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Immune checkpoint inhibitor-related hepatotoxicity: A review

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Abstract

The application of immune checkpoint inhibitors (ICI) in advanced cancer has been a major development in the last decade. The indications for ICIs are constantly expanding into new territory across different cancers, disease stages and lines of therapy. With this increased use, adverse events including immune checkpoint inhibitor-related hepatotoxicity (ICH) have emerged as an important clinical problem. This along with the introduction of ICI as first- and second-line treatments for advanced hepatocellular carcinoma makes ICH very relevant to gastroenterologists and hepatologists. The incidence of ICH varies between 1%-20% depending on the number, type and dose of ICI received. Investigation and management generally involve excluding differential diagnoses and following a stepwise escalation of withholding or ceasing ICI, corticosteroid treatment and adding other immunosuppressive agents depending on the severity of toxicity. The majority of patients with ICH recover and some may even safely recommence ICI therapy. Guideline recommendations are largely based on evidence derived from retrospective case series which highlights a priority for future research.

Key Words: Immunotherapy; Immune checkpoint inhibitors; Hepatitis; Adverse drug event; Drug-induced liver injury; Immunosuppression

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Core Tip: Immune checkpoint inhibitor (ICI)-related hepatotoxicity (ICH) is an increasingly encountered clinical problem for gastroenterologists. Although the diagnosis should be suspected in patients receiving ICI with liver function test derangements, a thorough history, examination and targeted liver investigations including cross-sectional imaging should be performed to exclude differential diagnoses. Once ICH is confirmed, its severity should be graded which then guides management. Management of ICH follows a stepwise approach beginning with cessation of ICI, followed by corticosteroids and other immunosuppressants with close monitoring after each step. The decision to recommence ICI after recovery is made on a case-by-case basis.

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INTRODUCTION

Immunological recognition of cancer cells involves an antigen presenting cell binding and presenting tumor antigens to a T cell *via* its T-cell receptor. The ensuing immune response depends on the presence of either co-stimulatory molecules (which results in immune activation) or inhibitory molecules (which results in immune downregulation and exhaustion). These inhibitory (so called checkpoint) molecules exist as a 'brake' to prevent excessive immune activation or autoimmunity. However, they are also exploited by tumor cells to evade detection by the immune system and facilitate tumor progression[1].

Immunotherapy has recently revolutionized the treatment of advanced malignancy. It involves the use of monoclonal antibodies to inhibit these immune checkpoint molecules leading to immune activation against cancer cells. The main immune checkpoint molecules currently targeted by immunotherapy are the programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Since the CTLA-4 inhibitor ipilimumab was approved for the treatment of metastatic melanoma in 2011[2], immunotherapies have been trialled in many other malignancies with varying success. With their increased use, the toxicities of immunotherapies have also emerged as an important clinical problem. As expected, the side effect of enhancing the body's immune response to cancer is unwanted inflammation. These immune related adverse events (irAEs) can affect almost any organ but most commonly the skin, liver, gastrointestinal tract and endocrine glands. Treatment of irAEs may require temporary or permanent cessation of immunotherapy with or without commencement of immunosuppression which is suboptimal (at least theoretically) in terms of anti-cancer effect.

For gastroenterologists and hepatologists, immunotherapy-related hepatotoxicity deserves special mention as it is commonly encountered. Furthermore, checkpoint inhibitors have recently been added to first- and second-line treatment options for advanced hepatocellular carcinoma (HCC) after promising clinical trial results[3-5]. These patients tend to have relatively limited liver reserve since most HCCs occur on a background of liver cirrhosis[6]. Thus, immunotherapy-related hepatotoxicity can result in liver failure and even death.

In this review, we summarize the latest literature on epidemiology, pathophysiology, diagnosis, assessment and management of immune checkpoint inhibitors (ICI)-induced hepatotoxicity (ICH).

EPIDEMIOLOGY OF ICH

Incidence

Although ICH is primarily considered a 'hepatitis' presenting with elevated transam-

inases, cases of immune-mediated ‘cholangitis’ with elevated biliary enzymes are generally also included in its definition. Further complicating the diagnosis of ICH (and therefore measurement of its incidence) is that ICI is increasingly being used in combination with other chemotherapies and targeted therapies which can themselves can cause hepatotoxicity. Indeed, distinguishing between ICH and drug-induced liver injury (DILI) secondary to co-administered therapy can be difficult.

