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EXPERT CONSENSUS

Chinese expert consensus on managing thrombocytopenia in patients with cancer and liver injury

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Abstract

Thrombocytopenia and liver injury are serious clinical problems in patients with cancer. The etiology of thrombocytopenia in patients with cancer and liver injury (TCLI) is complicated. Managing cancer therapy-induced thrombocytopenia has gradually become standardized, and managing liver injury-associated thrombocytopenia has become more effective with the approval and marketing of relevant drugs. However, the optimal strategy for managing thrombocytopenia in patients with cancer and liver injury remains unclear, and the superposition of thrombocytopenia and liver injury further increases the difficulty of cancer treatment. Therefore, the Committee of Cancer Support Therapy of the Chinese Anti-Cancer Association has organized experts to analyze and discuss relevant literature to form a Chinese expert consensus on managing thrombocytopenia in patients with cancer and liver injury (2022 Edition) to guide clinical practice.

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Thrombocytopenia, usually defined as a platelet count of $< 100 \times 10^9$/L in the peripheral blood [1], is a common complication in patients with cancer. Guidelines for cancer therapy-induced thrombocytopenia have been published. However, in clinical practice, when patients with cancer have concomitant liver injury, the risk and severity of thrombocytopenia are further increased because of secondary portal hypertension and hypersplenism; for such patients, doctors face more severe challenges in managing thrombocytopenia. Therefore, to bridge the gap in this field and scientifically manage thrombocytopenia in patients with cancer and liver injury, the Committee of Cancer Support Therapy of the Chinese Anti-Cancer Association has organized multidisciplinary expert discussions to formulate the first Chinese expert consensus on managing thrombocytopenia in patients with cancer and liver injury. The levels of evidence-based medical proof, recommendation grades, and their definitions are presented in Tables 1 and 2 [2].

Thrombocytopenia in patients with cancer and primary liver disease

Epidemiology of thrombocytopenia in patients with cancer and primary liver disease

In China, approximately 7 million people have liver cirrhosis, leading to 460,000 new liver cancer cases annually [3]. The prevalence of chronic liver disease-associated thrombocytopenia ranges from 6% among patients without cirrhosis to 85% among those with cirrhosis [4, 5]. Patients with hepatitis B and/or C have a higher incidence of thrombocytopenia than those with chronic liver disease caused by other etiologies (toxin/drug-induced hepatitis, alcoholic hepatitis, and non-alcoholic steatohepatitis) [6]. Initial thrombocytopenia is the most significant risk factor for hepatitis B virus-associated thrombocytopenia (HBV-TP) and hepatitis C virus-associated thrombocytopenia (HCV-TP). Splenomegaly and cirrhosis are significant risk factors for moderate HCV-TP. Hyperbilirubinemia is an important risk factor for moderate to severe HBV-TP. Anti-platelet antibodies are associated with HCV-TP severity, and anti-platelet autoantibody alone or in combination with splenomegaly may cause thrombocytopenia [7]. The prevalence of thrombocytopenia in patients with cancer and primary liver disease has not been reported. Given that multiple factors associated with tumors can also lead to thrombocytopenia, the risk of thrombocytopenia in patients with cancer and primary liver disease will be further increased.

Pathophysiology of thrombocytopenia in patients with cancer and primary liver disease

Thrombocytopenia in patients with liver disease was previously thought to be mainly caused by hypersplenism. However, thrombocytopenia in patients with liver disease is a complex and multifactorial process involving different mechanisms. It usually includes decreased platelet production, increased destruction, and splenic sequestration [8, 9].

Platelet production decreased

Thrombopoietin (TPO) is an important factor in promoting thrombopoiesis and is mainly synthesized in the liver parenchyma and sinusoidal endothelial cells. TPO regulates the proliferation, differentiation, and maturation of megakaryocytes by binding to c-mpl receptors on megakaryocytes and mediates thrombopoiesis [9]. As liver disease progresses and worsens in severity, the ability of the liver to synthesize TPO decreases [10]. In addition, the

Table 1 Levels of evidence-based medical proof and definitions

Level of Evidence	Definition
Level I (high quality)	Further research is very unlikely to change the confidence in the clinical efficacy assessment result. It is regarded as high-level evidence.
Level II (moderate quality)	Further research is likely to have an important impact on the confidence in the efficacy assessment result and may change the assessment result. It is regarded as medium-level evidence.
Level III (low quality)	Further research is very likely to have a significant impact on the confidence in the efficacy assessment results and is very likely to change the assessment result. It is regarded as low-level evidence.
Level IV (very low quality)	Any efficacy assessment is very uncertain. It is regarded as very low-level evidence.

Table 2 Recommendation grades and definitions

Recommended grade	Definition
Recommendation	Based on available evidence, recommendation is made if it is well established that the benefits outweigh the risks and burdens.
Weak recommendation	Based on available evidence, weak recommendation is made if the benefits, risks, and burdens are fairly balanced, or if there is significant uncertainty in the extent of the benefits and risks.

direct myelosuppressive effect of hepatitis virus is one of the causes of decreased platelet production [9, 10]. The toxic effects of alcohol on bone marrow megakaryocytes may also result in decreased platelet production [10].

Platelet destruction increased

The detection rate of platelet-related antibodies is significantly higher in patients with cirrhosis than in healthy individuals [11], and autoantibodies against platelet surface antigens can enhance platelet clearance by the splenic and hepatic reticuloendothelial systems [12]. Moreover, in patients with cirrhosis, decreased levels and activity of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 drive the accumulation of von Willebrand factor multimers, which mediate the enhancement of shear stress-induced platelet aggregation [13, 14].

