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Therapy-Related Cardio-Oncology in Hepatocellular Carcinoma: Mechanistic Insights and Strategies for Enhancing Efficacy While Reducing Toxicity

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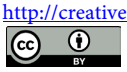

Abstract

Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality worldwide, and systemic therapies such as multikinase inhibitors and anthracyclines are central to the management of advanced disease. However, treatment-related cardiovascular toxicity has emerged as a major barrier to long-term benefit, highlighting the growing relevance of cardio-oncology in HCC. This review summarizes current knowledge on the mechanisms underlying HCC therapy-associated cardiotoxicity, focusing on ferroptosis, endoplasmic reticulum stress, mitochondrial dysfunction, and endothelial injury. Sorafenib-induced cardiotoxicity involves KLF11-mediated suppression of FSP1-dependent ferroptosis defenses, dysregulation of the ATF4-SLC7A11 axis, and PTX3-driven ERK/JNK signaling, whereas doxorubicin causes dose-limiting cardiomyopathy via oxidative stress, iron overload, and inflammatory pathways. We further discuss emerging mitigation strategies, including ferroptosis inhibitors, iron chelators, ion channel modulation, and rational drug combinations that enhance antitumor efficacy while attenuating myocardial damage. Special emphasis is placed on nanotechnology-based delivery systems—such as ligand-targeted, stimuli-responsive, and prodrug-based nanoparticles—which increase intratumoral drug deposition, prolong circulation time, and markedly reduce off-target, particularly cardiac, toxicity. Finally, we highlight the potential of biomarkers such as PTX3 and ATF4 for early cardiotoxicity monitoring and risk stratification, and outline key priorities for translational research and clinical validation.

Keywords

Hepatocellular Carcinoma, Cardio-Oncology, Cardiotoxicity, Sorafenib,

Doxorubicin, Ferroptosis, Nanomedicine

1. Introduction

Hepatocellular carcinoma (HCC), a highly heterogeneous malignancy arising from hepatocytes or intrahepatic biliary epithelium, ranks as the sixth most commonly diagnosed cancer and the third leading cause of cancer-related mortality worldwide. HCC accounts for approximately 90% of all primary liver tumors [1] [2]. As one of the malignancies with high global incidence and mortality, its therapeutic strategies are diverse and include surgical resection, local ablation, transarterial chemoembolization (TACE), and systemic pharmacologic therapy [3] [4]. In recent years, the advent of molecularly targeted agents and immune checkpoint inhibitors has markedly improved the prognosis of some patients with advanced disease; however, the accompanying cardiovascular toxicities have become increasingly prominent, underscoring the growing importance of cardio-oncology as a cross-disciplinary field [5] [6].

Tyrosine kinase inhibitors (TKIs), represented by sorafenib, can delay tumor progression but frequently induce adverse cardiovascular events such as hypertension, thromboembolic complications, and heart failure, which limit their clinical application and significantly impair patients' quality of life and treatment continuity [5] [7] [8]. Similarly, traditional chemotherapeutic agents such as doxorubicin remain integral to HCC management but are constrained by dose-dependent cardiotoxicity [9]-[11]. With rapid advances in nanotechnology and novel drug delivery systems, substantial progress has been made in elucidating the mechanisms underlying HCC treatment-related cardiotoxicity and in developing protective strategies to mitigate these effects [12]-[14]. This review aims to systematically summarize the mechanisms contributing to cardiovascular toxicity associated with HCC therapies and to discuss emerging strategies—including nanotechnology-based targeted delivery platforms, cardioprotective approaches for conventional chemotherapeutics, and novel drug combinations and biomarkers—thereby providing theoretical insights and research directions to inform future clinical practice.

2. Intervention Strategies for Sorafenib-Associated Cardiovascular Toxicity

Sorafenib, a multikinase inhibitor, exerts antitumor effects primarily by inhibiting vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), and kinases within the RAF/MEK/ERK signaling cascade. However, its cardiovascular toxicity has increasingly emerged as a major limitation to its clinical utility [7] [15]. Clinical investigations have demonstrated that sorafenib significantly elevates the risk of hypertension, arterial and venous thromboembolic events, and heart failure during treatment [16]-[18]. These car-

diovascular complications not only deteriorate patients' quality of life but may also necessitate dose reduction or treatment discontinuation, ultimately diminishing therapeutic efficacy.

