Review

Chemotherapy-Induced Liver Injury: Unveiling Emerging Mechanisms and Exploring Mitigation Strategies

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ABSTRACT

In this comprehensive overview of chemotherapy-induced liver injury, various classes of chemotherapeutic agents were reviewed to elucidate the complex cellular events contributing to hepatotoxicity and potential mitigation strategies. Alkylating agents, such as cyclophosphamide and busulfan, exhibited diverse mechanisms, with compounds like fucoidan and pyrroloquinoline quinone demonstrating protective effects through modulation of Nrf2/HO-1 and NF-κB pathways. Methotrexate-induced hepatotoxicity, characterized by oxidative stress and inflammation, highlighted the importance of addressing disruptions in lipid metabolism and the gut-liver axis. The multifaceted nature of cisplatin-induced liver damage emphasized the role of gastrointestinal microbiota and therapeutic interventions like curcumin. Anthracyclines, including doxorubicin and epirubicin, posed challenges in mitigating severe hepatotoxicity, with potential protective agents identified. Topoisomerase inhibitors, plant alkaloids, and antitumor antibodies showcased diverse impacts on liver function, emphasizing the need for tailored interventions. Targeted therapies, immune checkpoint inhibitors, and miscellaneous agents like L-asparaginase revealed distinct patterns of hepatotoxicity, prompting a nuanced understanding of patient safety. This comprehensive exploration offers a foundation for future research and therapeutic developments to enhance patient outcomes during chemotherapy.

Keywords: Antioxidants, Chemotherapy-induced liver injury, Hepatotoxicity, liver protection

1. Introduction:

Chemotherapy has revolutionized the treatment landscape for various malignancies, offering improved patient outcomes and prolonged survival (1). However, along with its undeniable benefits, chemotherapy is also associated with a spectrum of adverse effects, one of which is chemotherapy-induced liver injury (CILI) (2, 3). Liver injury resulting from chemotherapy poses a significant clinical challenge, as it can lead to treatment interruptions, compromised therapeutic efficacy, and, in severe cases, life-threatening complications(3-6). Understanding the underlying mechanisms of CILI and developing effective mitigation strategies are crucial steps toward improving patient safety and treatment outcomes.

The liver is essential for drug metabolism, detoxification, and overall homeostasis in the human body (7). Because it is constantly exposed to high concentrations of chemotherapeutic drugs, it is vulnerable to drug-induced injury (5). CILI is caused by a complex and heterogeneous set of processes that involve direct hepatotoxic effects, immune-mediated responses, oxidative stress, mitochondrial dysfunction, and impaired drug metabolism (5, 8, 9). Understanding these underlying pathways is critical for developing targeted therapies and individualized approaches to reduce liver damage while optimizing therapeutic efficacy.

In recent years, significant progress has been made in our comprehension of the emerging mechanisms that contribute to CILI. Significant progress has been made in elucidating the complex interplay between cellular signaling pathways, genetic factors, and environmental factors that influence liver injury (3, 10-12). These discoveries have illuminated the complexity of CILI and opened the door to the investigation of novel therapeutic strategies.

To address the challenge of CILI, various mitigation strategies have been proposed and implemented in clinical practice. These strategies include dose modifications, supportive care measures, and hepatoprotective interventions. In addition, novel approaches such as antioxidant therapy, targeted drug delivery systems, and the use of hepatoprotective agents have shown promise in minimizing liver injury while maintaining treatment efficacy. We will explore these emerging mitigation strategies and evaluate their potential clinical applications.

2. Mechanisms of Chemotherapy-Induced Liver Injury

2.1. Direct hepatotoxic effects of chemotherapeutic agents

Chemotherapeutic agents can cause either hepatocellular damage or cholestasis, or both. Phase I drug metabolism refers to the early oxidation, reduction, or hydrolysis of xenobiotics. This process occurs often in the liver, and liver impairment, when it occurs, is most likely the result of a phase I drug metabolite's direct toxicity (13).

Various pathways can be utilized by chemotherapeutic drugs with direct hepatotoxic effects to cause liver damage (4). Consequently, vigilant surveillance and dose reduction are required. The production of reactive metabolites or intermediates during drug metabolism is a frequent mechanism. These reactive metabolites can covalently bind to macromolecules within cells, such as proteins, DNA, and lipids, resulting in cellular dysfunction, oxidative stress, and inflammation. Alkylating drugs, antimetabolites, and specific targeted therapies are examples of chemotherapeutic agents that are known for their direct hepatotoxic effects, these drugs can also cause mitochondrial dysfunction, resulting in diminished energy generation and damage to hepatocytes. In addition, certain alkylating drugs can directly target hepatic stellate cells, inducing fibrosis and scarring of the liver. Consequently, vigilant surveillance and dose reduction are required (3, 14, 15).

Alkylating agents, such as cyclophosphamide and busulfan, can cause liver damage by interfering with DNA replication and repair mechanisms by forming DNA crosslinks and adducts. These drugs can also cause mitochondrial dysfunction, resulting in diminished energy generation and damage to hepatocytes. In addition, certain alkylating drugs can directly target hepatic stellate cells, inducing fibrosis and scarring of the liver (16-18).

Antimetabolites, such as methotrexate and 5-fluorouracil, can inhibit nucleotide synthesis and DNA replication in hepatocytes and cancer cells. These agents have the potential to cause hepatocellular damage and liver dysfunction. Methotrexate can cause hepatic necrosis and steatosis, further compromising liver function (6, 14, 19).

