Review Article

Hepatotoxicity Secondary to Chemotherapy

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Abstract

The difficult problem faced by multiple generation of practicing physicians is determining the cause of abnormal liver function tests in cancer patients on chemotherapy. Hepatotoxicity from chemotherapy occurs frequently from an unpredictable or idiosyncratic reaction. Despite remarkable advances in our understanding of the mechanisms of action, pharmacodynamics, and interrelationships between the liver and chemotherapy, the underlying etiology of hepatic toxicity for various agents remains unexplained. Here, we present a concise review of the broad differential diagnosis for abnormal liver function tests (LFTs) in oncology patients.

Introduction

In the complex world of cancer therapy, the administration of medications intentionally designed to be cytotoxic inevitably causes negative consequences. The liver is the primary site of metabolism for many of these drugs, and this liver-drug interaction must be accounted for while dosing chemotherapy. Preexisting liver disease can impair the process of recovery after injury,[1] and in preparation for chemotherapy, oncologists need to assess both liver function and potential liver involvement by the cancer.

Guidelines for monitoring potential hepatotoxicity

National Cancer Institute (NCI) common toxicity criteria for adverse events

Close liver function monitoring is advised for patients starting new chemotherapy regimen. It remains controversial how often liver testing should be performed and what constitutes liver dysfunction. The NCI in the "Common Toxicity Criteria for Adverse Events" has classified elevations of serum enzyme activities (alanine aminotransferase" (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT)) into mild (grade 1) if >ULN (upper limits of normal) to $2.5 \times$ULN; moderate (grade 2) if >2.5 to $5 \times$ULN; severe (grade 3) if >5 to $20 \times$ULN; and life-threatening (grade 4) if >$20 \times$ULN; and with no definition for fatal (grade 5). Similarly, they graded serum total bilirubin concentration as mild if >ULN to $1.5 \times$ULN, moderate if >1.5 to $3 \times$ULN, severe if >3 to $8 \times$ULN, and life-threatening if >$8 \times$ULN. Although this grading system is commonly used, this practice has been questioned since the elevation of enzymes by itself does not always reflect dysfunction of the liver and can therefore be misleading.

National Institute of Health Drug Induced Liver Injury (DILI) network

The National Institute of Health funded DILI network experts proposed to use clinical measures instead of laboratory values and defined liver injury as follows: level 1 (mild) if patient has isolated elevation of ALT and or ALP, level 2 (moderate) in presence of elevated bilirubin and coagulopathy, level 3 (serious) if it results in hospitalization or disability to do usual work; level 4 as acute liver failure, in which another organ that is dependent on liver function shows dysfunction (brain, encephalopathy; kidney, renal insufficiency; etc.); and level 5 as death or liver transplantation.[2] They also proposed a scale of increasing likelihood, ranging from unlikely to definite, of a suspected case of liver injury to be related to the imputed drug.

Dose modification guidelines

Liver metabolized agents

There is agreement on the need for dose reduction for agents that are dependent upon liver metabolism for clearance from the circulation. The major chemotherapeutic agents in this group include methotrexate, sorafenib, dactinomycin, ifosfamide, gemcitabine, etoposide, irinotecan, procarbazine, 6-mercaptopurine, cytarabine, crizotinib, and cyclophosphamide.

Chemotherapy to be used with caution

Certain chemotherapeutic agents must be used with extreme caution in patient with preexisting liver disease. These include the anthracyclines, taxanes, vinca alkaloids, temsirolimus, imatinib, axitinib, lapatinib, erlotinib, nilotinib, pazopanib, ponatinib, and ruxolitinib.

Overall guidelines

The clinical presentations of hepatotoxicity vary from asymptomatic, increase of liver chemistries, overt cholestatic hepatitis, progression to fibrosis and cirrhosis, malignant transformation, veno-occlusive disease/sinusoidal obstruction, and fulminant hepatic failure. Table 1 lists proposed mechanisms of hepatic injury for commonly used chemotherapeutics; it is based mainly on evidence derived from case-series and case reports.