The reported incidence of ICH depends on the severity grade [according to common terminology criteria for adverse events (CTCAE), discussed further below], type and dose of ICI and if it was used as monotherapy or in combination with another ICI. The reported incidence of all ICH (any grade) varies widely between 0%-30% while only 0%-20% experience severe ICH (grade 3 or 4) (Table 1). Fulminant hepatic failure and death following ICI has also been reported with an incidence of up to 0.4%, particularly with CTLA-4 inhibitors[7]. Indeed, ICH is overrepresented in cases of severe irAEs and accounts for 16% of all immunotherapy-related fatalities[8].

Among patients receiving monotherapy, CTLA-4 inhibitors (ipilimumab and tremelimumab) have the highest rate of hepatotoxicity[9]. The incidence of ICH following CTLA-4 inhibitor monotherapy ranges between mostly between 0%-30% (mostly 3%-15%) with 1%-20% (mostly 1%-10%) being grade 3/4 in severity[2,10-12]. The frequency of ICH appears to increase when higher doses of CTLA-4 inhibitors are administered. For ipilimumab, reported rates of hepatitis (any grade) were only 3%-5% in patients treated with standard doses (3 mg/kg) compared to 15%-16% in those treated with high dose (10 mg/kg)[13,14].

In large trials of PD-L1 inhibitors (*e.g.*, atezolizumab, durvalumab, avelumab) patients exhibited rates of ICH similar to those observed for CTLA-4 inhibitors (1%-17% overall, 3%-5% grade 3/4)[15-17]. In contrast, monotherapy with PD-1 inhibitors (*e.g.*, nivolumab, pembrolizumab) results in the lowest incidence of ICH with rates consistently reported between 0%-3% (mostly 1%-2%) and very few grade 3/4 reactions (< 1%) (Table 1). Unlike CTLA-4 inhibitors, the incidence of irAEs secondary to PD-1 and PD-L1 inhibitors does not appear to be dose-related[18].

Combination therapy with CTLA-4 and PD-1 blockade has been shown to have synergistic anti-tumor effect in advanced melanoma[19]. As expected, combination therapy also results in higher rates of irAEs including ICH. In this group, ICH of any grade occurs in 18%-22% overall with 8%-11% having severe hepatitis (Table 1).

As experience with ICI increases, real-world observational data on ICH have emerged and the incidence appears to be comparable to rates reported in clinical trials[20, 21].

Other risk factors

The type of underlying malignancy appears to impact on the risk of developing ICH. A meta-analysis of 17 phase II and III trials of ICI in advanced cancer found a higher likelihood of hepatotoxicity in melanoma patients compared to other types of cancer (odds ratio 5.66 *vs* 2.71, respectively)[22].

A small study of patients with pre-existing autoimmune disease observed high rates of irAEs (33% experienced grade 3-5 events) and exacerbations of autoimmune disease (27% experienced flares requiring treatment) following ipilimumab treatment[23]. However, none of these patients had autoimmune liver conditions nor experienced ICH. In a larger study of patients with pre-existing autoimmune conditions receiving anti-PD-1 therapy, rates of ICH were similar to those reported in studies of general patients (3% overall, 2% grade 3/4)[24]. Again, none of these patients had a liver-specific autoimmune condition. Unsurprisingly, irAEs are common when a patient with previous irAEs is rechallenged. However, irAE encountered after one ICI does not seem to predict the same irAEs when switching to a different class of ICI[24].

From trials in advanced HCC, ICI appears to be generally well-tolerated in patients with underlying liver disease. Although elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) were commonly reported adverse events in this population (15%-23% any grade, 6%-13% grade 3/4), the proportion attributable to ICH were similar to those seen in trials of patients without liver disease[3-5]. However, trials in patients with liver disease included primarily those with compensated (Child-Pugh class A) cirrhosis, thus limiting the generalizability of these findings to sicker patients. Reassuringly, sub-analyses of a small number of patients with Child-Pugh class B7-8 (decompensated) cirrhosis in the Checkmate-040 study (*n* = 49) revealed overall ICH rates of 8% following nivolumab treatment[25]. Thus, from limited initial data of patients with Child-Pugh class A or early Child-Pugh class B cirrhosis, the incidence of ICH does not appear to be significantly higher than in those without liver disease.