2.2. Oxidative stress and its contribution to liver injury

Although chemotherapy is effective against cancer cells, it can also cause an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defenses of the body.

This imbalance can result in oxidative stress, which is characterized by excessive ROS production, which can cause liver cell injury (20). Antioxidants are frequently depleted after cancer therapy due to overconsumption by chemotherapeutic drugs and irradiation, resulting in a decrease in radical-trapping capacity, accumulation of high levels of reactive oxygen species (ROS), and elevation of the lipid peroxidation product malondialdehyde (MDA) in plasma (21).

Doxorubicin is a well-known anti-cancer agent, but its metabolism can generate reactive oxygen species (ROS). These reactive oxygen species can cause oxidative injury by attacking lipids, proteins, and DNA within hepatocytes. As a result, the liver is susceptible to cellular dysfunction, inflammation, and necrosis (22, 23).

In addition, chemotherapeutic drugs, such as methotrexate, can interfere with folate metabolism. They indirectly induce oxidative stress as a result. When folate metabolism is impaired, glutathione, an antioxidant molecule that is essential for neutralizing ROS, can be depleted. Reduced glutathione levels render hepatocytes susceptible to oxidative damage, which contributes to liver impairment (24-26).

Chemotherapy drugs frequently overwhelm the liver's antioxidant defense mechanisms, including superoxide dismutase (SOD) and catalase. This increases the oxidative stress imposed on liver cells. As a result, lipid peroxidation may occur, producing toxic byproducts that harm cellular membranes and exacerbate liver damage (27, 28).

2.3. Inflammation and immune-mediated responses

Inflammation and immune-mediated reactions play crucial roles in the body's innate defensive mechanisms against pathogens and tissue damage (29). However, it has been observed that with the administration of chemotherapy treatment, these biological processes may become dysregulated, hence possibly causing liver injury (30).

Chemotherapeutic drugs have the potential to elicit an inflammatory response in the liver via several mechanisms (3, 31). A frequently observed process involves the stimulation of indigenous immune cells present in the liver, including Kupffer cells, hepatic stellate cells, and sinusoidal endothelial cells. These cells can identify chemotherapeutic drugs or their metabolites as foreign, thereby activating an immune response. Initiating an inflammatory cascade, the

activation of pattern recognition receptors such as toll-like receptors (TLRs) can result in the release of pro-inflammatory cytokines, chemokines, and other immune mediators (31-34).

Chemotherapy-induced liver inflammation is characterized by the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). Cytokines function as signaling molecules that have the ability for attracting immune cells, including neutrophils, monocytes, and lymphocytes, to the liver. The increased presence of immune cells has the potential to exacerbate the inflammatory response, resulting in the deterioration of tissue (32, 35).

Over time, chemotherapy-induced chronic inflammation can exacerbate liver damage and promote the development of fibrosis and cirrhosis. Persistent activation of inflammatory pathways can result in the activation of hepatic stellate cells, which are responsible for the excessive production of extracellular matrix proteins and thus contribute to liver fibrosis (36, 37).

Certain chemotherapy medications can induce cell death and the release of tumor-associated antigens or damage-associated molecular patterns (DAMPs). These DAMPs can stimulate the innate immune system, resulting in the recruitment and activation of immune cells, especially dendritic cells. These cells are capable of presenting antigens associated with tumors to T lymphocytes, thereby initiating an adaptive immune response. However, this immune response can sometimes target not only cancer cells but also normal hepatocytes, leading to immune-mediated hepatocellular injury (38-40).

2.4. Mitochondrial dysfunction and its impact on liver toxicity

Mitochondrial dysfunction is a significant factor contributing to chemotherapy-induced liver toxicity. Mitochondria are the energy-producing organelles within liver cells, and their proper functioning is essential for maintaining cellular energy levels and overall liver health. Multiple chemotherapeutic agents can impair mitochondrial function, resulting in decreased energy production, oxidative stress, and hepatocellular injury (41, 42).

Doxorubicin can accumulate in mitochondria and disrupt the electron transport chain (ETC), which is vital to ATP synthesis. This mitochondrial respiration disruption results in decreased ATP production, increased oxidative stress, and hepatocellular damage (43, 44). Additionally, drugs such as cisplatin, mitomycin C, tamoxifen, and trastuzumab have been shown to target

mitochondrial DNA (mtDNA), resulting in mitochondrial dysfunction. This disruption in mtDNA can impair the ETC and decrease ATP production, thereby contributing to liver injury (41, 45-48).

Multiple aspects of mitochondrial dysfunction influence liver toxicity. Protein synthesis, ion transport, and cellular homeostasis are all negatively impacted by ATP deficiency. Insufficient energy levels can initiate cellular dysfunction and cell death pathways such as apoptosis and necrosis. In addition, mitochondrial dysfunction can result in the production of reactive oxygen species (ROS) as a byproduct of impaired ETC function. ROS can cause oxidative stress, which can result in cellular damage, lipid peroxidation, and DNA damage, thereby exacerbating liver damage (9, 49, 50).