Table 1. Chemotherapy drugs and liver side effects

Drug	Hepatitis	Cholestasis	Biliary Stricture	Steatosis	Nodular Hyperplasia Fibrosis	Veno-Occlusive Disease
Actinomycin	Rare					Rare
Arsenic						
Asparaginase	Common			Common		
Azathioprine		Rare				Rare
Bleomycin	Rare					
Bortezomib	Rare					
Busulfan	Rare	Rare				Rare
Capecitabine	Rare					
Carmustine	Common					
Chlorambucil		Rare				
Cyclophosphamide	Rare					Common
Cytarabine		Rare	Common			
Dacarbazine						Rare
Docetaxel		Rare				
Doxorubicin	Rare	Rare				Rare
Erlotinib		Common				
Etoposide	Rare	Rare				
Floxuridine	Common	Common	Common			
Fluorouracil	Rare			Common		Rare
Gefitinib	Rare					
Gemcitabine	Rare	Rare				
Hydroxyurea	Rare					
Ifosfamide	Rare					
Imatinib	Common					
Interferon	Common					
Interleukin		Common				
Irinotecan				Rare		
Lomustine	Rare					
Melphalan	Rare					Rare
Mercaptopurine	Rare	Rare				
Methotrexate	Common				Common	
Mitomycin	Rare					Rare
Oxaliplatin				Rare	Rare	Common
Paclitaxel		Rare				
Pazopanib	Common					
Procarbazine	Rare					
Regorafenib	Rare					
Sorafenib	Rare	Rare				
Streptozocin	Rare					
Thioguanine					Rare	Rare
Topotecan		Rare				
Vincristine	Rare					
Vinorelbine		Rare				

Since there are no perfect laboratory tests that will predict the likelihood of serious liver injury prior to administration of the drug, clinicians are tasked with detecting the early signs of injury and determining whether the drug should be stopped due to hepatotoxicity or to continue chemotherapy if hepatic adaptation and tolerance development are likely. In most cases of DILI, the only effective treatment is discontinuation of the causal agent and supportive care. In the context of life-threatening disease, the risk and benefit need to be calculated based on the individual patient and disease course.

Specific chemotherapy

Anti-metabolites

6-Mercaptopurine (6-MP)

The largest series, Present et al. reported long-term results of 6-MP use in 396 patients with inflammatory bowel disease (IBD). There were 11 cases of hepatitis and one case of recurrence of jaundice after reinstitution of the drug.[3] Severe cholestasis associated with the use of conventional doses of 6-MP has also been reported after liver transplantation.[4] The most common pattern of described injury is intrahepatic cholestasis. Jaundice resolved with discontinuation of the drug. Cases of fulminant hepatic failure occurred with the doses of medication far exceeding the current recommended dose of 1.5 mg/kg body weight per day.

Azathioprine (AZA)

Despite being the parental drug of 6-MP, AZA has been linked to little hepatotoxicity. Nevertheless, caution is advised since cholestatic liver injury appears to be possible after prolonged use. Fulminant liver failure was reported in one patient after eight years of dose AZA therapy at levels higher than the currently recommended dose.[5] AZA related hepatotoxicity was also reported in liver transplant recipients.[6]

6-Thioguanine (6-TG)

6-TG was reported to cause hepatic vascular disease[7] and to present significant risk for nodular hyperplasia and early fibrosis.[8]

Cytarabine

Despite various degrees of hepatic enzyme abnormalities in 42 out of 116 patients in a study,[9] the definite association with the drug administration was not confirmed. This finding was echoed in a subsequent study with high dose of the drug. Abnormalities in liver function occurred in 14 (22%) patients (severe in three), but no treatment modifications were required.[10] Nevertheless, there are reports of severe drug-induced hepatic cholestasis related to cytarabine therapy.[11]

5-Fluorouracil (5-FU)