Table 1 Incidence of severe hepatotoxicity by immunotherapy agent used as reported in key phase II and III clinical trials

Class	Agent	Ref.	Indication	Incidence of hepatotoxicity (all grades) % (no. of patients)	Incidence of $\geq$ grade 3 hepatotoxicity % (no. of patients)
CTLA-4	Ipilimumab (standard dose) 3 mg/kg	Hodi <i>et al</i> [71], 2018	Melanoma	0.3 (1/311)	0 (0/311)
		Weber <i>et al</i> [72], 2009	Melanoma	15.5 (9/58)	10.3 (6/58)
		Hodi <i>et al</i> [2], 2010	Melanoma	3.8 (5/131)	0 (0/131)
			Melanoma	2.1 (8/380) Ipilimumab with gp100	1.1 (4/380) ipilimumab with gp100
		Wolchok <i>et al</i> [73], 2010	Melanoma	26.4% (19/72)	0 (0/72)
		Robert <i>et al</i> [74], 2011	Melanoma	29.1 (72/247)	20.6 (51/247)
	Ipilimumab (high dose) 10 mg/kg	Wolchok <i>et al</i> [73], 2010	Melanoma	70.4 (50/71)	15.5 (11/71)
	Tremelimumab	Ribas <i>et al</i> [75], 2013	Melanoma	0.6 (2/325)	0.6 (2/325)
Anti-PD-1	Nivolumab	Hodi <i>et al</i> [71], 2018	Melanoma	0.3 (1/313)	0.3 (1/313)
		Weber <i>et al</i> [76], 2017	Melanoma	1.9 (11/576)	0.7 (4/576)
		Brahmer <i>et al</i> [77], 2015	Squamous cell NSCLC	1.5 (2/131)	0 (0/131)
		Borghaei <i>et al</i> [78], 2015	Non-squamous NSCLC	3.1 (9/287)	0 (0/287)
		Robert <i>et al</i> [79], 2014	Melanoma	1.1 (1/89)	1.1 (1/89)
	Pembrolizumab	Robert <i>et al</i> [79], 2014	Melanoma	0 (0/84)	0 (0/84)
		Eggermont <i>et al</i> [80], 2018	Melanoma	1.8 (9/509)	1.4 (7/509)
	Cemiplimab	Migden <i>et al</i> [81], 2018	Cutaneous Squamous-Cell Carcinoma	8.5 (5/59)	0 (0/59)
Anti-PD-L1	Atezolizumab	Jotte <i>et al</i> [82], 2020	Squamous NSCLC	17.4 (58/334)	5.4 (18/334)
	Atezolizumab + Bevacizumab (anti-VEGF antibody)	Finn <i>et al</i> [3], 2020	HCC	33.4 (110/329)	10.6 (35/329)
	Avelumab	D'Angelo <i>et al</i> [83], 2020	Metastatic Merkel cell carcinoma	1.1 (1/88)	1.1 (1/88)
	Durvalumab	Garassino <i>et al</i> [84], 2018	Advanced NSCLC	0.2 (1/444)	0.2 (1/444)
Combination Therapy	Ipilimumab + Nivolumab	Hodi <i>et al</i> [71], 2018	Melanoma	3.2 (10/313)	2.6 (8/313)
		Postow <i>et al</i> [85], 2015	Melanoma	22.3 (21/94)	10.6 (10/94)
		Larkin <i>et al</i> [86], 2015	Melanoma	17.6 (55/313)	8.3 (26/313)
		Wolchok <i>et al</i> [73], 2010	Melanoma	20.8 (11/53)	11.3 (6/53)

Grading of severity is according to common terminology criteria for adverse events. CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; HCC: Hepatocellular carcinoma; no. of: Number of; NSCLC: Non-small cell lung cancer; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-

ligand 1; VEGF: Vascular endothelial growth factor.

High rates of allograft rejection and graft failure have been described in solid organ transplant recipients[26]. In particular, ICI treatment may be a consideration in liver transplant recipients for recurrent HCC or other malignancies (e.g., melanoma). Liver injury (due to allograft rejection, not ICH) has been reported in 29%-37% of liver transplant patients in small series ($n = 11-19$)[26-28]. Of concern, a high proportion (3/4, 75%) of these rejections were fatal, although patient numbers were small[26,28].