3. Examples of chemotherapy-induced liver injury: recent mechanisms and potential mitigation strategies

3.1. Alkylating agents

The fact that cyclophosphamide is known to cause liver damage among other adverse effects has prompted research into potential ameliorative interventions. In a series of studies, several compounds, including fucoidan, pyrroloquinoline quinone (PQQ), and N-acetylcysteine, were evaluated for their ability to inhibit the cellular events associated with cyclophosphamide-induced liver toxicity. Fucoidan demonstrated the ability to decrease liver and kidney toxicity indices, oxidative stress, and inflammatory cytokine levels via the up-regulation of the Nrf2/HO-1 pathway and the inhibition of the TLR4/NF-κB pathway. PQQ, on the other hand, exhibited a similar protective effect by activating the Nrf2-mediated antioxidant response pathway and inhibiting the NF-κB-mediated inflammation pathway, thereby reducing liver damage. In miniature pig models, N-acetylcysteine was found to increase immune cell numbers, decrease TNF- α production, and decrease markers of oxidative stress and liver injury, suggesting its potential therapeutic application for modulating immune reactions and mitigating the cellular events associated with cyclophosphamide-induced liver injury in both clinical and livestock settings. These findings highlight the importance of investigating novel strategies to mitigate the cellular events linked to cyclophosphamide-induced liver injury, offering hope for improved patient outcomes (51-53).

Busulfan-induced liver toxicity is characterized by a spectrum of complex cellular events that may have severe consequences. Although hepatotoxicity resulting from busulfan conditioning

for transplantation remains highly variable, recent research sheds light on key mechanisms. Alginate oligosaccharides (AOS) have been identified as a promising candidate for mitigating busulfan-induced liver injury, specifically by inhibiting inflammation and boosting the immune system. In contrast, studies involving primary human hepatocytes (PHH) and HepaRG cells indicate that busulfan can induce hepatic steatosis by interfering with lipid metabolism and endoplasmic reticulum (ER) stress. In addition, investigation into Pirfenidone's protective potential reveals a promising strategy for mitigating busulfan-induced hepatotoxicity, specifically by targeting hepatic sinusoidal endothelial cells (HSECs) and inhibiting collagen formation and hepatic stellate cell activation. These findings highlight the multifaceted nature of busulfan-induced liver injury and the significance of prospective therapeutic interventions, providing new avenues for enhancing patient outcomes in the context of transplantation conditioning (54-56).

Recent research reveals the multifaceted nature of cisplatin-induced liver damage. Curcumin and fraxin nano-formulations, as well as natural products abundant in antioxidants and anti-inflammatory properties, have the potential to reduce hepatic injury via mechanisms involving the reduction of oxidative stress, inflammation, and modulation of apoptotic pathways. Notably, as revealed by metagenomic studies, gastrointestinal microbiota plays a pivotal role in mediating inflammation and oxidative stress, thereby influencing an individual's susceptibility to cisplatin hepatotoxicity. In addition, L-carnitine, a pleiotropic agent, activates Wnt signaling pathways, thereby mitigating cisplatin-induced renal and hepatic damage. These results highlight the complex interplay of cellular events that contribute to cisplatin-induced liver injury and the promise of diverse therapeutic approaches to mitigate its hepatotoxic effects (57-61).

3.2. Antimetabolites

Methotrexate poses a significant risk of liver damage in patients, particularly those receiving long-term therapy. There is a cascade of molecular mechanisms involved in the complex cellular events that contribute to methotrexate-induced hepatotoxicity. Accumulation of intracellular methotrexate-polyglutamate induces oxidative stress and inflammation in hepatocytes, which results in steatosis, fibrosis, and apoptosis. This oxidative stress is caused by lipid peroxidation and the consequent release of reactive oxygen species, in conjunction with the suppression of antioxidant response elements. Contributing to the inflammatory response are pro-inflammatory signaling pathways and cytokines, such as TNF -α, NF- -κB, and interleukins. Depletion of hepatic

folate levels inhibits RNA and DNA synthesis, resulting in hepatocyte mortality, whereas inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase enzyme results in adenosine accumulation, activation of hepatic stellate cells, and fibrosis of the liver (62). Furthermore, methotrexate-induced apoptosis in hepatocytes is mediated by caspase 3 activation via the intrinsic pathway (25). Clinically, methotrexate may exacerbate non-alcoholic fatty liver to non-alcoholic steatohepatitis with fibrosis, highlighting the need for vigilant liver injury surveillance in patients with preexisting risk factors (62). In addition, evidence indicates that the gut-liver axis and gut microbiota are crucial in methotrexate-induced liver injury, with gut microbiota disruption contributing to inflammation and oxidative stress (63). Multiple strategies, including natural compounds, probiotics, and antioxidants, have the potential to mitigate methotrexate-induced liver injury via mechanisms such as oxidative stress mitigation, gut-liver balance restoration, and anti-inflammatory effects (64-66).

5-Fluorouracil is known to cause liver damage via complex processes within cells. The response of the liver to 5-fluorouracil is characterized by oxidative stress and impaired mitochondrial function (67). Additionally, 5-Fluorouracil induces notable changes in liver texture, detectable via computed tomography texture analysis, revealing early cellular responses before traditional markers of liver injury become evident (68). The total anthraquinone extract of Cassia seeds provided protection against 5-Fluorouracil-induced liver injury through an orchestrated response of effective components, including aurantio-obtusina, rhein, emodin, chrysophanol, and physcion, which mitigate the effects of 5-Fluorouracil and liver damage (69). Notably, Nigella Sativa and onion extract, along with Angelica polysaccharide, exhibit antioxidative, anti-lipid peroxidative, and anti-inflammatory properties, thereby reducing liver injury induced by 5-Fluorouracil via histological enhancements and alterations in liver enzymes, inflammatory markers, and antioxidant responses (70).