Splenic sequestration

A larger spleen volume suggests that hypersplenism is more pronounced, more blood cells are retained in the enlarged spleen, and macrophages in the spleen have stronger phagocytosis; hence, the spleen size is inversely proportional to the platelet count [10, 15]. In addition to the increased storage of platelets in the enlarged spleen, the mechanism by which hypersplenism results in decreased platelets involves increased vasoactive substances and cytokines released by the spleen [9, 10].

Diagnosis and evaluation of thrombocytopenia in patients with cancer and primary liver disease

Diagnostic criteria

The clinical diagnostic criteria for primary liver disease-associated thrombocytopenia include: (1) Peripheral blood platelet count < 100×10^9/L; (2) The liver disease meets relevant diagnostic criteria for viral liver disease, alcoholic liver disease, non-alcoholic fatty liver disease, or autoimmune liver disease due to primary etiologies [16-21] (Attached Table 1); (3) Excluding thrombocytopenia caused by other underlying diseases and/or comorbidities, such as aplastic anemia, leukemia, primary immune thrombocytopenia, and bone marrow tumor cell infiltration; (4) Excluding thrombocytopenia caused by anti-cancer therapy and/or other drugs, including radiotherapy, chemotherapy, targeted therapy, immunotherapy, antibiotics, antibody-drug conjugates, and heparin; (5) Excluding pseudothrombocytopenia caused by ethylenediaminetetraacetic acid anticoagulant.

Differential diagnosis

In patients with cancer therapy-induced thrombocytopenia, especially chemoradiotherapy-induced thrombocytopenia, platelet count fluctuations are often closely related to dose reduction or discontinuation of tumor therapy. For patients whose platelet count slowly declines over time compared with the baseline, which does not appear to be related to fluctuations in cancer treatment, tumor metastases to the bone or chronic liver disease should be considered. Patients with cancer are prone to co-infection due to iatrogenic reasons such as immunosuppression, indwelling catheters, and surgery, and infection can lead to thrombocytopenia through multiple mechanisms. In addition to cancer therapy, drugs such as heparin and antibiotics may also cause thrombocytopenia, and blood transfusion precipitation may lead to post-transfusion purpura [22]. Therefore, a detailed understanding of the clinical background of thrombocytopenia in patients and the completion of laboratory tests is helpful in identifying the complex etiology of thrombocytopenia. If

Table 3 Differential diagnosis of thrombocytopenia [1, 24–26]

Disorders		Examination items
Infection	Serious infections	Hematology: C-reactive protein; procalcitonin
	Viral infection	Epstein-Barr virus, cytomegalovirus, HIV
Hematological system disease	Hemolytic anemia; paroxysmal nocturnal hemoglobinuria	Lactate dehydrogenase
	Aplastic anemias, tumor metastases to bone marrow	Bone marrow smear, bone marrow biopsy
	Immune thrombocytopenia	Platelet glycoprotein-specific autoantibodies
Autoimmune disorders	Systemic lupus erythematosus, sicca syndrome, rheumatoid arthritis	Antinuclear antibodies, rheumatoid factor
Thrombotic disorders	Disseminated intravascular coagulation	Prothrombin time, partial activated prothrombin time, thrombin time, fibrinogen, D-dimer, fibrin degradation products
Renal impairment	Renal impairment-associated thrombocytopenia	Creatinine
Malnutrition	Malnutrition-associated thrombocytopenia	Vitamin B12, folic acid
Thrombocytopenia associated with anti-tumor therapy and/or other drug therapy	Chemotherapy (e.g., Platinum, Gemcitabine , Capecitabine, and Temozolomide), radiotherapy, checkpoint inhibitors, targeted therapy (e.g., Lenvatinib, Imatinib, Zanubrutinib, and Niraparib), antibody-drug conjugates (e.g., ADC-Trastuzumab Emtansine), antibiotics, and heparin	Hematology, a certain drug that can cause thrombocytopenia is administered exactly before the onset of thrombocytopenia, and platelet count returns to normal after discontinuation of the drug.

the diagnosis of thrombocytopenia cannot be confirmed by routine screening, laboratory tests to confirm the diagnosis can be selected based on medical history and clinical manifestations [1]. For example, anti-platelet-specific antibodies have important clinical significance in differentiating immune thrombocytopenia from non-immune thrombocytopenia [23] (Table 3).

Grading of thrombocytopenia

The most commonly used severity grading criteria for thrombocytopenia are the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). According to CTCAE (v5.0) grading for adverse event "thrombocytopenia," platelet count below the lower limit of normal (75×10^9/L) is considered as Grade 1; platelet count < 75 to 50×10^9/L is considered as Grade 2; platelet count < 50 to 25×10^9/L is considered as Grade 3; platelet count < 25×10^9/L is considered as Grade 4 [27]. When the platelet count is > 50×10^9/L, bleeding symptoms are less common; when the platelet count is (30–50) $\times 10^9$/L, the patient may present with skin purpura and ecchymosis; when the platelet count is (10–30) $\times 10^9$/L, the patient will have difficulty stopping bleeding due to trauma; when the platelet count is < 10 $\times 10^9$/L, the patient may be at risk of life-threatening bleeding [28].

Grading of bleeding severity

Mild to moderate: No bleeding symptoms or skin bleeding spots/ecchymoses only [29].

Severe: Bleeding symptoms, including mucocutaneous bleeding, gastrointestinal, respiratory, genitourinary, and intracranial bleeding [29].

Treatment of thrombocytopenia in patients with cancer and primary liver disease

Treatment goals

The treatment goals are: (1) to increase the platelet count and reduce the risk of spontaneous bleeding caused by it; (2) to minimize dose reduction or delay in systemic treatment of cancer due to thrombocytopenia; and (3) to maintain the platelet count above the reference threshold for invasive procedures or surgery, and to reduce the risk of traumatic bleeding related to perioperative procedures or surgery.