5-Fluorouracil is commonly used in combination regimen for neoadjuvant chemotherapy in patients with colorectal liver metastasis prior to surgical resection. In a study of 107 patients assigned to receive 5-FU, no significant hepatic toxicity was observed in a group receiving 5-FU orally and was seen infrequently in those receiving the drug intravenously.[12]

Another study retrospectively evaluated the surgical specimen with focus on liver parenchyma not involved by the resected tumor.[13] Overall, sinusoidal obstruction was present in 39 patients (10%), steatosis in 134 (35%), and steatohepatitis in 16 (4%). A recent study which attempted to stratify patients based on degree of hepatic dysfunction reported no difference in the 5-FU clearance in patients with elevated bilirubin.[14]

Fluorodeoxyuridine (5FUDR)

In a study comparing regional intra-arterial versus continuous systemic therapy with 5FUDR in patients with colorectal liver metastasis, there was considerable hepatotoxicity, including chemical hepatitis in 79% of patients and biliary sclerosis is 21% of patients. The small gain in survival seen with regional therapy was offset by toxicity of intra-arterial FUDR.[15] In later studies, biliary toxicity called for reduction of the dose and the duration of therapy with more than half of patients requiring treatment termination due to drug toxicity.[16] It is still a matter of debate whether bile duct injury is related to drug toxicity or ischemia.[17]

Capecitabine

Capecitabine is a drug that undergoes preferential conversion to 5-fluorouracil within the tumor. A study of 14 patients investigated the pharmacokinetics of the drug in patients with hepatic dysfunction and concluded that mild to moderate hepatic dysfunction had no clinically significant influence.[18] This was confirmed in a recent study, which examined the impact of hepatic dysfunction on the safety and pharmacology of gemcitabine/capecitabine in patients with advanced pancreatico-biliary cancer. Eight patients with hepatic dysfunction and bilirubin elevation (ranging 1.2–6.6 mg/dL) were included. Combination therapy was well tolerated, and hepatic dysfunction was not associated with drug-related toxicity.[19]

Gemcitabine

In a Phase I trial in patients with hepatic dysfunction, 25 patients were divided in two groups: elevated AST and mildly and moderately elevated bilirubin. AST levels ranged from 37 to 530 U/L, and bilirubin from normal up to 5.7 mg/dL. The most common dose limiting side effect was transient elevation in baseline bilirubin in seven patients from the second group. The authors of this trial recommended decreasing the initial dose of medication in patients with elevated baseline bilirubin.[20] This conclusion was not confirmed in a retrospective review of treatment with gemcitabine in seven patients with hepatic dysfunction and bilirubin elevation (total bilirubin>4.5 mg/dL). Full dose of gemcitabine in this study did not result in further deterioration of liver function.[21]

Methotrexate (MTX)

With MTX therapy, the incidence of abnormalities in hepatic function tests for ALT and AST were reported to be 14% and 8%, respectively.[22] This finding was replicated recently with a recent meta-analysis where the pooled frequency of liver enzyme abnormalities was 10.2%.[23] In a historic report, of the use of "antifolics" and "antipurins" in children with acute leukemia was associated with fibrosis in 80% of children based on histology and clinical evidence of liver disease in

almost all cases.[24] Cases of hepatocellular carcinoma (HCC) in long-term survivors of childhood leukemia have been reported.[25] In addition, methotrexate induced cirrhosis has resulted in liver transplantation in a number of patients.[26]

Despite the concerns spanning half of a century for the potential risk for hepatic cirrhosis with the use of methotrexate in nonmalignant diseases such as psoriasis,[27] later studies in patients with rheumatoid arthritis[28] alleviated some of the fears. However, "word of caution" still requires very close patient monitoring, in particular in those with concurrent obesity and diabetes.[29]