In general, capecitabine is recognized for its mild hepatotoxicity. However, case reports presented highlighted instances of severe and delayed acute liver injury associated with capecitabine therapy. A patient with metastatic breast cancer developed a severe drug-induced liver injury accompanied by dangerously elevated liver enzyme levels. The rapid recovery of the patient upon discontinuation of capecitabine suggests a link between the drug and the acute toxic liver reaction. During the fifth cycle of capecitabine, a patient with colon cancer developed a delayed

acute hepatic injury characterized by fatigue and jaundice. Notably, discontinuing capecitabine was enough to rectify the liver damage. These cases highlight the need for increased vigilance in monitoring for severe liver toxicity during capecitabine treatment, despite the drug's generally favorable safety profile, and the significance of discontinuing the drug promptly when necessary (71, 72).

3.3. Anthracyclines

Doxorubicin is a potent chemotherapeutic agent with life-saving potential, but its clinical application is hindered by severe hepatotoxicity. Several studies have delved into the cellular mechanisms underlying doxorubicin-induced liver injury. These investigations have identified a series of cellular events contributing to hepatotoxicity, including hepatocyte damage, oxidative stress, inflammation, and apoptosis. Notably, the toxic effects of doxorubicin extend beyond the liver itself, impacting DNA methylation and chromosomal stability. While the administration of creatine, pregnenolone, bone-marrow-derived mesenchymal stem cells, diosmin, misoprostol, astaxanthin, and urolithin A demonstrated hepatoprotective properties by alleviating oxidative stress, inflammation, and apoptosis, miR-128-3p emerged as a potential therapeutic target to mitigate doxorubicin-induced liver injury (73-82).

Epirubicin can cause liver damage, and various research has been conducted to better understand the biological mechanisms that cause this condition. Paeonol, an extract from Moutan Cortex, has shown hepatoprotective potential in breast tumor-bearing mice by alleviating epirubicin-induced liver damage. It protects the body by altering lipid, amino acid, and energy metabolism. Furthermore, paeonol appears to suppress the adenosine monophosphate-activated protein kinase/mammalian target of the rapamycin (AMPK/mTOR) signaling pathway, protecting liver function (83). In addition, the impact of hormonal status, particularly estradiol levels, was studied in breast cancer patients receiving epirubicin treatment. Surprisingly, higher estradiol levels in premenopausal women were linked to a lower risk of epirubicin-induced liver impairment, implying that hormonal considerations are at work (84). Genetic and clinical risk factors were also scrutinized to understand the combined effect on docetaxel, epirubicin, and cyclophosphamide (TEC) regimen-induced liver injury (TEC-ILI). Certain gene polymorphisms, such as SOD2 and ABCG2, were linked to increased TEC-ILI risk. The combination of clinical and genetic risk factors was shown to have a stronger predictive value for TEC-ILI, highlighting

the importance of personalized approaches in mitigating the liver injury risk associated with epirubicin-based chemotherapy (85).

3.4. Topoisomerase inhibitors

Etoposide, a chemotherapeutic agent derived from podophyllotoxin, frequently causes elevated liver enzyme levels in treated patients, typically without symptoms and without dose adjustment. It is uncommon for etoposide to cause clinically apparent liver damage, which can manifest as sinusoidal obstruction syndrome, acute hepatitis, or other liver damage patterns. Variably occurring between 1 and 5 months after treatment initiation, these injuries are characterized by an increase in hepatocellular enzymes. The mechanism of etoposide-induced liver damage involves toxic intermediate metabolites, which inhibit specific liver enzymes and may result in direct liver damage. Teniposide, a similar drug to etoposide, has unclear hepatotoxicity due to limited use. Etoposide is rated as a "probable cause" of liver injury, while teniposide is marked as an "unproven but suspected cause" of liver injury (86, 87).

Irinotecan is a widely used chemotherapeutic agent with known hepatotoxicity, and its underlying mechanisms have been explored through several studies (88-90). Irinotecan-induced liver injury is associated with various cellular events. In the liver, it can lead to elevated serum aminotransferase levels, hepatic lipid accumulation, and impaired autophagic flux, which is partly mediated by the activation of the HIF-1α/BNIP3 pathway. Inflammation plays a role, as evidenced by increased NLRP3, cleaved-caspase 1, and IL-1β levels (90). However, genetic factors like UGT1A1*28/*6 polymorphisms do not seem to be direct predictors of hepatotoxicity (91). Patients with liver metastasis, a history of alcohol consumption, or those receiving multiple cycles of irinotecan are at higher risk, warranting close liver function monitoring (92). Selenium-enriched probiotics have demonstrated potential in preventing irinotecan-induced hepatotoxicity, possibly through the regulation of oxidative stress and inflammatory pathways (88). Irinotecan-induced liver injury is multifaceted and influenced by a range of factors, including the treatment duration and specific patient characteristics, offering valuable insights for both clinical management and future research (91, 92).

