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EXPERTS' CONSENSUS

# Chinese experts' consensus on diagnosis, prevention, and treatment of chemotherapy-induced hepatotoxicity

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## Overview

Drug-induced liver injury (DILI) due to acetaminophen overdose and idiosyncratic drug reactions usually occurs 5–90 days after exposure to the causative drug. Ninety percent of DILI cases are acute. As one of the most common non-infectious liver diseases, DILI represents a growing challenge for clinicians. According to data from WHO [1], DILI is the fifth leading cause of liver disease mortality. In China, DILI accounts for 1%–5% of hospitalized patients with liver diseases, 10% of patients with acute hepatitis, and 12.2% of patients with fulminant hepatitis [2].

A significant number of antitumor drugs have been proven, or are at least suspected, to cause hepatotoxicity. Antitumor agents include cytotoxic drugs, hormones, molecular targeted drugs, biological response modifiers, and traditional drugs. A retrospective review including 279 studies and 24,112 patients found that in China, antitumor drugs ranked fifth among all DILI-inducing drugs [3]. Petronijevic [4] investigated data from 6370 patients with liver failure from 38 countries and found that antitumor drugs were the second most common cause of acute liver failure and accounted for 11.9% of all hospital admissions for hepatotoxicity.

The mechanisms for DILI remain unclear. DILI is thought to occur via multiple molecular mechanisms. Without specific symptoms or signs, DILI is often discovered through routine laboratory testing. We are limited in our ability to predict and prevent DILI.

## Factors affecting the susceptibility to DILI

Compared to healthy individuals, patients with underlying disease are more vulnerable to DILI after exposure to chemotherapeutic agents. Consensus opinion suggests that clinicians should minimize the dose of anti-tumor agents and avoid introducing two or more cytochrome p450 inhibitors simultaneously.

It is also known that the elderly, infants, and women are more vulnerable to DILI. Other general risk factors include prior history of an adverse reaction to a drug, history of drug-induced hepatotoxicity, underlying hepatic disorder, administration of a drug with potential hepatotoxicity, administration of radiation or transarterial chemoembolization (TACE), usage of immunosuppressive agents, infection, diabetes, kidney disease, rheumatism, organ transplantation, disorder of lipid metabolism, alcohol abuse, obesity, and primary or secondary hepatic malignancy.

## Diagnosis

The diagnosis of DILI is extremely challenging and is based on circumstantial evidence. Accurate diagnosis depends on the patient history, biochemical tests, imaging studies, and liver biopsy. There is no distinctive symptom or serological marker to clearly indicate DILI. The credibility of a DILI diagnosis depends on the integrity of the clinical data and history. Since histological evaluation of

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the liver only allows recognition of the type and extent of injury, rather than indicating a drug-induced liver injury, liver biopsy is not mandatory for the diagnosis of DILI.

## Clinical presentation

The clinical presentation of DILI is extremely varied, ranging from transient, asymptomatic elevations in serum transaminases to slight fatigue, anorexia, and painless jaundice, even fulminant hepatic failure.

## Liver function test

(1) Alanine transaminase (ALT): ALT is a more specific marker for hepatocellular injury than aspartate aminotransferase (AST) in diagnosing DILI. In 2009, the FDA confirmed that ALT was a major factor in the evaluation of DILI. Monitoring ALT during drug administration can help lower the incidence of DILI and allow proper dosage modifications [5–6].

(2) Aspartate aminotransferase (AST): AST is less specific and less sensitive than ALT in diagnosing DILI. AST may be a complementary indicator along with ALT and is often measured along with ALT in clinical practice. The ALT/AST ratio may be an ideal indicator to use to distinguish other causes of hepatic injury from DILI.

(3) Alkaline phosphatase (ALP): ALP is an indicator of cholestatic liver injury and severe DILI. Since malignancy, bone disease, and pregnancy also increase ALP, ALP measurement is usually combined with the ALT/AST determination to avoid confusion.

(4) γ-glutamyl transpeptidase (γ-GT): The serum levels of γ-GT often parallel those of ALP. However, in bone disease, γ-GT levels remain normal while ALP levels are elevated.