Treatment principles

Treatment of thrombocytopenia in patients with cancer and primary liver disease begins with the treatment of etiology, with graded management based on the bleeding status and treatment goals. Comprehensive treatment with platelet transfusion, drugs (e.g., thrombopoietic drugs and immunosuppressants), or surgery (e.g., splenectomy and partial splenic artery embolization) should be considered in a timely manner to avoid fatal bleeding caused by low platelets. Treatment measures should be selected based on the etiology and pathophysiological mechanism of thrombocytopenia in patients. Considering the management of liver injury, drugs with approved indications without hepatotoxicity should be preferred. Platelet count should be closely monitored during treatment to avoid excessive elevation, which can increase the risk of thrombosis.

Treatment measures

Platelet transfusion: *In vitro* studies have suggested that platelet counts above 56×10^9/L improve thrombin production in patients with cirrhosis [30], but platelet transfusion has not been shown to significantly improve thrombin generation or normalize thromboelastometry tests in patients with cirrhosis [31]. The American Gastroenterological Association Institute recommends risk stratification based on the type of surgery and surgical site, with no safety margin for routine laboratory tests related to preoperative bleeding and coagulation in patients with cirrhosis. For managing bleeding and coagulation, individualized treatment can be guided by thromboelastography while avoiding unnecessary blood transfusions and volume overload, and routine use of blood products (e.g., fresh frozen plasma or platelets) is not recommended to prevent bleeding [32, 33]. The American Society of Clinical Oncology believes that the threshold

Table 4 TPO-RAs approved for marketing in China [35, 36]

	Romiplostim	Eltrombopag	Avatrombopag	Hetrombopag
TPO receptor binding	Extracellular	Transmembrane	Transmembrane	Transmembrane
Route of administration	Subcutaneous injection	Oral	Oral	Oral
Dietary effects	No	Yes	No	Yes
Interaction with cations	No	++	No	++
Dose reduction required for East Asian population	No	Yes	No	Yes
Dose reduction required for patients with hepatic insufficiency	No	Yes	No	Yes
Additional liver function tests	No	+	No	?
Use in patients with renal failure	Yes	May be used	May be used	No data
Use during pregnancy	No	No	No	No
Approved indications in China	ITP	ITP	Liver disease-associated thrombocytopenia	ITP\SAA

for platelet transfusion should be adjusted according to the patient's diagnosis, clinical condition, and treatment modality. The risk of bleeding during chemotherapy-induced thrombocytopenia in patients with solid tumors is related to the duration of the nadir platelet count. The panel recommends a prophylactic platelet transfusion threshold of 10×10^9/L, whereas the platelet transfusion threshold is higher than 10×10^9/L for patients with active bleeding. In the absence of relevant coagulation abnormalities, the platelet transfusion threshold is 40×10^9/L–50×10^9/L for high-risk invasive procedures, and it is critical that platelet count meets the safety threshold required for invasive procedures or surgery if platelets are transfused preoperatively [34].

Thrombopoietin receptor agonists: TPO receptor agonists (TPO-RAs) have improved immunogenicity compared with first-generation TPO analogs. Currently, TPO-RAs approved for marketing in China include romiplostim, eltrombopag, avatrombopag, and hetrombopag, mainly for treating immune thrombocytopenia (ITP), severe aplastic anemia (SAA), and chronic liver disease (CLD)-associated thrombocytopenia [22], of which only avatrombopag is approved for CLD-associated thrombocytopenia (Table 4).

Two Phase III studies with avatrombopag showed that the proportion of patients who did not require platelet transfusion or any rescue for bleeding was significantly higher in the avatrombopag group than in the placebo group, and the proportion of patients with platelet counts ≥ 50×10^9/L on the day of invasive procedures was also higher in the avatrombopag group than in the placebo group [37]. Eltrombopag significantly reduced the proportion of patients treated with platelet transfusions from pre-procedure to 7 days after the procedure. However, portal vein thrombotic events occurred in six patients treated with eltrombopag, leading to premature termination of the study [38]. A small sample size research with romiplostim suggested that the preoperative use of romiplostim for HCV infection-associated thrombocytopenia (platelet count < 50×10^9/L) could result in a platelet count of ≥ 70×10^9/L and surgery in most patients [39]. A meta-analysis showed that TPO-RA significantly increased the proportion of patients with a preoperative platelet count of > 50×10^9/L and decreased the platelet transfusion rate, without increasing the risk of thrombosis [40].

Recombinant human thrombopoietin: Recombinant human thrombopoietin (rhTPO) was first developed abroad, but its development was terminated because of concerns about the generation of neutralizing antibodies [41]. In 2005, rhTPO was approved for marketing in China, mainly for adjuvant treatment of thrombocytopenia caused by chemotherapy for solid tumors and primary immune thrombocytopenia. A retrospective analysis showed that for patients with liver disease-associated thrombocytopenia treated with rhTPO before surgery, the platelet count was significantly higher on day 8 than at baseline and peaked on day 12 [42]. In addition, another study found that rhTPO was more effective in patients with cirrhosis but without splenomegaly [43].