PATHOGENESIS OF ICH

The exact pathogenesis of ICH is not fully understood but likely to be multifactorial. The general theory is that ICI-induced immune activation leads to not only a tumor-specific T cell response but also loss of peripheral tolerance against the patient's own cells[29]. In the case of ICH, immune activation against hepatocytes leads to a T-cell mediated hepatitis and hepatocyte death.

Mechanistically, proposed processes involved in irAEs include: T cell reactions to shared antigens expressed on both tumors and target organs, development of auto-antibodies, of ICI antibodies directly binding to target organs and/or overactivation of immune cells leading to excessive cytokine secretion[29]. The precise mechanism(s) underlying ICH development has not been elucidated.

It also remains unclear why certain patients develop ICH but not others. It has been proposed that genetic factors play an important role, however, no obvious high-risk genetic loci have been identified to date. Although it is a focus of active research, there are currently no reliable biomarkers to predict ICH in routine clinical use.

CLINICAL FEATURES

Presentation

ICH is usually asymptomatic and detected incidentally on routine liver function tests (LFTs) performed during monitoring after ICI treatment. The median time to onset of ICH is most commonly reported as 8-12 wk[14,30,31], however it can manifest as early as 2-3 wk after initiating ICI treatment[14,32-34]. Patients with more severe disease can present clinically with fever, jaundice, right-sided abdominal pain, dark urine and easy bruising. As aforementioned, acute liver failure (encephalopathy and coagulopathy) is rare, especially as the initial presentation[35]. Clinical presentations may vary depending on the class of ICI with fever found to be a more prominent feature in ICH secondary to CTLA-4 inhibitors compared to anti-PD-1 or anti-PD-L1 antibodies in one study[36].

A hepatocellular pattern of LFTs elevation (or transaminitis) is the most common pattern seen with ALT typically being higher than AST[36]. However, a cholestatic or mixed pattern of LFTs derangement is more common with PD-1/PD-L1 inhibitors compared to CTLA-4 inhibitors[36,37]. Rarely, cases of immune-mediated cholangiopathy (discussed further below) have also been described particularly with PD-1/PD-L1 inhibitors[38]. Elevations in total bilirubin can also be seen which reflects either prolonged injury or a sign of more severe disease.

Diagnosis, differentials and work-up

Although clinicians should be vigilant in looking for ICH in patients receiving ICI, not all cases of newly deranged LFTs are due to ICH. Indeed, a diagnosis of ICH only accounts for a fraction (less than 20%-30%) of all patients who were reported to have elevated AST and/or ALT as an adverse event in clinical trials[4,5,39]. Therefore, ICH is a diagnosis of exclusion and it is still important to conduct a thorough assessment to exclude other common differentials. A list of differential diagnoses with suggested investigations (or 'liver screen') is shown in Table 2.

A few key differential diagnoses deserve mention. Liver function abnormalities are more common when ICI are used in combination with other systemic chemotherapies such as dacarbazine or vemurafenib in melanoma[32], paclitaxel and carboplatin in lung cancer[40,41], or bevacizumab in HCC[3]. Furthermore, patients should be asked about other recent medications including non-prescription treatments (over-the-

Table 2 Differential diagnosis and suggested investigations

System	Differential diagnosis	Investigations
Drug-induced liver injury	(1) Other co-administered anti-cancer drugs; (2) Alcohol related liver disease; and (3) Acetaminophen toxicity	Medication history
Tumor-related	Metastatic disease	Abdominal imaging with ultrasound, CT or MRCP
Infectious	(1) Sepsis; (2) Acute HAV infection; (3) Acute HBV or flare of chronic HBV; (4) Chronic HCV; (5) Acute HEV; (6) Acute CMV or reactivation; and (7) Acute EBV	(1) Septic screen as appropriate; (2) Anti-HAV (IgM); (3) HBsAg, Anti-HBc IgG, IgM, $\pm$ HBV DNA; (4) Anti-HCV $\pm$ HCV RNA; (5) Anti-HEV (IgM); (6) CMV IgM and IgG $\pm$ CMV DNA; and (7) EBV IgM and IgG
Biliary disease	(1) Cholecystitis; (2) Cholangitis; and (3) Pancreatitis	(1) Abdominal imaging; and (2) Serum lipase
Autoimmune	Autoimmune hepatitis ¹	ANA, Anti-SMA, Anti-LKM1, serum IgG levels
Musculoskeletal	(1) Myositis (potentially an irAEs); and (2) Rhabdomyolysis	Serum CK
Metabolic	Underlying NASH	(1) Metabolic risk factors; and (2) Abdominal imaging for hepatic steatosis
Vascular	(1) Portal-vein/hepatic vein thrombosis; and (2) Ischemic hepatitis	Abdominal imaging and clinical history

¹Although anti-nuclear antibodies is frequently positive at low-titres in IC (< 1:80), specific auto-antibodies seen in autoimmune hepatitis are usually negative.

