and reduction of eNOS expression, contributing to oxidative stress, apoptosis, and vascular dysfunction. DAP treatment reversed these changes, upregulating VEGF and eNOS, thereby enhancing vascular integrity and function.
4. Role of eNOS: The cardioprotective effects of DAP were significantly reduced when combined with L-NNA, underscoring the critical role of eNOS in mediating DAP's benefits.

DAP effectively mitigates CP-induced cardiotoxicity through modulation of the HIF1α/VEGF/eNOS pathway and its antioxidative, anti-inflammatory, and anti-apoptotic effects. This study highlights DAP's potential as a cardioprotective agent in cancer therapy, though further clinical studies are needed to confirm its efficacy in patients undergoing CP treatment.

This study emphasizes the importance of understanding molecular pathways to develop new strategies for protecting the heart during chemotherapy, suggesting that DAP could serve as a promising adjunct therapy to minimize cardiotoxic side effects associated with anticancer drugs.

6. Safety and Tolerability in Oncology Patients

This systematic review of 479 identified records was held by Zhao G et al. [10] to assess the cardioprotective effects SGLT2i in patients undergoing breast cancer therapy, particularly those treated with trastuzumab and/or anthracyclines. Trastuzumab is effective but poses significant cardiotoxic risks, which can lead to discontinuation and negatively impact cancer outcomes. The review involved a comprehensive search of Embase, Medline, The Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials. gov. Two cardio-oncologists independently screened and assessed the studies based on eligibility criteria, focusing on cardiotoxicity prevention with SGLT2i during breast cancer treatment. 479 identical records, 19 studies were included, comprising case reports, retrospective cohort studies, and mechanistic studies. No completed randomized controlled trials (RCTs) were found. The included studies provided preliminary evidence suggesting that SGLT2i could reduce cardiotoxicity in patients receiving breast cancer therapy. Observational data and animal studies highlighted potential cardioprotective effects, including enhanced cardiac function and reduced heart failure risk. Although evidence supports the potential cardioprotective role of SGLT2i in cancer therapy, prospective RCTs are necessary to confirm these findings and guide clinical practice. This review underscores the urgent need for well-designed trials to establish SGLT2i as a standard approach for managing cancer therapy-related cardiac dysfunction (CTRCD).

The Path Forward: Integrating SGLT2 Inhibitors into Cardio-Oncology Care. The expanding evidence base supports the integration of SGLT2 inhibitors into cardio-oncology protocols. Their use, particularly in high-risk patients undergoing anthracycline or HER2-targeted therapies, could substantially mitigate cardiotoxicity and improve long-term cardiac outcomes. Future research should focus on randomized controlled trials to validate these findings further and explore optimal dosing strategies, duration of therapy, and combination approaches with other cardioprotective agents.

7. Conclusion

SGLT2 inhibitors have shown promising potential as cardioprotective agents in oncology, specifically in preventing cardiac dysfunction associated with cancer therapies such as anthracyclines and trastuzumab. The growing body of evidence from observational studies and animal models suggests that SGLT2 inhibitors can reduce cardiotoxicity through anti-inflammatory, antioxidative, and anti-apoptotic mechanisms. However, there remains an urgent need for large-scale randomized controlled trials to validate these findings, refine treatment protocols, and establish SGLT2 inhibitors as standard care in cardio-oncology. Integrating SGLT2 inhibitors into clinical practice could revolutionize the management of cancer therapy-related cardiac dysfunction, improving outcomes for high-risk patients. Future research should focus on optimizing dosing, exploring combination therapies, and confirming long-term safety and efficacy in diverse patient populations.

8. Recommendations

1. *Consideration of SGLT2 Inhibitors in High-Risk Oncology Patients:* at risk of cardiotoxicity, especially for those who are undergoing anthracycline or trastuzumab therapy.
2. *Personalized Risk Assessment and Therapy Adjustment:* It's crucial to assess individual patient risk for cardiotoxicity when considering SGLT2 inhibitors. This includes monitoring cardiac function and biomarkers to tailor treatment protocols effectively.
3. *Combination Therapy for Enhanced Cardioprotection:* preliminary studies indicate potential benefits in combining SGLT2 inhibitors with traditional cardioprotective agents. This combination may offer synergistic effects, further reducing the risk of heart failure and improving outcomes during cancer treatment.
4. *Encourage Further Research Participation:* Engaging

patients in ongoing research or clinical trials can aid in validating the efficacy of SGLT2 inhibitors in reducing chemotherapy-related cardiotoxicity and potentially establish these drugs as a new standard in cardio-oncology care.

Abbreviations

SGLT2	Sodium-Glucose Co-Transporter 2
HFpEF	Heart Failure with Preserved Ejection Fraction
CTRCD	Cancer Therapy-Related Cardiac Dysfunction
LVEF	Left Ventricular Ejection Fraction
GLS	Global Longitudinal Strain
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
TZM	Trastuzumab
HER2	Human Epidermal Growth Factor Receptor 2
hiPSC	Human Induced Pluripotent Stem Cell
HFA/ICOS	Heart Failure Association/International Cardio-Oncology Society
RCT	Randomized Controlled Trial
CP	Cyclophosphamide
HIF1α	Hypoxia-Inducible Factor 1-alpha
VEGF	Vascular Endothelial Growth Factor
eNOS	Endothelial Nitric Oxide Synthase
L-NNA	Nω-Nitro-L-Arginine
MDA	Malondialdehyde
GSH	Glutathione
TAC	Total Antioxidant Capacity
CK-MB	Creatine Kinase-MB
LDH	Lactate Dehydrogenase
EMPACT	Empagliflozin in Patients with Acute Myocardial Infarction
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
CANVAS	Canagliflozin Cardiovascular Assessment Study
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire

Author Contributions

Tora Sadigova is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The author declares no conflicts of interest.

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Research Fields

Tora Sadigova: Cardiology, Cardio-oncology, Cardiotoxicity, Primary evaluation of cardiotoxicity, Prevention of cardiotoxicity, İndividual approach to different types of cardiotoxicity