3.5. Plant alkaloids

Studies have demonstrated that vincristine administration can lead to significant hepatotoxicity, characterized by elevated levels of liver enzymes, oxidative stress, and alterations

in various signaling pathways. Vincristine-induced liver injury may involve the upregulation of pro-inflammatory factors like NF-kB and STAT3, as well as the activation of apoptotic pathways, as indicated by increased caspase 3, Bax, and MAP LC3 expression. Furthermore, vincristine treatment can lead to a reduction in antioxidant defenses such as SIRT1 and Nrf2, contributing to oxidative damage and hepatocellular injury (93-95). Interestingly, a case report in a pediatric patient at 7 months of age revealed an unexpected, significant increase in transaminases upon switching from carboplatin and vincristine to vinblastine, underscoring the potential age-related differences in drug-induced liver toxicity, which might be crucial for toxicity screening in pediatric patients undergoing chemotherapy protocols. Subsequently, at 4 years of age, when the patient resumed treatment with vinblastine, no recurrence of severe liver toxicity was observed, indicating the possibility of an age-dependent variation in drug-related hepatotoxicity among pediatric patients (96).

Paclitaxel is a highly recognized chemotherapeutic medication for its efficiency against numerous malignancies, yet its usage can be limited by its tendency for multi-organ toxicity. Several investigations have highlighted the hepatic consequences of paclitaxel treatment, revealing that it causes a considerable increase in liver enzymes, oxidative stress, and inflammatory markers, as well as a decrease in antioxidant defense. The studies show that paclitaxel-induced liver injury increases the expression of pro-inflammatory mediators (NFκ-B, TNF-α, IL-1, and IL-6) and apoptotic factors (Caspase-3, Bax, MMP2, and MMP9) while decreasing the expression of anti-inflammatory and antioxidant factors (Nrf2, HO-1, SIRT1, and PGC-1α). It also causes histological changes such as steatosis and hepatocellular damage. Treatments with flavonoids (hesperidin, naringin, naringenin) and silymarin significantly reduced these adverse effects by reducing inflammation, apoptosis, and oxidative stress, highlighting their potential as hepatic protectants during paclitaxel chemotherapy (97-99).

Docetaxel has increasingly been linked to cases of drug-induced liver injury, with the underlying mechanisms and risk factors being a focus of investigation. In a retrospective cohort study on metastatic breast cancer patients, various non-genetic risk factors were identified for docetaxel-induced liver injury, prominently associated with premenopausal status, past hepatitis B virus infections, the presence of liver metastasis, and the specific regimens incorporating docetaxel. Genetic polymorphisms in specific genes such as IL10 and TNF were also found to

significantly impact the susceptibility to docetaxel-induced liver injury. Studies involving Magnesium isoglycyrrhizinate (MgIg)demonstrated impacts on the expression of key proteins and immune markers involved in liver injury. Notably, upregulation of CYP3A1 and downregulation of P-gp were observed in MgIg-treated groups, indicating potential mechanisms for mitigating liver injury. Additionally, the pharmacokinetics of docetaxel remained largely unaltered in the presence of MgIg, but potential drug interactions were highlighted. The findings suggested that MgIg may exert its hepatoprotective role through modulation of specific immunological and cytochrome activities in response to docetaxel-induced liver injury (100-103).

Vinorelbine-induced liver injury is a rare but serious complication, as highlighted in the case of a 61-year-old woman with metastatic breast cancer undergoing chemotherapy with lapatinib and vinorelbine. Although she had not experienced elevated liver function tests during previous treatments, the second cycle of chemotherapy triggered severe cholestatic liver injury, potentially causing secondary sclerosing cholangitis (SSC). Discontinuing chemotherapy and implementing hepatoprotective measures did not improve her condition, leading to the diagnosis of lapatinib and vinorelbine-induced SSC. This case emphasizes the importance of recognizing and monitoring this adverse drug reaction in patients undergoing vinorelbine-based chemotherapy and calls for further case reports to optimize management strategies (104).

3.6. Antitumor antibodies

Trastuzumab, a prominent antibody-drug combination used to treat HER2-positive metastatic breast cancer, has been linked to hepatotoxicity, providing a hurdle to its clinical use. Cellular and animal models have been used to provide mechanistic insights into trastuzumab-induced liver injury. Trastuzumab internalization results in cytotoxicity, as evidenced by disorganized microtubules, nuclear fragmentation, and inhibition of cell proliferation. Hepatotoxicity is characterized by increased serum levels of liver enzymes, inflammation, necrosis, and increased TNF- α gene expression in liver tissues (105). Unusual aspects, such as sinusoidal obstruction syndrome (SOS), have been reported in rare cases, emphasizing the need for careful hepatic monitoring during trastuzumab treatment (106). Additionally, garlic has demonstrated hepatoprotective effects against trastuzumab-induced toxicity, mitigating structural changes, inflammation, and oxidative stress in rat liver tissues (107).

Rituximab, a CD20 monoclonal antibody, is used in B-cell lymphomas and autoimmune disorders. Hepatitis B reactivation-induced rituximab liver injury is well-documented, whereas autoimmune-type idiopathic drug-induced liver injury is not. After the second dosage of rituximab for mucosa-associated lymphoid tissue lymphoma, a 40-year-old woman developed necro-inflammatory hepatitis with autoimmune characteristics, a rare liver complication (108).