Recombinant human interleukin-11: In 1997, recombinant human interleukin-11 (rhIL-11) was formally approved by the United States Food and Drug Administration (FDA) and became the first specific platelet-elevating drug to be used in chemotherapy or radiotherapy-induced thrombocytopenia [44]. In 2003, the first rhIL-11 was approved for marketing in China,

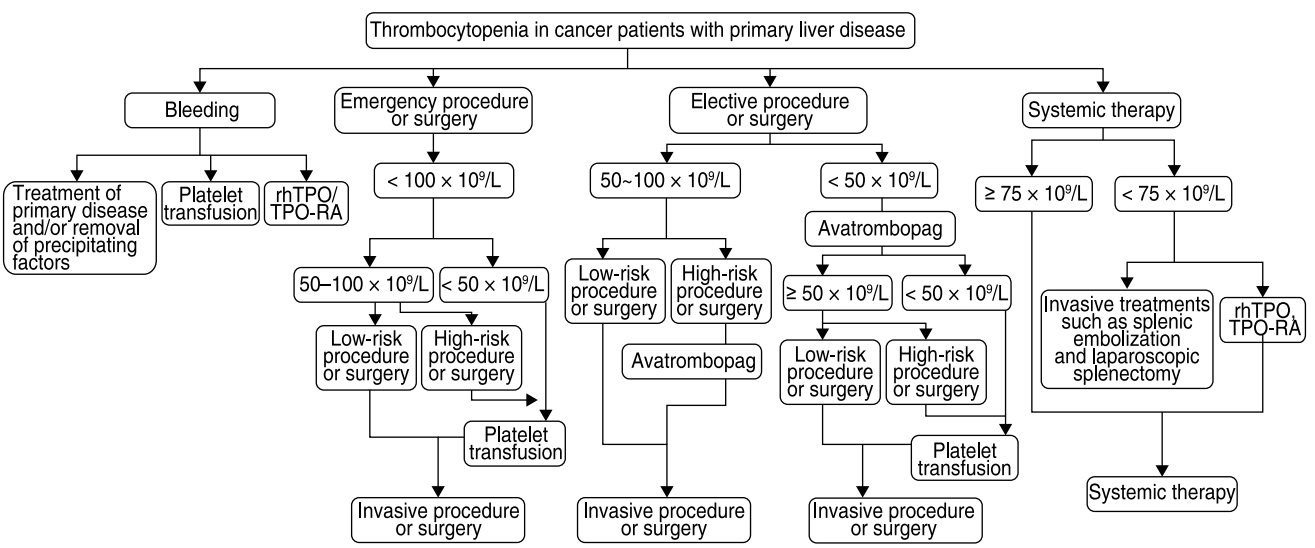

Fig. 1 Algorithm for managing thrombocytopenia in patients with cancer and primary liver disease

mainly for treating grade 3 or 4 thrombocytopenia after chemotherapy for solid tumors and non-myeloid leukemia [45]. RhIL-11 was used in patients with thrombocytopenia caused by cirrhosis and hypersplenism (platelet count ≤ 75×10^9/L), while the mean increase in platelet count was only $(5.95 \pm 12.31) \times 10^9$/L after treatment [46].

Surgical treatment: Splenectomy, partial splenic artery embolization (PSAE), and radiofrequency ablation (RFA) are the main invasive treatments for splenomegaly/hypersplenism-associated thrombocytopenia [47]. Invasive treatment measures can achieve relatively long-term sustained improvement in platelet count in patients with splenomegaly/hypersplenism-associated thrombocytopenia [48-50], but the duration of sustained platelet improvement after PSAE or RFA treatment tends to correlate closely with embolized or ablated spleen volume [50]. In addition, patients undergoing invasive treatment have a worse short-term prognosis, with a significantly increased incidence of postoperative complications, such as venous thrombosis, but no significant improvement in long-term prognosis [51-54].

Management of thrombocytopenia in patients with cancer and primary liver disease

PSAE and splenectomy are effective treatment options for splenomegaly/hypersplenism-induced thrombocytopenia; however, these invasive treatments often increase the risk of complications and even death. TPO-RAs have been approved for treating CLD-associated thrombocytopenia and can elevate platelet count with a low adverse event rate. However, the selection of specific treatment measures should be based on the pathophysiological mechanism of thrombocytopenia in patients, such as the severity of hypersplenism/splenomegaly, treatment purpose, and physical status. Invasive treatment may even need to be conditionally applied to specific populations after multidisciplinary discussion.

Recommendation 1: For patients with thrombocytopenia and cancer complicated by primary liver disease who develop bleeding, platelet transfusion, rhTPO, or TPO-RAs may be considered if the primary disease and/or precipitating factors are actively managed (Level of Evidence: III, Recommendation Grade: weak recommendation).

Recommendation 2: For patients with thrombocytopenia and cancer complicated by primary liver disease who are scheduled to undergo invasive procedures or surgery, platelet transfusion may be administered in emergency situations. TPO-RAs (e.g., avatrombopag) or rhTPO, with less effect on liver function, may be considered in non-emergency situations to increase the platelet count to a safe threshold required for invasive procedures or surgery. (Level of Evidence: II, Recommendation Grade: Recommendation).

Recommendation 3: Among patients with thrombocytopenia and cancer complicated by primary liver disease who intend to undergo systemic therapy, invasive treatments such as splenic embolization and splenectomy may be considered for patients with severe hypersplenism/splenomegaly because of the long-term nature of systemic therapy. RhTPO or TPO-RA may be considered for patients with contraindications to invasive treatment (Level of Evidence: III, Recommendation Grade: weak recommendation).

Managing thrombocytopenia in patients with cancer therapy-induced thrombocytopenia complicated by primary liver disease

For managing thrombocytopenia in patients with cancer therapy-induced thrombocytopenia complicated by primary liver disease, please refer to the Guidelines for the Diagnosis and Treatment of Cancer Therapy-Induced Thrombocytopenia (2022 edition) [29]. The Guidelines recommend prophylactic platelet-stimulating growth factor for patients with a nadir platelet count of < 50×10^9/L in the last chemotherapy cycle or patients with a nadir platelet count of ≥ 50×10^9/L and < 75×10^9/L in the last chemotherapy cycle combined with at least one high-risk factor for bleeding to ensure that the chemotherapy is conducted smoothly [29]. There is a lack of evidence-based secondary prevention for patients with cancer therapy-induced thrombocytopenia complicated by primary liver disease. Since liver disease affects the production, destruction, and distribution of platelets, it will increase the risk of cancer therapy-induced thrombocytopenia and the difficulty of its recovery. Therefore, more aggressive secondary prevention strategies should be adopted.