(5) Total bilirubin (TBIL) and direct bilirubin (DBIL): When an elevated TBIL level is detected, the clinician should initially rule out other conditions which might induce an elevation in TBIL. Since bilirubin clearance in humans is solely the function of the liver, TBIL is one of the most characteristic indicators of liver dysfunction. Additionally, TBIL is an important indicator in determining the DILI subtype and in predicting the prognosis. DBIL levels allow the clinician to identify the type and extent of jaundice, as both hepatocellular and obstructive jaundice are often accompanied by an elevation in DBIL.

In 1989, experts from Europe and America developed the "Paris Consensus" regarding the diagnosis of DILI. Diagnostic criteria included: (1) an elevated ALT or DBIL [> 2 × upper limit of normal (ULN)] or (2) an elevated ALT, AST, and TBIL simultaneously, with one measurement > 2 × ULN.

If the serum levels are < 2 × ULN, the term "liver function abnormality" is more suitable than "liver function injury". Simultaneous increases in transaminase and TBIL levels are a key feature of DILI.

## Pathological manifestations

Histological evaluation of the liver allows recognition of the type of injury present and the extent of that injury, but usually does not indicate that liver injury has occurred from a specific drug. Few hepatic drug injuries have a distinctive pathological manifestation, such as "blue liver" (oxaliplatin) and "yellow liver" (irinotecan). Mild DILI often demonstrates a single pathological process confined to only a portion of the liver, while severe DILI demonstrates multiple pathological findings involving a whole lobe or the entire liver. Patients with severe hepatic pathological findings from DILI have a worse prognosis than DILI patients with mild hepatic pathological findings.

## Diagnostic criteria

According to the criteria of Karach and Lasagna [7], diagnostic criteria for DILI are:

(1) A sequential relationship between the administration of a drug and an elevation in the serological biomarkers. DILI often occurs 5–90 days after exposure to the suspected drug.

(2) The suspected drug has been previously reported to cause hepatotoxicity.

(3) Other factors potentially causing hepatotoxicity have been ruled out.

(4) Recurrent hepatotoxicity: similar hepatotoxicity occurs when the suspected drug is reintroduced.

The diagnosis of DILI is established if criteria 1, 2, and 3 occur simultaneously or if the 4th criteria occurs with and any two of the first three criteria.

## Exclusion criteria

(1) Hepatotoxicity occurs before exposure to the suspected drug. Hepatocellular liver injury occurs > 15 days after exposure to the suspected drug. Cholestatic/mixed liver injury arises > 30 days after exposure to the suspected drug, except in the case of slowly metabolized drugs.

(2) Liver function does not recover soon after discontinuation of the implicated drug. For hepatocellular DILI, the value of ALT should decrease > 50% within 30 days, while for cholestatic/mixed DILI, the value of ALP or TBIL should decrease > 50% within 180 days.

(3) Evidence supporting the induction of hepatotoxicity by other factors.

The diagnosis of DILI can be excluded in the presence of criteria (3) and any one of the other two exclusionary criteria.

## Necessity for liver biopsy

(1) Liver function continues to deteriorate after the suspected drug is withdrawn.

(2) After the suspected drug is withdrawn the value of ALT decreases < 50% within 30 days in hepatocellular DILI, or within 180 days in cholestatic/mixed DILI.

(3) If liver function abnormalities persist more than 180 days, liver biopsy is recommended to rule out the possibility of a chronic liver disorder or chronic DILI.

### Differential diagnosis

The manifestations of DILI are extremely varied owing to a wide heterogeneity in the clinical presentation, incomplete historical data, the absence of specific markers for DILI, and the frequent presence of potential confounding drugs. Clinicians should always rule out other potential causes of hepatic injury before making a diagnosis of DILI. Many conditions can mimic DILI including viral hepatitis, acute alcoholic hepatitis, autoimmune hepatitis, malignancy of the hepatobiliary tract or pancreas, hepatolenticular degeneration, primary biliary cirrhosis, incarcerated choledocholithiasis, primary sclerosing cholangitis, Budd-Chiari syndrome, right heart failure, hemochromatosis, alpha-1-antitrypsin deficiency, and Epstein Barr, cytomegalovirus, and herpes simplex virus infections.

### Classification and grade of DILI

In 1989 the Drug Hepatotoxicity Steering Committee of the Council for International Organizations of Medical Science identified three DILI subtypes:

(1) Hepatocellular DILI: ALT > 2 × ULN with a normal ALP or an ALT/ALP > 5.