The mechanisms underlying sorafenib-induced cardiotoxicity are complex and multifactorial, with ferroptosis identified as a key contributor [19] [20]. Sorafenib markedly increases the expression of Krüppel-like transcription factor 11 (KLF11) in cardiomyocytes. KLF11 suppresses the transcription of ferroptosis suppressor protein 1 (FSP1), thereby promoting lipid peroxidation and iron-dependent cell death [21]. Additionally, the endoplasmic reticulum (ER) stress-responsive transcription factor ATF4 is significantly upregulated following sorafenib exposure and modulates ferroptosis sensitivity by regulating SLC7A11 expression, glutathione synthesis, and redox homeostasis. Loss of ATF4 exacerbates sorafenib-induced myocardial injury, whereas its overexpression enhances cardiomyocyte survival, suggesting a protective role for the ATF4-SLC7A11 axis [22].

Beyond ferroptosis, sorafenib-induced cardiotoxicity also involves endothelial dysfunction, mitochondrial injury, ER stress, and impaired autophagic regulation [23]-[26]. Sorafenib treatment has been shown to reduce cardiomyocyte contractility, suppress sodium currents, and disrupt mitochondrial respiration, changes that correlate with upregulation of pentraxin 3 (PTX3). PTX3 colocalizes with CD44 and modulates ERK1/2 and JNK signaling, altering cytoskeletal remodeling and apoptotic protein expression, ultimately further impairing cardiac contractile performance. Clinically, elevated PTX3 levels have been reported in HCC patients receiving TKIs, with QTc prolongation observed in 38% of male and 33% of female patients, suggesting PTX3 as a potential biomarker for sorafenib-induced cardiotoxicity [27].

Although ferroptosis, endoplasmic reticulum (ER) stress, and mitochondrial injury are often described as independent mechanisms of sorafenib-induced cardiotoxicity, increasing evidence indicates that these pathways are mechanistically interconnected. Sorafenib-induced oxidative stress and calcium dysregulation promote mitochondrial dysfunction and excessive reactive oxygen species production, which in turn exacerbate ER stress and lipid peroxidation in cardiomyocytes [28]. Sustained ER stress further disrupts redox homeostasis and antioxidant defenses, thereby lowering the threshold for ferroptosis [22]. Notably, stress-responsive regulators such as ATF4 and KLF11 modulate key ferroptosis defense systems, including the SLC7A11-GPX4 axis and FSP1-dependent pathways, linking organelle stress responses to iron-dependent cell death [21]. Collectively, these findings support a feed-forward model in which mitochondrial injury and ER stress act as upstream triggers that converge on ferroptosis, amplifying sorafenib-associated myocardial damage.

Emerging studies have identified promising approaches for mitigating sorafenib-associated cardiotoxicity. Ferroptosis inhibitors and iron chelators have been shown to alleviate sorafenib-induced myocardial damage [21] [22]. Cardiac-specific overexpression of FSP1 or AAV9-mediated silencing of KLF11 significantly

improves cardiac dysfunction in sorafenib-treated mice [21]. Additionally, the TRPM7 inhibitor carvacrol (CARV) has demonstrated synergistic effects when combined with sorafenib; in a thioacetamide-induced HCC rat model, CARV/sorafenib combination therapy significantly prolonged survival, improved liver function, and ameliorated cardiac and hepatic histopathology [29]. These findings suggest that therapeutic strategies targeting ferroptosis regulation, ion channel inhibition, and combinatorial regimens may offer multiple viable avenues for protecting against sorafenib-induced cardiac injury in clinical practice.

3. Immune Checkpoint Inhibitors-Associated Cardiotoxicity in HCC

Immune checkpoint inhibitors (ICIs) have reshaped first-line systemic therapy for unresectable HCC. A clinical trial established atezolizumab plus bevacizumab as a standard first-line regimen, improving survival compared with sorafenib and accelerating global adoption of ICI-based strategies in HCC care [30]. As the use of ICIs expands in HCC, immune-related adverse events affecting the cardiovascular system have become increasingly relevant to contemporary HCC cardio-oncology practice.