Recommendation 4: For patients with cancer therapy-induced thrombocytopenia complicated by primary liver disease, drugs with less effect on liver function (e.g., avatrombopag) should be selected when developing a management scheme for thrombocytopenia. In addition, the timing of treatment should be differentiated, such as active secondary prevention (Level of Evidence: III, Recommendation Grade: weak recommendation).

Managing adverse reactions

Overview of adverse drug reactions

Adverse drug reactions (ADRs) caused by TPO-RAs mostly occur within 6 months of treatment, mainly affecting the circulatory and hematological systems, with clinical manifestations of arteriovenous thrombosis, myelofibrosis, and hepatotoxicity. The dose and duration of such drugs were not significantly correlated with the time and severity of thrombosis [55]. However, if patients have concomitant thrombotic diseases, such as coronary atherosclerotic disease, myocardial infarction, and stroke, the control of the primary disease should be

closely monitored during treatment with TPO-RAs, and regular reexamination should be performed. Ghanima et al. summarized the clinical application progress of TPO-RAs in the past decade of marketing, and moderate myelofibrosis was observed in few patients; however, the correlation between this adverse event and the type, dose, or duration of the therapeutic agent has not been clearly established [56]. The literature reported that two pediatric patients developed acute liver failure after treatment with eltrombopag [55, 57], and the FDA and National Medical Products Administration gave a black box warning regarding the hepatotoxicity for eltrombopag, suggesting it may increase the risk of serious and potentially life-threatening hepatotoxicity. Hence, patients should be monitored for liver function and the medication should be adjusted appropriately during use [58].

Adverse reactions to rhTPO mainly include fever, chills, general malaise, and asthenia, which are generally mild [59-61]. A nonrandomized, parallel-controlled study showed that the incidence of adverse reactions after treatment with rhTPO was 11.4%, whereas that after treatment with rhIL-11 was 78.4% [62].

As an inflammatory factor, rhIL-11 is prone to systemic adverse reactions, including asthenia, slight fever, vomiting, joint soreness, and thrombosis. In addition, rhIL-11 causes damage to the heart and kidney, which can cause tachycardia, vasodilatation, atrial fibrillation, atrial flutter, and body fluid retention. It can also affect the digestive, nervous, and respiratory systems, causing serious allergic reactions [63].

Recommendation 5: Most adverse reactions to TPO-RAs, rhTPO, and rhIL-11 are mild to moderate and can resolve rapidly after drug withdrawal. In cases of suspected adverse reactions, appropriate symptomatic management should be provided after differential diagnosis (Level of Evidence: III, Recommendation Grade: recommendation).

Managing thrombosis/thromboembolism

Portal vein thrombosis (PVT) is a common complication in patients with cirrhosis, with a prevalence of 10–25% [64, 65]. Malignancies are the most important risk factors for venous thromboembolism (VTE), and 20%–30% of cases with the first occurrence of VTE are associated with tumors [66]. Venous thrombosis has been reported with drugs and invasive treatment of liver disease-associated thrombocytopenia [38, 52, 53]. The Expert Consensus on the Management of Portal Vein Thrombosis in Cirrhosis (2020) recommends endoscopic and hematologic examinations to fully assess the risk of bleeding before anticoagulant therapy in patients with cirrhosis and PVT. The main indications for anticoagulant therapy are acute symptomatic PVT, waiting for liver transplantation, and concomitant mesenteric vein thrombosis. Anticoagulant therapy should be suspended in patients with cirrhosis and PVT with a recent history of bleeding, severe gastroesophageal varices, and severe thrombocytopenia [67]. The 2022 European Hematology Association Guidelines on the Management of Antithrombotic Therapy in Patients with Cancer and Thrombocytopenia recommend that patients with grade 1/2 thrombocytopenia can continue oral or parenteral anticoagulant therapy if the platelet count is stable or use low-molecular-weight heparin for anticoagulation if the platelet count is unstable. For patients with grade 3 thrombocytopenia, anticoagulant therapy with a halved dose of low-molecular weight heparin may be considered if the risk of thrombosis is high, thrombocytopenia is expected to remain stable for weeks to months, and platelet count should be closely monitored. Anticoagulant therapy should be discontinued in patients with grade 4 thrombocytopenia [68]. The Guidelines for the Prevention and Treatment of Venous Thromboembolism in Patients with Cancer (2020 Edition) recommend that platelet count should be closely monitored during the treatment of patients with cancer and VTE or those at high risk of VTE, and prophylaxis or treatment should be performed according to the assessed risk of venous thromboembolism [69].

Recommendation 6: Platelet count should be closely monitored during the treatment of thrombocytopenia in patients with cancer and primary liver disease to prevent excessive elevations in platelet count and an increased risk of thrombosis. Anticoagulant therapy should be considered in cases of grade 1/2 thrombocytopenia with thrombosis. In cases of grade 3/4 thrombocytopenia with thrombosis, caution should be exercised with anticoagulant therapy (Level of Evidence: II, Recommendation Grade: recommendation).