ANA: Anti-nuclear antibodies; Anti-HBc: Anti-Hepatitis B core antibody; anti-LKM1: Anti-liver-kidney microsomal 1 antibody; Anti-SMA: Anti-smooth muscle antibody; CK: Creatine kinase; CMV: Cytomegalovirus; CT: Computed tomography; EBV: Epstein-Barr virus; HAV: Hepatitis A virus; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; irAEs: Immune-related adverse events; MRCP: Magnetic resonance cholangiopancreatography; NASH: Non-alcoholic steatohepatitis.

counter, complementary and herbal medications) and their alcohol intake. All the above can cause a non-immune mediated (direct or idiosyncratic) DILI. Hence, a detailed medication history should be performed. Practically, it can be difficult differentiating between ICH *vs* non-ICI mediated DILI and further investigations such as liver biopsy may not reliably separate these entities.

Patients with malignancy can also have direct tumor spread to the liver or regional lymph nodes which can lead to LFTs derangement from either biliary obstruction by bulky metastases or widespread infiltration of the liver. One study of 70 patients with liver injury after receiving pembrolizumab (mainly for melanoma) found the cause of liver injury as determined by 'expert adjudication' was due to progressive hepatic metastases or malignant biliary obstruction in 60% of cases (double the number of cases judged to be due to ICH)[39]. Cross-sectional imaging with either abdominal ultrasound or more commonly computed tomography scan can be useful to identify biliary obstruction and the extent of liver metastases. As advanced cancer patients tend to get regular scans to monitor response to therapy, there may be a recent scan for review or comparison. Otherwise, imaging findings in patients with ICH are mild and non-specific even in severe cases and may include hepatomegaly, periportal edema, or periportal lymphadenopathy[42]. Extensive bone metastases can draw attention to the liver by causing elevations in total alkaline phosphatase (without a rise in gamma-glutamyl transferase)[43], which can be clarified by checking the bone-specific isoform (ostase).

Patients receiving certain systemic chemotherapies are at increased risk of reactivation of chronic hepatitis B. Although hepatitis B reactivation is very rare (< 1%) with ICI therapy[44], it can also occur with other co-administered chemotherapies or during treatment of ICH with corticosteroids. Therefore, patients should have their hepatitis B status checked routinely prior to commencing treatment with ICIs[45] and be considered for prophylactic antiviral therapy. Although a flare of hepatitis C virus (HCV) secondary to ICI therapy has not been previously reported[4,5], patients with untreated HCV should have close monitoring of their viral load and LFTs, which may both fluctuate during treatment[46]. Indeed, anti-PD1 treatment has been shown to facilitate control of chronic HCV infection[47] with some patients achieving dramatic reductions in their viral load and normalization of their ALT[46].

Role of liver biopsy

Although a liver biopsy is useful to exclude differential diagnoses and assess the degree of liver inflammation, it is usually not necessary in the work-up and ma-

nagement of ICH. Its invasive nature and cost, means it is generally reserved for situations when the diagnosis is unclear despite non-invasive investigations or the clinical course is atypical and not responding to standard treatments. Histological findings in ICH is variable but typically demonstrate lobular and/or periportal inflammation[36]. Centrilobular necrosis and central endothelialitis may also be present. Some distinct phenotypes may exist with granulomatous hepatitis reported in patients treated with CTLA-4 inhibitors, and a lobular, non-granulomatous hepatitis in those treated with anti-PD-1/anti-PD-L1 antibodies. Inflammatory infiltrates in ICH are predominantly activated T-lymphocytes (mainly CD8+) and histiocytes with few or no plasma cells[36]. Comparatively, patients with autoimmune hepatitis flares have proportionately more CD20+ B lymphocytes and CD4+ T-lymphocytes[48]. **Figure 1** presents two distinct histologic presentations of ICI-induced hepatotoxicity.