ICI-associated cardiovascular adverse events (CVAEs) include myocarditis, pericarditis, arrhythmias and conduction disease, acute coronary syndromes/vasculitis, and new or worsening heart failure [31]-[33]. Although the overall incidence is low, the clinical impact is disproportionate because ICI-myocarditis can be fulminant and carries high short-term mortality. In a large systematic review/meta-analysis of clinical trials, ICI-related CVAEs occurred in approximately ~1% of treated patients, and myocarditis was associated with substantial fatality [33]. Importantly, dual ICI regimens (PD-1/PD-L1 plus CTLA-4 blockade) appear to confer a higher myocarditis risk than monotherapy, reinforcing the need for heightened vigilance when combination immunotherapy is used in HCC or in clinical trial settings.

Mechanistically, ICI-myocarditis is thought to reflect immune disinhibition with T-cell-mediated myocardial inflammation, potentially facilitated by shared antigens between tumor and myocardium and loss of peripheral tolerance [34]. Given the severe consequences of missed early myocarditis, a structured surveillance strategy is recommended, particularly during the first weeks to months of therapy. Contemporary cardio-oncology guidance emphasizes baseline cardiovascular assessment (history, risk factors, prior cardiotoxic therapies, and ECG), consideration of echocardiography in patients with cardiac history or planned combination regimens, and biomarker-based monitoring (notably troponin) when feasible. In HCC, these principles should be adapted to the clinical reality that many patients have advanced age, metabolic syndrome, cirrhosis-associated hemodynamic changes, and competing risks that complicate symptom interpretation (fatigue, dyspnea, volume shifts). Therefore, low thresholds for ECG/troponin testing and early cardiology consultation are warranted if new chest pain,

dyspnea out of proportion to liver disease status, palpitations/syncope, or unexplained biomarker elevation occurs [35]. As ICIs are now integral to first-line HCC management, systematic cardiovascular risk assessment, early-cycle monitoring (especially troponin/ECG), and rapid response pathways for suspected myocarditis should be embedded into routine HCC care. Adoption of guideline-informed algorithms and multidisciplinary collaboration between oncology, hepatology, and cardio-oncology is essential to maximize anticancer benefit while minimizing avoidable cardiac morbidity and mortality [36].

4. Applications of Nanotechnology in Enhancing Efficacy and Reducing Cardiotoxicity in Hepatocellular Carcinoma Therapy

Nanotechnology has demonstrated substantial potential in improving the therapeutic efficacy of hepatocellular carcinoma (HCC) treatments while mitigating associated cardiotoxicity. Through strategies such as active targeting, stimuli-responsive drug release, and multifunctional synergistic approaches, nanocarrier systems enable precise drug delivery [37] [38]. The design of novel nanoplatforms not only enhances drug accumulation within tumors but also markedly decreases off-target toxicity, particularly to cardiac tissue [39] [40]. Compared with conventional administration routes, nanodelivery systems optimize pharmacokinetic behaviors—prolonging circulation time, improving tumor uptake, and enhancing tissue penetration—thereby emerging as a key avenue in advancing the concept of efficacy enhancement and toxicity reduction.

Active-targeting nanomedicines utilize surface-modified ligands to selectively deliver therapeutic agents to tumor tissues, increasing intratumoral drug concentration while minimizing exposure to normal organs. Glycyrrhetinic acid (GA)-based targeting strategies have gained considerable attention. Leveraging GA's inherent bioactivity and hepatocyte affinity, researchers constructed a polymerizable GA monomer to form a poly (glycyrrhetic acid) (PGA) carrier, which was subsequently PEGylated to develop the PGA-PEG-GA nanoplatform. This system achieves nearly 100% theoretical drug-loading efficiency and exhibits an ultra-low critical micelle concentration, enhancing both encapsulation capacity and *in vivo* stability [41] [42]. Doxorubicin-loaded PGA-PEG-GA nanoparticles (DOX@PGA-PEG-GA) demonstrated approximately 2.5-fold higher cytotoxicity toward tumor cells compared with normal cardiomyocytes and reduced doxorubicin-induced cardiomyocyte apoptosis by 54%. *In vivo*, the nanoplatform achieved a tumor inhibition rate of 89.7% ± 5.2%, with an 18.3-fold increase in tumor drug accumulation relative to free doxorubicin, while nearly eliminating cardiotoxicity [41]. These findings highlight the promise of GA-based integrated "structure-function-safety" nanodesign for achieving selective and safer HCC therapy.