Table 5 Common anti-cancer drugs causing liver injury in clinical practice [71-77]

Classification of anti-cancer drug	Typical drugs
Platinum	Oxaliplatin, and Carboplatin
Antimetabolites	Methotrexate, Cytarabine, and Gemcitabine
Alkylating agents	Cyclophosphamide, Ifosfamide, and Busulfan
Molecular targeted drugs	Imatinib, Dasatinib, Lapatinib, Erlotinib, and Lenvatinib, Sorafenib, Bevacizumab, Gemtuzumab, and Trastuzumab
Immune checkpoint inhibitors	Nivolizumab , Pembrolizumab, and Ipilimumab
Others	Irinotecan, and antibody-drug conjugates (ADCs)

Thrombocytopenia with liver injury secondary to tumor therapy

Overview

Anti-cancer drugs or immunomodulators account for 8.34% of patients with drug-induced liver injury (DILI) [70]. Hepatic sinusoidal obstruction syndrome (HSOS) occurs in up to 50% of patients treated with oxaliplatin for colon adenocarcinoma [71]. Anti-cancer drugs such as 5-fluorouracil, irinotecan, azathioprine, carmustine, cyclophosphamide, and dacarbazine also increase the risk of HSOS [72, 73]. Immune checkpoint inhibitor-induced hepatitis occurs in 9%–20% of patients treated with programmed cell death protein 1/programmed cell death ligand 1 inhibitors [74]. Increased serum transaminase levels were observed in 52% of patients treated with lenvatinib [75]. The incidence of DILI after treatment with antibody-drug conjugates (ADCs) was 7.9% [76]. In addition, radiation therapy, especially for thoracic and abdominal tumors, can lead to clinical subacute and chronic liver injuries [77].

Thrombocytopenia is a common hematologic toxicity associated with anticancer therapies. Studies have reported an incidence of chemotherapy-induced thrombocytopenia of 9.7% [78], an incidence of thrombocytopenia associated with different targeted therapies ranging from 2% to 78% [79, 80], and an incidence of immune checkpoint inhibitor-associated thrombocytopenia ≥ grade 3 of 1.73% [81]. Therefore, secondary liver injury and thrombocytopenia often coexist during cancer treatment (Table 5).

Diagnosis

The clinical diagnosis of DILI relies on exclusion methods. The diagnosis of DILI is inferred by collecting complete medical history, comprehensive blood tests, hepatobiliary imaging, and liver biopsy to exclude other etiologies. To reduce the subjective tendency of clinical diagnosis, there are currently some relatively objective causality scoring systems, including the Roussel-Uclaf Causality Assessment Method (RUCAM) scale (Attached Table 4) [82]. The etiological diagnosis of thrombocytopenia is often complicated because cancer therapy can directly lead to hematological toxicity and may also be associated with liver injury secondary to cancer therapy. Therefore, accurate knowledge of the history of drug exposure and the course of hepatic dysfunction and thrombocytopenia is important.

Treatment principles and schemes

The principles for treating thrombocytopenia with liver injury secondary to cancer therapy [83] are as follows: (1) Suspected drugs that can injure the liver should be discontinued promptly, and reuse of suspected or similar drugs should be avoided whenever possible; (2) The risk of primary disease progression caused by drug withdrawal and aggravation of liver injury caused by continued medication should be fully weighed; (3) Appropriate drug therapy should be selected according to the clinical type of DILI; (4) Thrombocytopenia should be managed with reference to primary liver disease-associated thrombocytopenia and cancer therapy-induced thrombocytopenia.

Clinical treatment measures for oxaliplatin immune-induced syndrome include permanent discontinuation of oxaliplatin. The use of corticosteroids and intravenous immunoglobulin has not been demonstrated, but it can be considered [84]. Jácome et al. retrospectively analyzed the use of PSAE for chemotherapy-induced hypersplenism. After PSAE, 80% of patients had a platelet count of ≥ 100 × 10^9/L, 81% of patients resumed systemic treatment, and the proportion of splenic infarction was linearly correlated with increased platelet count [85]. A cohort study by Overman et al. showed that the addition of bevacizumab to oxaliplatin-based chemotherapy reduced the risk of splenomegaly and thrombocytopenia in patients with metastatic colorectal cancer [86].

Recommendation 7: For patients with thrombocytopenia and liver injury secondary to cancer therapy, the selection of a treatment regimen for thrombocytopenia can refer to the management of primary liver disease-associated thrombocytopenia and cancer therapy-induced thrombocytopenia. Drugs with less effect on liver function (e.g., avatrombopag) are recommended as platelet-elevating drugs (Level of Evidence: III, Recommendation Grade: weak recommendation).

Multidisciplinary management and health education of thrombocytopenia

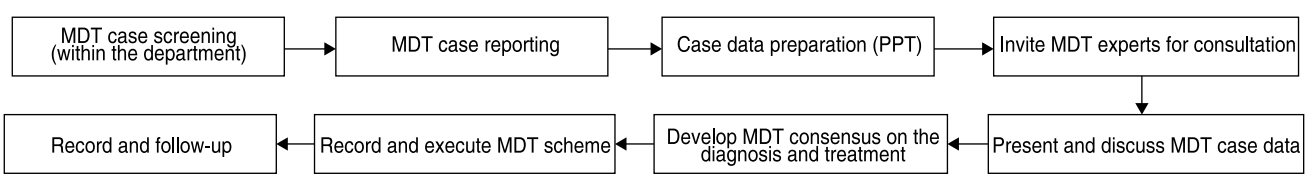

Fig. 2 MDT execution process

in patients with cancer and liver injury

Multidisciplinary management of thrombocytopenia in patients with cancer and liver injury

The etiology and pathogenesis of thrombocytopenia in patients with cancer and liver injury are complex, and its diagnosis and treatment involve multidisciplines, such as oncology, hepatology, hematology, intervention, and surgery. Through multidisciplinary collaborative diagnosis and treatment, the professional advantages of each discipline can be maximized for patient benefit. For patients with unknown etiology of thrombocytopenia, patients with severe thrombocytopenia and critically ill condition, and patients who experience poor recovery of platelet count after conventional treatment, which affects further diagnosis and treatment of cancer, it is recommended to report them to the intra- or inter-hospital multidisciplinary team (MDT), invite relevant experts of MDT to perform consultation, formulate the diagnosis and treatment plan, and conduct follow-up.

Recommendation 8: Multidisciplinary collaborative diagnosis and treatment are recommended for patients with unknown etiology of thrombocytopenia, severe thrombocytopenia and critically ill condition, and poor recovery of platelet count after conventional treatment (Level of Evidence: IV, Recommendation Grade: recommendation).