3.7. Targeted Therapies

Imatinib, a pivotal drug in targeted molecular therapy, has been associated with hepatotoxicity, prompting an exploration of the underlying mechanisms. The incidence and time to onset of imatinib-induced hepatotoxicity were retrospectively analyzed in 177 patients, revealing a noteworthy occurrence of 33.9% within 90 days. Several factors were identified as contributors to hepatotoxicity, including the use of proton pump inhibitors, liver disease or hepatitis B virus carriage, body weight below 55 kg, and an imatinib dose exceeding 400 mg. Notably, proton pump inhibitor use increased the risk nearly fourfold and doubled the hazard of hepatotoxicity onset. The studies further delved into the cellular events, employing rat models and HepG2 cells, elucidating that imatinib-induced liver injury is characterized by inflammatory infiltration and heightened expression of NOD-like receptor protein 3 (NLRP3) inflammasome-related proteins. In vitro studies on HepG2 cells underscored imatinib's dose-dependent impact on cell viability, instigating oxidative stress, NF-κB activation, and subsequent NLRP3 inflammasome activation, ultimately leading to a cascade of inflammatory responses. Antioxidants and NF-κB inhibitors exhibited mitigating effects, emphasizing the involvement of oxidative stress and NLRP3 inflammasome activation in the hepatotoxicity induced by imatinib, thereby providing valuable insights for potential prevention and treatment strategies (109, 110).

Sunitinib, a powerful tyrosine kinase inhibitor employed in cancer therapy, has been linked to hepatotoxicity, with potentially life-threatening consequences. The drug's adverse effects include transient elevation in liver enzymes. Cellular events associated with sunitinib-induced hepatotoxicity involve the initiation of oxidative stress, marked by heightened reactive oxygen species (ROS) production and activation of mitogen-activated protein kinases (MAPKs) signaling pathways. Sunitinib triggers apoptosis and autophagy in human hepatocytes, with ROS playing a crucial role in MAPKs phosphorylation. Notably, protective measures against this hepatotoxicity encompass the use of antioxidants such as glycyrrhetinic acid (GA), showcasing its efficacy in

mitigating sunitinib-induced cell damage by inhibiting apoptosis and autophagy. These findings underscore the importance of understanding the intricate cellular mechanisms involved in sunitinib-induced liver injury to pave the way for the development of targeted therapeutic interventions (111-113).

Sorafenib, a powerful multi-kinase inhibitor used to treat renal cell carcinoma and hepatocellular carcinoma, has hepatotoxicity, limiting its clinical use. The mechanism of sorafenib-induced liver damage is unknown despite its extensive use. In adult Wistar rats, sorafenib increased liver damage indicators, alanine aminotransferase, and alkaline phosphatase. The molecular study showed increased NF-κB-p65 expression and decreased antioxidant enzymes. By upregulating cleaved Caspase-3, Bax, and Bid and downregulating Bcl-2, sorafenib activated apoptotic pathways. These data imply that sorafenib-induced hepatotoxicity may be caused by oxidative stress and apoptosis, revealing novel molecular targets for intervention (114).

Lapatinib, a tyrosine kinase inhibitor employed in the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer, has been associated with severe adverse event-drug-induced liver injury (DILI). Several studies have investigated the genetic factors influencing susceptibility to lapatinib-induced hepatotoxicity, emphasizing the major histocompatibility complex (MHC) variants such as HLA-DRB107:01. The incidence of elevated liver enzymes, particularly alanine aminotransferase (ALT), was significantly higher in lapatinib-treated patients carrying these HLA variants. Notably, lapatinib-induced liver injury demonstrated an immune pathology, implicating an immunological mechanism. Moreover, a meta-analysis corroborated the strong association between HLA-DRB107:01 and lapatinib-induced hepatotoxicity, urging genetic screening for patient safety. Despite the recognized risk, the specific cellular events leading to lapatinib-induced liver injury remain intricate and necessitate further exploration (115, 116).

3.8. Immune checkpoint inhibitors

Ipilimumab, the first FDA-approved immune checkpoint inhibitor (ICI), revolutionized cancer treatment. Used across hepatobiliary neoplasia, ICIs, including nivolumab and pembrolizumab, present a breakthrough for advanced hepatocellular carcinoma. However, up to 16% experience immune-related hepatotoxicity, limiting utility (117).

De Martin et al. (2018) explored hepatic immune-related adverse events (IRAEs) linked to anti-programmed cell death protein 1 (PD-1)/PD ligand 1 (PD-L1) and anti-cytotoxic T

lymphocyte antigen 4 (CTLA-4) monoclonal antibodies (mAbs) in 536 patients undergoing immunotherapies. Of the 19 cases with grade ≥3 hepatitis, nine were treated with anti-PD-1/PD-L1, and seven with anti-CTLA-4 mAbs. Liver investigations, including biopsy and immunostaining, unveiled distinctive histological patterns: granulomatous hepatitis with anti-CTLA-4 and lobular hepatitis with anti-PD-1/PD-L1. The majority of cases were not severe, and personalized management, considering both biology and histology, involved spontaneous improvement, corticosteroids, or immunosuppressive drugs (118). A 42-year-old man treated with nivolumab for malignant melanoma developed Grade 4 alanine aminotransferase (ALT) elevation, leading to sustained liver injury despite steroid therapy, highlighting nivolumab-associated hepatotoxicity (119). In a recent report, a unique case reveals two forms of nivolumab-associated liver injury in a patient post-liver transplantation: mild acute cellular rejection and classic drug-induced liver injury (120). An autopsy revealed steroid-refractory hepatotoxicity following nivolumab immunotherapy for malignant mesothelioma. Elevated biliary enzyme levels and randomly distributed endothelial damage emphasized the challenging management of immune-related toxicities (121).