(2) Cholestatic DILI: ALP > 2 × ULN with a normal ALT or an ALT/ALP < 5.

(3) Mixed DILI: ALT > 2 × ULN with 2 < ALT/ALP < 5.

In December 2008, the National Institutes of Health (NIH) identified five grades of DILI [8–9]:

Grade 1 (Slight): Increased serum aminotransferase or ALP levels with a TBIL value < 2.5 mg/dL. The changes in laboratory parameters are reversible and there is no abnormality in coagulation function (INR < 1.5).

Grade 1+ is further subdivided into symptomatic (S) or asymptomatic (A). The symptoms consist of fatigue, nausea, right upper abdominal tenderness, pruritus, rash, jaundice, weakness, anorexia, and weight loss.

Grade 2+ (Moderate): Increased serum aminotransferase or ALP levels with a TBIL value > 2.5 mg/dL. Cases with abnormal coagulation function (INR ≥ 1.5) and no hyperbilirubinemia are also classified into this subtype.

Grade 3+ (Severe): Increased serum aminotransferase or ALP levels with a TBIL value > 2.5 mg/dL requiring hospitalization (or prolonged preexisting hospitalization).

Grade 4+ (Acute liver failure): Increases in serum aminotransferase and ALP and at least one of the following: prolonged jaundice > 3 months duration, signs of hepatic decompensation (INR ≥ 1.5, ascites, hepatic encephalopathy), or other organ failure related to hepatic injury caused by DILI.

Grade 5+ (Fatal): Death or liver transplantation caused by DILI.

## Management and treatment

### Principles of treatment

(1) Upon establishing a diagnosis of DILI, administration of the chemotherapeutic agent or other suspected drugs must be discontinued immediately. If the symptoms are mild in a patient who requires the suspected drug, the dosage should be decreased with ongoing monitoring.

(2) Early intervention with a liver-protective drug is essential to prevent progression to acute liver failure.

(3) Any underlying hepatic disorder should be treated simultaneously.

(4) A healthy life style (abstinence from alcohol, smoking cessation, weight reduction) should be strongly encouraged.

(5) Timely referral to a tertiary care center is important. The use of high-dose corticosteroids, artificial liver, or liver transplantation should be considered in severe cases.

### Role of liver-protective drugs in DILI

There are five categories of liver-protective drugs: anti-inflammatory agents, antioxidants, hepatocellular membrane protectants, choleresis promoters, and enzyme-eliminators. Liver-protective agents should be introduced in patients with chemotherapy induced DILI. Corticosteroids are effective in DILI induced by immune-mechanisms or hypersensitivity, but their role in treating non-immune mediated hepatotoxicity is controversial. Administration of corticosteroids is highly recommended in severe and refractory DILI, but is contraindicated in patients with viral reactivation.

### Treatment of DILI

For DILI induced by intermittent intravenous chemotherapy, anti-inflammatory agents combined with antioxidant agents are recommended. If hepatotoxicity resolves, clinicians may switch to anti-inflammatory agents combined with hepatocellular membrane protective agents. Re-administration of chemotherapy is contraindicated unless hepatotoxicity resolves.

When DILI is induced by a slightly hepatotoxic drug requiring long-term administration (such as drugs for molecular targeted therapy), several articles have reported that anti-tumor treatment can continue at a reduced dosage combined with the administration of a liver-protective drug. The liver-protective drug can be discontinued when liver function tests return to normal.

If the liver function tests are slightly elevated above the ULN, anti-tumor treatment can proceed with the in-

troduction of a liver-protective drug with continued strict monitoring (ALT, AST, ALP, and TBIL levels weekly).

If liver function abnormalities do not significantly improve after the addition of a liver-protective drug, clinicians should consider the use of other liver-protective agents. Because some liver-protective drugs may be "hepatotoxic" to a certain extent, the combination of drugs from three or more of the categories of liver-protective drugs is not recommended.

### Treatment of acute liver failure

Treatment for DILI is focused on the elimination of DILI-inducing factors, protecting the remaining healthy hepatocytes, and promoting the regeneration of hepatocytes. In clinical practice, this consists of the withdrawal of any hepatotoxic drugs, aggressive supportive care, the maintenance of fluid, electrolyte, and acid-base balance, the protection of the remaining liver function, and the prevention of complications such as stress ulcer formation [10]. The use of artificial liver or liver transplantation should be considered in critical patients.