Health education of thrombocytopenia in patients with cancer and liver injury

Hemorrhage caused by severe thrombocytopenia in patients with cancer and liver injury is one of the main causes of death. Patients with concomitant ruptured esophagogastric varices, gastric and duodenal peptic ulcers, or esophageal/gastric/duodenal mucosal erosions

Appendix Table 1 Diagnostic criteria for primary liver disease [16-21]

Type of primary liver disease	Clinical diagnostic criteria
Viral liver disease	The etiological diagnosis of viral liver disease should be made based on the results of serology and etiology tests. Infection with hepatitis viruses includes hepatitis A, B, C, and E. Clinically, the diagnosis is usually further subdivided based on the results of serology, virology, biochemistry, radiography, pathology, and other ancillary examinations in infected patients.
Alcoholic liver disease	There is no specific clinical diagnostic method for alcoholic liver disease. Careful inquiry about long-term alcohol consumption history is very important. For patients who meet Item 1, exclude other causes of liver disease, and if they meet Items 3 and 4, the diagnosis of alcoholic liver disease can be confirmed; for patients who meet Items 1, 3, and 4, with evidence of viral hepatitis infection, the diagnosis of alcoholic liver disease with viral hepatitis can be confirmed: 1. A history of long-term alcohol consumption for more than 5 years, equivalent to ethanol ≥ 40 g/d for men and ≥ 20 g/d for women; or a history of heavy alcohol consumption within 2 weeks, equivalent to ethanol > 80 g/d. However, attention should be paid to the influences of factors such as sex and genetic susceptibility. The conversion formula of ethanol amount (g) = alcohol consumption (mL) × ethanol content (%) × 0.8. The Alcohol Use Disorders Identification Test, the Michigan Alcoholism Screening Test, CAGE questionnaire and other scales can be used to screen for ethanol (alcohol) abuse and ethanol (alcohol) dependence. 2. The clinical symptoms are nonspecific and may be asymptomatic or accompanied by right upper abdominal distending pain, inappetence, asthenia, body weight loss, and jaundice; with the aggravation of the disease, there may be neuropsychiatric symptoms, spider naevus, liver palms, and other manifestations. 3. The parameters such as serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total bilirubin (TBil), prothrombin time (PT), mean corpuscular volume (MCV), and carbohydrate-deficient transferrin (CDT) are increased. Among these parameters, AST/ALT > 2, increased GGT, and increased MCV are characteristic of alcoholic liver disease. CDT test is specific; however, it is not routinely conducted in clinical practice. These parameters can decrease significantly after abstinence and usually return to normal within 4 weeks (but GGT recovers more slowly), which is helpful in diagnosis. 4. There are typical findings in B-mode ultrasound, X-ray computed tomography, magnetic resonance imaging or transient elastography of the liver. 5. Current infection with hepatotropic virus, drug-induced and toxic liver injuries, and autoimmune liver disease are excluded.
Non-alcoholic fatty liver disease	The diagnosis of non-alcoholic fatty liver disease (NAFLD) requires radiographic or histologic evidence of diffuse hepatocellular steatosis, and other causes of hepatic steatosis such as ethanol (alcohol) abuse should be ruled out. Considering the absence of specific symptoms and signs, NAFLD is suspected in most patients owing to incidental findings of elevated serum ALT and GGT or diffuse fatty liver on imaging examination. NAFLD is assessed by quantifying the degree of hepatic steatosis and fibrosis, determining the presence or absence of metabolic and cardiovascular risk factors and complications, the presence or absence of hepatic inflammatory injury, and the presence or absence of other causes of liver disease.
Autoimmune liver disease	The International Autoimmune Hepatitis Group (IAIHG) developed descriptive diagnostic criteria and diagnostic scoring systems for AIH in 1993 and revised them in 1999 (Attached Table 2). In 2008, IAIHG proposed a simplified diagnostic scoring system for AIH (Attached Table 3). The simplified scoring system is prone to missed diagnosis of some atypical patients, such as those with low or negative autoantibody titers and/or low or even normal serum IgG levels. Therefore, for patients with suspected AIH or undiagnosed by simplified diagnostic scoring system, it is recommended that the integrated diagnostic scoring system be used for comprehensive evaluation to avoid missed diagnosis.

Appendix Table 2 Integrated diagnostic scoring system for AIH (1999) [17]

Parameter/Clinical Feature	Score	Parameter/Clinical feature	Score
Female	+2	Drug history	
Ratio of ALP (fold upper limit of normal) to AST (or ALT) (fold upper limit of normal)		Positive	–4
< 1.5	+2	Negative	+1
1.5–3.0	0	Average alcohol intake daily (g/day)	
> 3.0	–2	< 25	+2
Ratio of serum gamma-globulin or IgG to normal value		> 60	-2
> 2.0	+3	Liver histology	
1.5–2.0	+2	Interface hepatitis	+3
1.0–1.5	+1	Lymphoplasmacytic infiltrate	+1
< 1.0	0	Rosette-like changes in hepatocytes	+1
ANA, ASMA or LKM-1 titer		None of the above	–5
> 1:80	+3	Bile duct changes	–3
1:80	+2	Other changes	–3
1:40	+1	Other immune diseases	+2
< 1:40	0	Other available parameters	
AMA positivity	–4	Positive for other specific autoantibodies (SLA/LP, LC-1, ASGPR, pANCA)	+2
Hepatitis virus markers		HLA-DR3 or DR4	+1
Positive	–3	Response to treatment	
Negative	+3	Complete	+2
		Relapse	+3
Total Score Interpretation			
Before treatment		After treatment	
Unequivocal AIH	≥ 16	Unequivocal AIH	≥ 18
Possible AIH	10–15	Possible AIH	12–17