Pembrolizumab is associated with hepatotoxicity in a subset of patients. In a large cohort study (122), 14.3% of pembrolizumab-treated patients developed liver injury, predominantly presenting as cholestatic injury. Notably, hepatic metastases and prior systemic/liver-directed therapies were more common in patients with liver injury. These individuals exhibited poorer outcomes, with reduced tumor remission (10%) and higher mortality (67.1%) during follow-up. Only 28.6% of liver injury cases were confirmed as drug-induced hepatotoxicity, emphasizing the importance of comprehensive medical evaluation before initiating corticosteroids. A separate case report (123) highlighted cholestatic liver injury in a lung adenocarcinoma patient treated with pembrolizumab, emphasizing the significance of histological evaluation and the efficacy of ursodeoxycholic acid in managing cholestatic liver injury. Another case (124) reported a unique instance of simultaneous acute kidney injury and acute liver injury in response to pembrolizumab therapy, underscoring the need for early recognition and intervention. Additionally, an 85-year-old patient with laryngeal carcinoma experienced severe liver injury secondary to pembrolizumab (125). Collectively, these findings underscore the diverse manifestations of pembrolizumab-induced liver injury, ranging from cholestatic patterns to concurrent kidney and liver injury, necessitating vigilant monitoring and tailored management strategies.

Atezolizumab has demonstrated efficacy in treating various solid malignancies. However, its use is associated with immune-related adverse events, with hepatotoxicity being a notable concern. Studies reveal that atezolizumab-induced liver injury is characterized by immune-related acute hepatitis, marked by acute inflammatory infiltrate predominantly comprising CD3+, CD4+, and CD8+ T lymphocytes (126). Interestingly, hepatotoxicity extends beyond immune-mediated inflammation, involving a novel mechanism observed in human hepatocytes. Atezolizumab treatment induces necroptosis in human hepatocytes, evidenced by increased release of lactate dehydrogenase (LDH), reduced cell viability, and inhibited cell growth. This necroptosis is mediated by programmed cell death Ligand 1 (PD-L1), and inhibitors targeting necrosome components mitigate atezolizumab-induced LDH release, highlighting a molecular basis for the observed hepatotoxicity (127). Additionally, a comprehensive study emphasizes that patients treated with atezolizumab may experience liver injury, leading to worsened outcomes, including ascites and exacerbation of underlying liver diseases (128). Therefore, while atezolizumab demonstrates therapeutic potential, vigilance is essential in monitoring and understanding the cellular events underpinning its hepatotoxic effects.

3.9. Other Miscellaneous Agents

L-asparaginase, a crucial agent in acute lymphoblastic leukemia (ALL) therapy, is associated with significant hepatotoxicity, as elucidated by recent studies. In a steatotic rat liver model (129), chemotherapy with L-asparaginase induced toxicity, particularly in fatty livers, while the co-administration of L-carnitine demonstrated a protective effect, emphasizing its potential to mitigate hepatotoxicity in individuals with preexisting liver disorders. The pegylated form, PEG-l-asparaginase, used in pediatric ALL treatment, was investigated in mice (130), revealing drug-induced lipolysis and lipid redistribution to the liver as key mechanisms of hepatic steatosis. Additionally, the study observed exacerbated liver injury in obese and aged mice, aligning with clinical observations. A broader perspective by Kumar et al., (2021) emphasized the role of asparaginase in ALL treatment, discussing various formulations and their systemic toxicities, with severe liver impairment documented in rare cases (131). These findings collectively underscore the intricate cellular events and challenges associated with L-asparaginase-induced liver injury, emphasizing the need for careful consideration in ALL therapy.

Hydroxyurea, a commonly prescribed medication for various hematologic conditions, has been associated with hepatotoxicity, as illustrated by recent clinical reports. In a refractory leukemia case (132), a substantial increase in liver enzymes, marked by elevated serum AST and ALT levels, occurred swiftly after hydroxyurea administration, accompanied by symptoms of fever and gastrointestinal distress. Discontinuation of hydroxyurea resulted in a prompt return of liver function to baseline levels, with a subsequent positive drug-induced lymphocyte stimulation test supporting the role of drug allergy in the observed hepatic dysfunction. While investigating the mechanistic insights of hydroxyurea-induced hepatic injury and the potential protective effects of royal jelly (RJ). In an experimental rat model (133), hydroxyurea administration led to a significant disruption in liver function markers, oxidative stress, pro-inflammatory cytokines, and the apoptotic pathway, with histopathological evidence of hepatic lesions. Co-administration of RJ mitigated these effects, demonstrating antioxidant, anti-inflammatory, and anti-apoptotic properties. These findings collectively underscore the cellular events associated with hydroxyurea-induced liver injury and suggest potential avenues for ameliorating its hepatotoxic effects.

Procarbazine hydrochloride, an alkylating agent used in lymphoma and glioma chemotherapy, is generally associated with hepatic dysfunction as a potential adverse reaction. Despite limited documented cases linking procarbazine to liver injury, Fesler et al., (2010) reported a 65-year-old man developing liver injury during salvage chemotherapy for non-Hodgkin's lymphoma. Notably, the patient exhibited no liver issues during initial treatment with R-CHOP. Subsequent therapy with C-MOPP-R, including procarbazine, prompted fever and aminotransferase elevation. Rechallenge confirmed a definitive association between hepatic injury and procarbazine, resolving upon discontinuation. This case underscores the importance of periodic hepatic function assessment in procarbazine-treated patients, aligning with prescribing recommendations (134).