Lactoferrin (Lf), a natural ligand with affinity for hepatocyte-specific receptors, has also been widely utilized in designing liver-targeted nanocarriers [43]. An Lf-functionalized DSPE-mPEG liposomal system encapsulating norcantharidin acid

(NCA) achieved an encapsulation efficiency of 89.3% ± 1.25% and an Lf conjugation efficiency of over 65.97%, demonstrating excellent long-term and serum stability with <10% variation in dynamic size and encapsulation rate [44]. Compared with injectable sodium norcantharidate, NCA-Lips-Lf significantly enhanced tumor accumulation and prolonged systemic circulation, increasing AUC and $t_{1/2}$ by 4.28- and 5.17-fold, respectively. Animal studies showed a tumor inhibition rate of 85.29% without detectable cardiotoxicity, vascular irritation, or nephrotoxicity. These results underscore the value of Lf-mediated active targeting in improving therapeutic efficacy while maintaining favorable safety profiles.

Stimuli-responsive nanosystems enable controlled drug release tailored to the unique features of the tumor microenvironment, thereby further improving therapeutic precision [45]. Researchers have developed mixed micelle nanoparticles (DCMMs), composed of polymer-ss-DOX and polymer-Ce6 prodrugs, functionalized with nimotuzumab for targeted delivery. The reductive cleavage of disulfide bonds in the tumor microenvironment triggers DOX release, while Ce6 generates singlet oxygen under laser irradiation to augment cytotoxicity. Biodistribution studies confirmed significantly enhanced intratumoral accumulation following surface targeting. *In vivo*, DCMMs markedly inhibited tumor growth and significantly reduced cardiotoxicity compared with free drugs [37]. Such systems demonstrate the advantages of tumor-specific, on-demand drug release, offering potential to expand the therapeutic window.

Multifunctional combination strategies leverage multiple therapeutic modalities to achieve synergistic antitumor effects while reducing toxicity [46]. A Timosaponin AIII (TAIII)-based multifunctional liposomal system has innovatively utilized TAIII as both a bilayer stabilizer—substituting cholesterol—and a chemotherapeutic agent to synergize with doxorubicin. TAIII and doxorubicin exhibited synergistic cytotoxicity in HCC cells at molar ratios of 1:1, 1:2, and 1:4. In subcutaneous and orthotopic tumor models, TAIII liposomes combined with low-dose DOX (2 mg/kg) significantly enhanced antitumor activity without detectable cardiotoxicity. Moreover, mild photothermal heating accelerated the release of both TAIII and DOX within tumors, while TAIII-enhanced cellular permeability facilitated increased DOX uptake, further amplifying synergy [47]. Overall, this multifunctional liposomal system integrates "structural stability + synergistic chemotherapy + photothermal enhancement" to improve therapeutic outcomes with advantageous safety.

Physical-energy-assisted nanodelivery approaches offer new pathways to improve intratumoral drug penetration. Multifocused acoustic radiation force impulse (MF-ARFI) applied to murine hepatic xenografts enhanced the delivery efficiency of PEGylated liposomal DOX (DOX@Lip) by modulating tumor permeability and retention. MF-ARFI pretreatment facilitated measurable displacement of DOX@Lip in tumor-mimicking matrices and saline. Mice receiving combined MF-ARFI and DOX@Lip therapy exhibited significantly reduced tumor growth and only mild weight loss. Histological analysis showed no increase in myocardial

injury compared with DOX@Lip alone; however, MF-ARFI treatment decreased BCL-2 expression and elevated the BAX/BCL-2 ratio in tumor tissues, enhancing the antitumor effect [48]. These results suggest that modulating tumor tissue properties using physical energy represents an effective means to improve nanodrug delivery efficiency.