Alkylating agents

Busulfan

Oral Busulfan has been implicated in severe cases of hepatic veno-occlusive disease.[30] In a study with intravenous Busulfan in 55 pediatric patients, mild to moderate transient elevation in liver enzymes and bilirubin was described. Although veno-occlusive disease (VOD) occurred in up to 15 % of patients, reported cases were mild and resolved in ten days after diagnosis.[31]

Cyclophosphamide

Cyclophosphamide is used in the most liver toxic myeloablative regimen, and when combined with total body irradiation, has been reported to result in VOD in 38% of the patients.[32] The hepatotoxicity appeared to be greatly potentiated by radiation. Cyclophosphamide was demonstrated in seven patients with liver dysfunction to have a significantly longer half-life.[33]

Chlorambucil

There are few available reports regarding liver toxicity of chlorambucil, but the largest one found jaundice in 7.2% patients undergoing treatment for lymphoma and leukemia.[34]

Ifosfamide

Ifosfamide is not commonly associated with hepatotoxicity. In one phase II trial of 19 patients with HCC in the background of viral hepatitis and cirrhosis (bilirubin <3.0 mg/dL), direct intra-arterial delivery of the drug to the tumor was reported to worsen liver function in two patients.[35]

Melphalan

Hepatotoxicity with melphalan has been reported infrequently. Its use has been associated with transient elevation of transaminases[36] and VOD.[37] In the past decade, isolated hepatic perfusion of the liver for metastatic disease was advocated and more severe hepatotoxicity was observed in a study where 16 of 71 patients exhibited level 3–4 hepatic toxicity after one week of treatment.[38]

Antitumor antibiotics

Actinomycin

Hypersensitivity reaction to actinomycin has been reported with acute presentation and a sharp drop in platelet count,

fever, and a rise in transaminases.[39] In a study analyzing the toxicity data for 511 children, 64 (12.5%) had at least one episode of hepatotoxicity and 41 satisfied the criteria for VOD, with 94% overall survival in this group.[40]

Bleomycin

Studies with bleomycin described mild transient abnormalities in liver enzymes with a return to baseline upon cessation of drug treatment and no specific pathological liver abnormalities.[41]

Doxorubicin/Adriamycin

Adriamycin dosing in hepatic dysfunction received attention because of reported excessive life –threatening toxicity, as demonstrated with liver test abnormalities, in eight patients.[42] The investigators reduced the dose of the drug in the subsequent nine patients to 50% of the dose in patients with bilirubin of 1.2–3.0 mg and 75% of the dose if bilirubin measured >3.0 mg. This approach succeeded and was adopted by clinical community. In contrast, liver cirrhosis did not seem to affect drug metabolism in a study of seven patients, three of which had biopsy proven cirrhosis.[43]

Mitomycin

Mitomycin can cause transient jaundice[44] and has been implicated in VOD.[45]

Dacarbazine

Dacarbazine was associated in one report with hepatic necrosis with thrombotic occlusion of the small vessels in two of sixty-eight patients (3%).[46]

Nitrosoureas

Carmustine

With carmustine, liver enzymes were elevated, unexplained by the primary disease, in 26% of patients.[47]

Lomustin

In a trial of lomustin with 142 patients with advanced solid tumors, reports of transient hepatic toxicity was reported much less frequently and consisted of elevation of ALP, ALT, and AST in two patients.[48]

Streptozotocin

In a study of streptozotocin with 88 patients with advanced malignancy, hepatotoxicity, manifesting as elevation of transaminases, was demonstrated in 13 (15%). The enzymes rapidly returned to normal after discontinuation of therapy, and no signs of hepatocellular necrosis were found on histological examination.[49]

Taxanes

Paclitaxel

In a study of paclitaxel with 81 patients with solid tumors and abnormal hepatic function, three groups were evaluated

based on the level of bilirubin and AST.[50] The elevation of bilirubin above 1.5 mg/dL with any level of AST predicted drug-related toxicity with 24 hour infusion, and dose reduction was recommended. The study with 3-hour infusion confirmed a higher incidence of toxicities in severe liver dysfunction groups (bilirubin >2.0 mg/dL). The study included two patients with liver cirrhosis.[51]