Appendix Table 3 Simplified diagnosis criteria for AIH in IAIHG [17]

Variable	Criteria	Score	Remark
ANA or SMA	1:40	1	Equivalent to the lowest titer of ANA 1:100 commonly used in China
ANA or SMA	1:80	2	Maximum score of 2 for multiple simultaneous occurrences
LKM-1	1:40	2	
SLA	Positive	2	
IgG	> upper limit of normal	1	
	> 1.1 times upper limit of normal	2	
Liver histology	Compatible with AIH	1	Interface hepatitis, lymphoplasmacytic infiltrate in portal tracts and lobules, rosette-like changes in hepatocytes, and penetration phenomena are characteristic of liver histological changes. When three of the four items are met, it is considered as typical.
	Typical of AIH	2	
Exclude viral hepatitis	Yes	2	

score = 6: possible AIH; score ≥ 7: confirmed AIH

have a higher risk of acute upper gastrointestinal bleeding, which is the most common emergency of the digestive system. Qdaisat et al. analyzed the characteristics and outcomes of intracranial hemorrhage in patients with cancer in the emergency department and found that low platelet count was significantly associated with in-hospital and 30-day mortality [87]. Therefore, it is particularly important to strengthen the risk management and health education for thrombocytopenia in patients with cancer and liver injury.

Risk management and health education

(1) Carefully inquire about medical history, menstrual history, medication history, especially medical history related to liver disease, bleeding history, and concomitant medications, such as anticoagulant and anti-platelet drugs.

(2) Monitor blood chemistry and hematology regularly during tumor treatment. Graded management

Appendix Table 4 RUCAM table [82]

	Hepatocyte type		Cholestasis or mixed		Evaluation
1. Time of onset (d)	Initial treatment	Retreatment	Initial treatment	Retreatment	Score
1a: Time from drug initiation to disease onset					
Suggestive	5–90	1–15	5–90	1–90	+2
Suspected	< 5 or > 90	>15	< 5 or > 90	>90	+1
1b: Time from drug discontinuation to disease onset					
Related	≤ 15	≤ 15	≤ 30	≤ 30	+1
2. Course	Difference between peak ALT and ALT upper limit of normal		Difference between peak ALP (or TBIL) and ALP upper limit of normal		
2a: Changes after drug discontinuation					
Highly suggestive	Decrease > 50% within 8 days		Not applicable		+3
Suggestive of being related	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		+2
No conclusion	Not applicable after 30 days		Decrease < 50% within 180 days		+1
Contrary to drug effect	No relevant data or decrease ≥ 50% after another 30 days		No change, increase, or no information		0
2b: If the drug is still being used					
	Decrease < 50% or re-increase after 30 days		Not applicable		–2
No conclusion	All of the above		All of the above		0
3. Risk factors	Alcohol		Alcohol or pregnancy		
Yes					+1
No					0
Age ≥ 55 years					+1
Age < 55 years					0
4. Concomitant medications					
None, relevant information is absent, or concomitant medications are inconsistent with the time of disease onset					0
Concomitant medications are appropriate to the time of disease onset, or suggestive					–1
Concomitant medications have known hepatotoxicity, and are consistent with the time of disease onset, or suggestive					–2
Evidence of liver injury with concomitant medications (re-challenge reaction or valuable testing)					–3
5. Exclusion of other reasons					
(1) Recent HAV infection (anti-HAV-IgM), HBV infection (anti-HBc-IgM), or HCV infection (anti-HCV and HCV RNA); biliary obstruction (B-ultrasonography); alcoholism (AST/ALT ≥ 2), recent history of acute hypotension (especially underlying cardiac disease)			Exclude all reasons in (1) and (2)		+2
			Exclude all reasons in (1)		+1
			Exclude 4–5 reasons in (1)		0
			Exclude less than 4 reasons in (1)		–2
			High suspicion of non-drug reasons		–3
(2) Important disease complications; clinical and/or biological indicators suggest CMV, EBV, or herpesvirus infection					
6. Reports of previous drug-induced liver injury					
Drug-induced liver injury is labeled in the Instructions for Use					+2
Previously reported but not labeled in the Instructions for Use					+1
Not reported					0
7. Re-challenge reactions					
Positive	ALT increased to ≥ 2 ULN after re-administration of the drug alone		Other conditions, ALP (or TBIL) increased to ≥ 2 ULN after re-administration of the drug alone		+3
Suspected	ALT increased to ≥ 2 ULN after re-administration of the same drugs		ALP or TBIL increased to ≥ 2 ULN after re-administration of the same drugs		+1
Negative	ALT increased after re-administration with the same drug		ALP (or TBIL) still within normal range after re-administration with the same drug		–2
Not done or not judged	Still within normal range		Other conditions		0

Final judgment: > 8, highly probable; 6-8, probable; 3-5, possible; 1-2, impossible; ≤ 0, unrelated

should also be performed according to the degree of thrombocytopenia.

(3) Follow the instructions, clinical guidelines, and expert consensus for rational drug use. Strictly follow the indications for medication, avoid the use of non-standard, inappropriate, and unusual prescriptions, and avoid drug

abuse.

(4) Strengthen the remote health management. Realizing remote care and management during treatment intermissions can improve the accessibility of medical support to patients.

(5) Perform multidisciplinary and dynamic management of patients with cancer and liver injury as recommended owing to their pathophysiological characteristics and the complexity of anticancer therapy.

(6) Strengthen the risk awareness management of patients, inform patients of the risk of thrombocytopenia and possible symptoms, avoid excessive exertion and trauma during thrombocytopenia, monitor platelet count, pay attention to symptoms such as skin ecchymosis, mucocutaneous bleeding, gingival bleeding, and gastrointestinal and urinary tract bleeding, and urge patients to remain alert to thrombocytopenia.

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