Despite promising preclinical efficacy, the clinical translation of nanomedicines for reducing therapy-induced cardiotoxicity faces multiple challenges. First, large-scale, reproducible manufacturing with consistent physicochemical properties remains difficult due to complexity in formulation and batch-to-batch variability. Second, regulatory approval pathways for nanotherapeutics are often prolonged and uncertain, as traditional frameworks may not fully capture the unique pharmacokinetic and biodistribution characteristics of nanoscale platforms. Finally, defining patient selection criteria for nanomedicine application is hindered by limited predictive biomarkers and lack of stratified clinical evidence, which complicate trial designs and clinical decision-making. Addressing these translational hurdles will be essential for successful integration of nanotechnology-based cardioprotective strategies into routine clinical practice.

5. Doxorubicin-Induced Cardiotoxicity and Nanotechnology-Based Detoxification Strategies

Doxorubicin, a classic anthracycline chemotherapeutic, remains an important component of hepatocellular carcinoma (HCC) treatment. However, its dose-dependent cardiotoxicity severely restricts its clinical application. The mechanisms underlying doxorubicin-induced cardiac injury are multifaceted, involving oxidative stress, mitochondrial damage, dysregulated iron metabolism, and inflammatory responses. A comprehensive understanding of these mechanisms is crucial for developing safer therapeutic alternatives and detoxification strategies [49] [50]. Clinically, doxorubicin administration is associated with irreversible congestive heart failure and cardiomyopathy, representing its most significant cumulative dose-limiting toxicity [51] [52].

Nanocarrier-based drug delivery systems provide promising approaches to mitigate doxorubicin cardiotoxicity. Among them, bacterial magnetosomes (BMs)—natural magnetic nanoparticles characterized by intrinsic magnetism, biocompatibility, and highly ordered lipid membrane structures—have been explored as targeted delivery platforms. Doxorubicin-loaded magnetosomes (DBMs) exhibited potent antitumor activity in H22 tumor-bearing mice, achieving a tumor inhibition rate of 86.8%, outperforming free doxorubicin (78.6%) and BMs alone (4.3%) [53]. Histopathological analysis revealed markedly reduced cardiac toxicity with DBMs compared with free doxorubicin, highlighting the potential of magnetosome-based nanocarriers to enhance therapeutic efficacy while improving cardiac safety.

Self-assembled nanostructures derived from hyaluronic acid (HA) conjugated with glycyrrhetinic acid (GA) also represent an effective doxorubicin delivery

strategy. The HA-glycyrrhetinic acid succinate (HSG) nanoparticles significantly prolonged doxorubicin circulation time and increased its hepatic accumulation [39]. Pharmacokinetic assessments indicated that HSG/DOX substantially increased the area under the curve (AUC), while biodistribution studies demonstrated reduced drug accumulation in the heart and kidneys, thereby lowering associated toxicities. This platform effectively expands the therapeutic window of doxorubicin and addresses key obstacles in its clinical application.

Combination therapy strategies can further enhance antitumor efficacy and enable dose reduction, thereby decreasing systemic toxicity. Ellagic acid (EA), a natural polyphenolic compound, has demonstrated strong synergistic interactions when combined with doxorubicin or cisplatin. In HCC cell lines such as HepG2 and SMMC7721, EA potentiated the cytotoxic activities of doxorubicin and cisplatin while exerting relatively low toxicity toward normal hepatocytes (HL-7702) [54]. Mechanistically, the synergistic effect is associated with the activation of mitochondrial cytochrome c-mediated apoptotic pathways. In nude mouse xenograft models, EA combined with low-dose doxorubicin effectively inhibited tumor growth without inducing the cardiotoxicity typically seen with high-dose doxorubicin therapy, supporting its potential as a feasible low-dose, high-efficacy strategy.