4. Summary

This comprehensive review delves into the complex landscape of chemotherapy-induced hepatotoxicity, investigating causes, risk factors (genetic polymorphism), and preventative interventions across various chemotherapeutic classes. **Table 1** summarizes major data, highlighting the complex patterns of liver injury caused by alkylating drugs, topoisomerase inhibitors, plant alkaloids, antimetabolites, anthracyclines, targeted treatments, and immune

checkpoint inhibitors among other chemotherapeutic agents. The table presents an overview of key therapies, such as antioxidants and genetic considerations, that either alleviate or increase hepatotoxic consequences. These findings highlight the importance of personalized monitoring and targeted therapies in clinical settings, furthering our understanding of the intricate interplay between chemotherapeutic drugs and liver function.

Table 1. Overview of chemotherapy-induced hepatotoxicity mechanisms and interventions.

Chemotherapeutic agent	Mechanisms of liver injury	Protective measures	References
Alkylating agents			
Cyclophosphamide	Nrf2/HO-1 up-regulation, TLR4/NF-κB pathway inhibition	Fucoidan, PQQ, N-acetylcysteine	(51-53)
Busulfan	Complex cellular events, hepatic steatosis, ER stress	Alginate oligosaccharides, Pirfenidone	(54-56)
Cisplatin	Oxidative stress, inflammation, gut microbiota influence	Curcumin, Fraxin nano-formulations, L-carnitine	(57-61)
Antimetabolites			
Methotrexate	Oxidative stress, inflammation, disruption of gut-liver axis	Natural compounds, probiotics, antioxidants	(64-66)
5-Fluorouracil	Oxidative stress, impaired mitochondrial function	Anthraquinone extract, Nigella Sativa, Onion extract	(67-70)
Capecitabine	Generally mild hepatotoxicity, rare severe cases	Discontinuation for severe cases	(71, 72)
Anthracyclines			
Doxorubicin	Hepatocyte damage, oxidative stress, inflammation	Creatine, Pregnenolone, Astaxanthin, miR-128-3p	(73-82)
Epirubicin	Various mechanisms, hormonal influence	Paeonol, Genetic factors, Magnesium isoglycyrrhizinate	(83-85)
Topoisomerase inhibitors			
Etoposide	Toxic metabolites, direct liver damage		(86, 87)

Chemotherapeutic agent	Mechanisms of liver injury	Protective measures	References
Irinotecan	Elevated aminotransferase, hepatic lipid accumulation	Selenium-enriched probiotics	(88-92)
Plant alkaloids			
Vincristine	Pro-inflammatory factors, apoptotic pathways, NF-kB, STAT3 upregulation		(93-95)
Paclitaxel	Increased liver enzymes, oxidative stress, inflammatory markers	Flavonoids (hesperidin, naringin, naringenin), Silymarin	(97-99)
Docetaxel	Cases of drug-induced liver injury	Magnesium isoglycyrrhizinate	(100-103)
Vinorelbine	Rare but serious complications, potential SSC	Discontinuation of chemotherapy	(104)
Targeted therapies			
Imatinib	NLRP3 inflammasome activation, oxidative stress	Antioxidants, NF-κB inhibitors	(109, 110)
Sunitinib	Oxidative stress, apoptosis, autophagy	Antioxidants (glycyrrhetinic acid)	(111-113)
Sorafenib	Oxidative stress, apoptosis		(114)
Lapatinib	HLA-DRB107:01 association, immune pathology		(115, 116)
Immune Checkpoint Inhibitors			
Ipilimumab	Immune-related hepatotoxicity		(117)
Pembrolizumab	Cholestatic injury, poor outcomes		(122-125)
Atezolizumab	Immune-related acute hepatitis, necroptosis in hepatocytes		(126-128)
Other miscellaneous agents			
L-asparaginase	Toxicity in fatty livers, lipolysis	Co-administration with L-carnitine	(129-131)
Hydroxyurea	Liver enzyme elevation, symptoms of fever	Royal jelly (RJ)	(132, 133)
Procarbazine hydrochloride	Potential hepatic dysfunction	Periodic hepatic function assessment	(134)

5. Conclusion

In conclusion, the diverse chemotherapeutic agents explored in this comprehensive analysis underscore the intricate and multifaceted nature of chemotherapy-induced liver injury. The mechanisms contributing to hepatotoxicity vary across drug classes, emphasizing the need for tailored approaches to both understanding and mitigating these adverse effects. The protective effects demonstrated by certain compounds, such as fucoidan, pyrroloquinoline quinone, and antioxidants, provide promising avenues for future therapeutic interventions.

6. Recommendations

Recommendations for clinical practice and further research emerge from these findings. Vigilant monitoring of liver function is crucial during chemotherapy, especially with agents known to pose a risk of hepatotoxicity. Personalized risk assessments, considering genetic factors and preexisting liver conditions, could enhance patient safety. Additionally, the potential of novel compounds and antioxidants in ameliorating liver injury warrants further investigation and clinical trials.

The intricate interplay between chemotherapy and liver function, as highlighted in this review, necessitates ongoing research to unravel specific molecular pathways and identify targeted interventions. Collaborative efforts between clinicians, pharmacologists, and researchers are essential to translate these findings into effective strategies for preventing and managing chemotherapy-induced liver injury. Ultimately, enhancing our understanding of these complex mechanisms will contribute to improved patient outcomes and the development of safer and more effective chemotherapeutic regimens.

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