## Modification of drug dosage

### Chemotherapy withdrawal

Until now, there has been no consensus opinion regarding the withdrawal of chemotherapy because of DILI. Most clinicians have relied on recommendations published by the FDA in 2009 [11]. According to those recommendations, withdrawal of the medication is necessary when:

(1) ALT or AST > 8 × ULN.

(2) ALT or AST > 5 × ULN for > 2 weeks.

(3) ALT or AST > 3 × ULN with TBIL or INR 1.5–2 × ULN.

(4) ALT or AST > 3 × ULN with fatigue, nausea, vomiting, tenderness of the right upper abdomen, fever, rash, and eosinophilia.

Jaundice or hyperbilirubinemia develops when the majority of hepatic cells are injured. Hyman Zimmerman proposed "Hy's law" (ALT > 3 × ULN，TBIL > 2 × ULN, normal ALP after exposure to drug) [12–14], which has been adopted by many clinicians and the FDA as a indicator for the withdrawal of chemotherapy in DILI patients. DILI patients meeting the requirements for "Hy's law" are more likely to develop acute liver failure and have a poor prognosis. Among DILI patients with hyperbilirubinemia, 10% require liver transplantation or die.

### Re-administration and permanent withdrawal

With intermittent intravenous chemotherapy, if patients have no underlying hepatic disorder, most patients recover normal liver function before the next cycle of chemotherapy. If a patient's liver function is still abnormal, the following is suggested:

(1) For DILI patients with ALT/AST ≥ grade 3, ALP ≥ grade 3, and TBIL ≥ grade 1, if the ALT/AST and ALP decrease to grade 1 and TBIL is normal before next cycle of treatment or within 3 weeks after the second exposure to chemotherapy, the chemotherapeutic agent can be re-introduced at a reduced dosage.

(2) Otherwise, if the ALT/AST, ALP, and TBIL levels do not decrease to the values above within three weeks, it is recommend that the chemotherapeutic drug not be readministered.

(3) If the ALT or AST levels > 3 × ULN after re-exposure to the suspected drug, in accordance with Hy's law the chemotherapeutic agent should not be used again.

### Modification of dosage

There is no consensus on how to modify the dosage of chemotherapeutic and target drugs in the face of DILI. While modulating the dosage, clinicians should take gender, age, underlying disease, extent of liver functional abnormality, and drug category into account.

## Prognosis

Although most DILI patients have an increased ALT/AST (even > 10 × ULN), they have a good prognosis and their liver function usually recovers within 2–12 weeks after initiating liver-protective treatment. For DILI patients who have used a hepatotoxic drug for > 6 months, their liver damage may be refractory or irreversible. Chronic liver damage is highly likely if hepatic function tests are still abnormal 12 months after administration of the drug. For cholestatic DILI, the patient's liver function usually recovers completely if jaundice disappears within 4 weeks, hepatic biomarkers return to normal within several months, and there is no sign of bile duct injury. Chronic liver disease may occur in cholestatic DILI with the development of fatty hepatitis and fibrosis. For patients with underlying liver disease, if the aminotransferase levels increase along with TIBL and INR levels, the clinician should institute appropriate and aggressive treatment as soon as possible. For patients with viral reactivation treatment should also include antiviral therapy. The use of artificial liver or liver transplantation should be considered in cases of fulminant hepatic failure.

## Prevention

Clinicians should be familiar with the potential hepatotoxicity of chemotherapeutic agents. Clinicians should also keep the following in mind:

(1) Do not combine hepatotoxic chemotherapeutic agents if possible.

(2) For patients with underlying liver disease, hepato-

toxic chemotherapeutic agents should be introduced very carefully.

(3) For patients with liver functional damage after exposure to chemotherapeutic agents, the dosage of the causative drug should be reduced depending on the extent of hepatotoxicity.

(4) Liver function should be monitored during and after chemotherapy. Do not hesitate to discontinue chemotherapy and to initiate liver protective therapy if hepatotoxicity develops.

(5) For patients with a high risk of DILI, liver protective drug treatment can be administered along with antitumor treatment.

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