Chloroquine (CQ) has also been shown to enhance doxorubicin's antitumor effects in HCC models. CQ sensitizes tumor cells to doxorubicin by upregulating the TRAIL/TRAILR2 signaling pathway. In thioacetamide-induced HCC models, CQ/DOX combination therapy significantly reduced hepatic malondialdehyde (MDA) levels, decreased serum CK-MB and LDH activity, and increased hepatic glutathione (GSH) content [55]. These changes indicate that CQ can partially counteract doxorubicin-induced oxidative stress and cardiomyocyte injury, thereby enhancing antitumor efficacy while improving cardiac safety.

Although the systemic use of doxorubicin in hepatocellular carcinoma (HCC) has become increasingly limited due to its modest survival benefit and well-recognized dose-dependent cardiotoxicity, it remains a cornerstone agent in locoregional therapies, particularly transarterial chemoembolization (TACE) [56] [57]. In the setting of TACE, doxorubicin is administered at high intra-tumoral concentrations to achieve effective cytotoxicity while minimizing systemic exposure; however, repeated procedures and incomplete vascular confinement can still result in cumulative systemic leakage [58]. Consequently, doxorubicin-associated cardiotoxicity remains a clinically relevant concern in patients undergoing multiple TACE sessions, especially those with pre-existing cardiovascular comorbidities.

6. Advances in Novel Drug Combinations, Therapeutic Compounds, and Biomarkers for Prevention and Management

The development of novel drug combinations and therapeutic compounds offers new avenues for preventing and managing treatment-associated cardiotoxicity in

hepatocellular carcinoma (HCC). At the same time, the identification of emerging biomarkers provides opportunities for early detection and timely intervention [29] [59]. Multitarget inhibition strategies, which simultaneously modulate multiple signaling pathways, enable synergistic antitumor effects while reducing toxicity [60]. Dual PARP/PI3K inhibitors exemplify such an approach; by concurrently regulating DNA repair and proliferative signaling pathways, these agents demonstrate potent anticancer activity. Representative compounds 9a and 23a exhibited strong antiproliferative effects in both BRCA-deficient and BRCA-proficient tumor cell lines and demonstrated comparable *in vivo* efficacy in MDA-MB-468 xenograft models [61]. Notably, compound 23a showed superior kinase selectivity and reduced cardiotoxicity, positioning it as a promising candidate with improved safety profiles. Multitarget inhibition thus holds potential for enhancing therapeutic outcomes while minimizing the toxic burden associated with high-dose monotherapy.

Natural product derivatives have also been explored to achieve safer HCC treatment strategies. Resibufogenin (RBG), an active anticancer component derived from traditional Chinese medicine, has long been limited by cardiotoxicity and poor aqueous solubility. These challenges were addressed by developing galactose-decorated SP188-PLGA nanoparticles (RGPPNs), which exhibited superior cellular uptake, cytotoxicity, and apoptosis-inducing capabilities in vitro, as well as potent therapeutic efficacy in HCC mouse models [60]. Such carrier systems not only elevate the therapeutic index of natural compounds but also provide new solutions for reducing drug-related toxicity. Similarly, a redox-responsive self-assembled prodrug nanoparticle system (MPSSV-NPs), constructed from a periplocymarin-vitamin E conjugate via a single disulfide linkage, significantly prolonged circulation time and enhanced tumor distribution. In mice bearing malignant H22 tumors, MPSSV-NPs effectively inhibited tumor growth without inducing notable systemic toxicity [62]. By integrating prodrug design with redox-responsiveness, this system improves drug selectivity and mitigates adverse effects.

The discovery of predictive biomarkers has opened new possibilities for early identification and risk stratification of cardiotoxicity associated with HCC therapies. Pentraxin 3 (PTX3) has been shown to play a critical role in sorafenib-induced myocardial injury by activating ERK/JNK signaling pathways, leading to cytoskeletal remodeling, impaired contractile function, and mitochondrial dysfunction [27]. Clinical studies further demonstrate that patients receiving tyrosine kinase inhibitors exhibit significantly elevated PTX3 levels, accompanied by QTc prolongation, supporting its potential as a toxicity-monitoring biomarker, as it has been mechanistically linked to tyrosine kinase inhibitor-associated cardiomyocyte contractile impairment and mitochondrial dysfunction and correlates with electrophysiological abnormalities during therapy. Additionally, ATF4, a key regulator of endoplasmic reticulum stress, modulates ferroptosis sensitivity through the SLC7A11-glutathione metabolic axis. Upregulation of ATF4 exerts protective effects against sorafenib-induced cardiomyocyte injury, while knockdown of