Docetaxel

In a study of 42 patients with moderate hepatic impairment, the docetaxel dose had to be reduced due to increased incidence of drug-related toxicities following treatment.[52] However, in a study of patients with hepatic dysfunction secondary to metastatic breast cancer, almost half of group allowed initial dose escalation due to improved liver function as an indicator of the tumor response to treatment.[53]

Vinca alkaloids

Vincristine

Transient elevation of transaminases following vincristine therapy has been described, and it seems to be greatly potentiated by radiation therapy.[54] Since neurotoxicity, the most feared side effect, has been shown to be dose dependent, much attention has been paid its reduced elimination in liver dysfunction. A study of 39 patients suggested that elevation in ALP is the most sensitive parameter in predicting reduced clearance.[55]

Vinorelbine

In a study of oral and intravenous vinorelbine, the drug exposure was not affected by mild to moderate hepatic dysfunction (bilirubin <3.0 mg/dL).[56] In contrast, another study assessed patients with impaired liver function due to metastatic disease and established that increased systemic exposure with high risk of toxicity occurred in the group with hyperbilirubinemia (>1.5 mg/dL).[57]

Topoisomerase inhibitors

Topotecan

Rapid transient elevation of serum bilirubin without significant elevation in transaminases was noticed in patients in a phase I trial of topotecan.[58] Due to its known hepatic route of elimination, a study of 21 patients (mean bilirubin 4.3 mg/dL) was conducted to establish dosing guidelines in patients with impaired liver function.[59] No increase in toxicity was observed, and worsening of hepatic function in several patients was attributed to disease progression. This study concluded that no dose adjustment is necessary with impaired liver function.

Irinotecan

Dose reduction was suggested for irinotecan in patients with elevated baseline bilirubin and transaminases, as one study showed an increased incidence of neutropenia and dose-limiting elevation in transaminases in a group with hepatic dysfunction (AST 134–394 U/l, bilirubin 0.7–5.5 mg/dl).[60] Irinotecan is used in a preoperative chemotherapy regimen

prior to resection of hepatic colorectal metastasis. It has been linked to the development of steatohepatitis, which contributed to increased postoperative mortality in a large cohort of patients.[61]

Etoposide

Topoisomerase II inhibitor Etoposide had been described to cause severe hepatocellular injury.[62] Studies in patients with impaired hepatic function (bilirubin up to 23 mg/dL) showed no change in etoposide clearance.[63]

Platinum agents

A pilot study of 11 patients with hepatic dysfunction (bilirubin >1.5 times ULN) due to breast cancer metastatic to the liver reported normalization of the liver function tests, a marker of tumor responsiveness, to administered therapy in ten patients.[64]

Oxaliplatin

Oxaliplatin associated hepatic vascular injury has been described in multiple studies. A large series that evaluated 153 liver resection specimens found sinusoidal congestion of various degrees in 44 patients, perisinusoidal fibrosis and fibrotic venular occlusion in 21 patients, nodular regenerative hyperplasia in seven patients, and hepatic steatosis in 75 patients.[65] Another study assessed the risk of preoperative chemotherapy in patients undergoing liver resection for colorectal cancer metastasis. Out of 166 patients treated with oxaliplatin, 11% developed sinusoidal dilatation. No increase in postoperative morbidity was found, suggesting this histopathology finding does not independently increase the operative risk.[66]

A phase I study administered reduced schedule dose of oxaliplatin to 47 patients with impaired liver function, including 16 patient with severe dysfunction (bilirubin >3.0 mg/dL). No dose limiting toxicities were observed in any cohort of the patients with escalation of the dose to the conventionally used level.[67]

Tyrosine kinase inhibitors

The discovery of targeted inhibition of tyrosine kinase (a family of proteins frequently dysregulated in various cancers) marked a breakthrough in the fight against cancer. The unique properties of these medications helped to avoid conventional toxicities, while hepatotoxicity emerged as a dose-limiting event. The risk of grade 3 hepatic adverse events with TKIs has been reported in the range of 1% to 12%.[68]