Assessing causality and grading severity

Establishing causality for ICI causing hepatotoxicity begins with excluding differential diagnoses as outlined above. Formal scoring systems such as the Roussel Uclaf Causality Assessment Method (RUCAM) provide a useful framework and are often used in the DILI research setting but less so in clinical practice[49]. One problem with RUCAM is the difficulty in achieving scores to classify patients as having 'definite' or 'highly probable' DILI without rechallenging the patient with ICI which is not always safe to do. Instead the majority of patients are labelled as 'probable' DILI[39].

Once a diagnosis of ICH is judged to be the likely cause of the patient's deranged LFTs, the severity of hepatotoxicity should be graded as it determines the treatment. Most oncology clinical trials report the severity of liver injury according to the CTCAE whereas the DILI Network (DILIN) severity index is commonly used for grading DILI severity. Both grading systems take into account the patient's symptoms, degree of liver enzyme and bilirubin derangement and/or international normalized ratio (DILIN only) (**Table 3**). It should be noted that neither CTCAE nor DILIN systems were devised specifically for grading ICH, but rather for raised LFTs secondary to any anti-cancer therapy.

MANAGEMENT OF ICH

As ICH is a relatively new entity, there have been no prospective randomized controlled trials evaluating different treatment recommendations. Thus, current international treatment guidelines are all based on low level evidence (case series and expert opinion). **Table 4** outlines treatment recommendations from major oncology and hepatology societies for each CTCAE grade of ICH. Importantly, treatment should be patient-centred with their active involvement in decision making throughout.

As with any other DILI, temporary or permanent discontinuation of the culprit agent should be the first step and is recommended by all society guidelines for moderate ($\geq$ grade 2) ICH. Therefore, LFTs should be checked at baseline and prior to each dose of ICI. Since the pathogenesis of hepatotoxicity is immune-mediated, immunosuppression is the other mainstay of treatment. Although minor differences exist between guidelines, they generally all follow a stepwise algorithm involving withholding or ceasing ICI, followed by corticosteroid treatment [oral prednisolone or intravenous (IV) methylprednisolone] and further immunosuppression [mycophenolate mofetil (MMF), calcineurin inhibitors and anti-thymocyte antibodies *etc.*] depending on the initial severity and response to subsequent treatment.

Withdrawal of ICI

A considerable proportion of patients can undergo resolution of ICH without need for immunosuppressive therapy. At least three small case series ($n = 6-16$) have reported ICH resolution rates of 38%-50% by simply withholding the ICI even in those with grade 3/4 disease[36,50,51]. However, most society guidelines recommend starting corticosteroids for patients with $\geq$ grade 2 ICH, highlighting that guideline recommendations should always be applied in the appropriate clinical context. Therefore, a period of close LFTs monitoring after withholding ICI (daily to weekly depending on severity of ICH) may be useful in helping some patients avoid unnecessary immunosuppression and their related side effects. This period of observation is particularly important in cases where ICI has been co-administered with other potentially hepatotoxic drugs. Cessation of these drugs (without immunosuppression) may lead to recovery if they were the main culprit for the liver injury. Whether ICI therapy should be temporarily or permanently ceased will be discussed later.

Table 3 Comparison of common grading systems for inhibitor-related hepatotoxicity

Grade					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE [87]	(1) Asymptomatic; (2) AST or ALT > 1-3 × more than ULN; and (3) T. Bil > 1-1.5 × more than ULN	(1) Asymptomatic; (2) AST or ALT > 3-5 × more than ULN; and (3) T. Bil > 1.5-3 × more than ULN	(1) Symptomatic liver dysfunction; (2) Fibrosis on biopsy; (3) Compensated cirrhosis; (4) Reactivation of chronic hepatitis; (5) AST or ALT > 5-20 × more than ULN; and (6) T. Bil > 3-10 × more than ULN	(1) Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma); (2) AST or ALT > 20 × more than ULN; and (3) T. Bil > 10 × more than ULN	Death due to hepatotoxicity
DILIN [73]	(1) Elevations in serum ALT and/or ALP levels; (2) T. Bil < 2.5 ULN; (3) INR < 1.5; and (4) Present with or without symptoms (fatigue, asthenia, nausea, anorexia, RUQ pain, jaundice, pruritus, rashes, or weight loss)	(1) Elevated serum ALT and/or ALP; (2) T. Bil ≥ 2.5 ULN or INR ≥ 1.5; and (3) Symptoms may become aggravated	(1) Elevated serum ALT and/or ALP; (2) T. Bil ≥ 5 ULN ± INR ≥ 1.5; (3) Symptoms are further aggravated; (4) Indication for hospitalization; and (5) No evidence of hepatic encephalopathy	(1) Coagulation abnormality indicated by INR ≥ 1.5; (2) Signs of hepatic encephalopathy; (3) T. Bil ≥ 10 ULN or daily elevation ≥ 1.0 mg/dL in 26 wk after the DILI onset; and (4) Ascites and DILI-related dysfunction of another organ	(1) Death due to DILI; and (2) Or need to receive liver transplantation for survival