ATF4 exacerbates ferroptotic damage [22]. Thus, the ATF4-SLC7A11 axis not only represents a mechanistic therapeutic target but may also serve as a biomarker for pre-treatment risk stratification and for identifying patients with heightened vulnerability to sorafenib-related myocardial injury.

7. Conclusion and Future Perspectives

As an emerging interdisciplinary field, cardio-oncology in the context of hepatocellular carcinoma (HCC) has gained increasing importance with the widespread application of targeted therapies and immunotherapies. Current evidence demonstrates that multikinase inhibitors (TKIs), represented by sorafenib, and traditional anthracyclines play critical roles in prolonging survival in patients with advanced HCC; however, their associated cardiovascular toxicities have become key limiting factors affecting treatment adherence, quality of life, and long-term outcomes. Mechanistic investigations reveal that ferroptosis, endoplasmic reticulum stress, mitochondrial dysfunction, and endothelial injury collectively contribute to the development of cardiotoxicity, suggesting that risk evaluation for systemic HCC therapies should be grounded in an integrated, multi-mechanism framework. In terms of preventive and therapeutic strategies, ferroptosis inhibitors, molecular interventions targeting the ATF4-SLC7A11 axis, TRPM7 channel inhibitors, and various drug combination regimens have shown promising cardioprotective effects in preclinical studies. Concurrently, rapid advances in nanotechnology have provided new avenues for enhancing therapeutic efficacy while mitigating toxicity. Active-targeting nanocarriers, tumor microenvironment-responsive release systems, and multifunctional synergistic platforms enable significant improvements in intratumoral drug accumulation while minimizing cardiac exposure, thereby expanding the therapeutic window. Prodrug-based nanostructures and physical energy-assisted delivery approaches further optimize pharmacokinetics and tissue distribution. In addition, biomarkers such as PTX3 and ATF4 offer potential tools for early cardiotoxicity monitoring and risk stratification, with prospects for incorporation into clinical evaluation and intervention frameworks. In addition to drug-specific mechanisms, patient-related factors substantially influence the risk, presentation, and management of therapy-induced cardiotoxicity in hepatocellular carcinoma. Many patients with HCC are elderly and have a high burden of cardiovascular comorbidities, including hypertension, coronary artery disease, diabetes mellitus, and metabolic syndrome. Hepatic dysfunction can further alter drug metabolism and systemic exposure, thereby amplifying cardiovascular toxicity. Prior exposure to cardiotoxic agents, reduced baseline left ventricular function, and pre-existing arrhythmias also increase vulnerability during systemic therapy. These considerations underscore the importance of baseline cardiovascular risk assessment, individualized treatment selection, and close cardio-oncology collaboration when managing patients with advanced HCC.

Despite encouraging progress, several challenges remain. Most cardioprotective strategies are still limited to cellular and animal studies, with a lack of large-scale

clinical validation. The synergistic mechanisms underlying combined therapeutic modalities are not yet fully elucidated. Moreover, the long-term safety, translational potential, and manufacturing standardization of nanodelivery systems continue to pose significant challenges. Future studies should focus on: 1) dissecting the molecular mechanisms of treatment-associated cardiotoxicity, particularly the synergistic toxicity arising from multimodal therapies; 2) developing highly precise and multifunctional nanodelivery systems capable of integrating both therapeutic and diagnostic functions; 3) establishing robust biomarker-based monitoring systems to enable early detection and intervention; 4) conducting large-scale clinical trials to validate novel cardioprotective strategies; and 5) strengthening multidisciplinary collaboration to facilitate the formulation of clinical practice guidelines in cardio-oncology. Through the close integration of basic research and clinical practice, it may ultimately be possible to maximize therapeutic efficacy for HCC while minimizing the risk of cardiotoxicity.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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