Erlotinib

Transient grade 1–2 hyperbilirubinemia was reported in a phase I clinical trial of erlotinib.[69] However, in a recent study, grade 3–4 bilirubin elevation was described in 47% of patients with preexisting moderate hepatic dysfunction.[70]

Gefitinib

Use of Gefitinib in treatment of advanced metastatic non-small cell lung cancers was linked with grade 3 elevation of ALT 2% of 147 patients receiving medication.[71]

Imatinib

In a study of 89 patient with solid cancers and liver dysfunction, up to 58% of patients with moderate to severe HD, defined as bilirubin >1.5 ULN, had to be withdrawn from the study prematurely due to progressive elevation of LFTs.[72] Another study of 551 patients with chronic myeloid leukemia treated with Imatinib reported elevation of serum aminotransferases in 43% of patients, with grade 3–4 in 5%.[73]

Pazopanib

Due to concern of hepatotoxicity, a phase I study attempted to define the appropriate dose of Pazopanib in patients with solid tumors and lymphoma and hepatic dysfunction. It was concluded that no dose reduction was necessary in mild cases and reduced dose can be used in patients with moderate dysfunction, defined as bilirubin elevation 1.5–3X ULN.[74]

Sorafenib

In a phase I study of sorafenib in patients with hepatic dysfunction, dose limiting elevation of bilirubin occurred in 10 out of 72 patients, leading to recommendation to lowering the dose to half in patients with bilirubin >1.5 × ULN and not reaching conclusive safe dose guidelines in patients with bilirubin >3× ULN.[75]

Immunotherapy

Interferon

In patients receiving high-dose Interferon therapy for melanoma, 63% had hepatic toxicities (all grades). If AST or ALT levels increased >5 times normal, this was considered dose-limiting toxicity with recommended dose modifications.[76]

Interleukin-2

With interleukin-2 therapy, profound reversible intrahepatic cholestasis was reported in 261 retrospectively and 10 prospectively evaluated patients with cancer, with normalization, on average, in 5.6 days.[77]

Miscellaneous agents

Arsenic trioxide

In a study examining of the use of arsenic trioxide for newly diagnose promyelocytic leukemia, severe hepatotoxicity resulted in the death of two out of 11 treatment naïve patients.[78]

Asparaginase

Liver enzyme abnormalities with asparaginase were reported in 33 out of 35 patients in an early study, where liver biopsies found reversible fatty metamorphosis in two patients.[79]

Bortezomib

Bortezomib was studied in 61 patients with advanced malignancies and varying degrees of hepatic dysfunction.[80] Since liver failure was reported in one patient, dose adjustment was recommended in patients with moderate to severe hepatic impairment defined as bilirubin>1.5 ULN.

Hydroxyurea

Hepatotoxicity appears to be uncommon with hydroxyurea, but there is case report of a self-limiting hepatitis[81] that recurred upon drug reintroduction.

Procarbazine

Liver toxicity is not commonly reported with procarbazine, although it has been implicated in the development of hepatic granulomas.[82]

Conclusions

Collateral damage to the liver in cancer therapy is not uncommon. Hepatotoxicity from chemotherapy occurs frequently in an unpredictable or idiosyncratic fashion, ,and preexisting liver disease increases this risk. The pattern of presentation can vary from that of an inflammatory hepatitis, cholestasis, steatosis, and finally a vascular presentation as hepatic VOD. The severity ranges from asymptomatic liver function test elevation, acute liver failure, or a progressive fibrosis culminating in end stage liver disease. Various groups have produced liver toxicity classifications that lay out dose modification guidelines for various chemotherapeutic agents. Nevertheless, with knowledge and caution, many potential side effects and serious damage to the recipient can be avoided.

Conflict of interest

None

Author contributions

Writing this article (AG, CBO).

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