ALT: Alanine Aminotransferase; AST: Aspartate aminotransferase; CTCAE: Common terminology criteria for adverse events; DILI: Drug induced liver injury; DILIN: Drug-induced Liver Injury Network; ICH: Immune checkpoint inhibitor-induced hepatotoxicity; INR: International normalized ratio; RUQ: Right upper quadrant; T. Bil: Total bilirubin; ULN: Upper limit of normal.

Corticosteroids

As discussed above, commencement of corticosteroids is not essential but something to be considered depending on the severity of ICH and initial response in LFTs after withholding ICI. Oral prednisolone at a dose of 0.5-1 mg/kg of body weight is the recommended for patients with grade 2 hepatotoxicity and IV boluses of methylprednisolone 1-2 mg/kg of body weight for patients with grade 3/4 toxicity. It is important to note these dosing regimens are not derived from comparative studies but were instead extrapolated from treatment of other irAEs or autoimmune hepatitis. Indeed, higher doses of corticosteroids (> 60 mg daily of oral prednisolone) has not been shown to confer additional benefit in time to hepatitis resolution compared to lower doses[20]. A therapeutic response and eventual resolution of ICH is achieved in the majority of patients by withholding ICI and commencing corticosteroids[36]. This should be evident after 2-3 d of treatment[52]. Once a response is seen, steroids should then be tapered gradually over at least 4 wk to minimize the risk of rebound hepatitis [53]. As for other conditions, patients receiving systemic corticosteroids should be monitored for its complications including infection, hyperglycemia, and psychosis.

Refractory disease

A minority of patients either do not respond or fail to normalize their LFTs back to baseline despite corticosteroid treatment. If there is no response with oral prednisolone, IV methylprednisolone can be considered. In the setting ICH that is refractory to both oral and IV corticosteroids, MMF has been the preferred second-line agent at a dose of 500-1000 mg twice daily (Table 4). Azathioprine is the first-line steroid-sparing agent used in autoimmune hepatitis. Although its use has been reported in ICH, it is usually not favored because its immunosuppressive effect takes several months to peak and its metabolites can cause hepatotoxicity[54-56]. The main side effects from MMF are gastrointestinal upset (abdominal pain, nausea, vomiting and diarrhea) and cytopenia.

For ICH refractory to corticosteroids and MMF, collective experience is limited to case reports. Calcineurin inhibitors (tacrolimus and cyclosporine) have been used with varying success in autoimmune hepatitis and form the backbone of liver transplant rejection treatment[57]. Their mechanism of action against T cell mediated liver inflammation makes them a logical choice in treatment-refractory ICH. Calcineurin inhibitors [20,56] along with other agents including anti-thymocyte globulin therapy[58], tocilizumab[59], plasma exchange[60] and even infliximab have all been used successfully to treat steroid-refractory ICH[61]. However, infliximab is not recommended by most guidelines since it can cause an autoimmune phenotype DILI, albeit rarely[62]. If not done prior, a liver biopsy should be strongly considered before commencing these third-line immunosuppressive agents.

Table 4 Comparison of management recommendations for inhibitor-related hepatotoxicity by major expert societies

Grade	FDA[88]	Society of Immunotherapy of Cancer[89]	American Society of Clinical Oncology [90]	European Society for Medical Oncology[91]	Australian (eVIQ Guidelines)[53]	European Association for the Study of Liver[52]
Grade 1	(1) Monitor closely; (2) Continue ICI; and (3) Investigate for other causes of hepatitis	(1) Monitor closely; (2) Continue ICI; and (3) Investigate for other causes of hepatitis	(1) Monitor closely; (2) Continue ICI; (3) Check LFTs twice a week; and (4) Investigate for other causes of hepatitis	(1) Monitor closely; (2) Continue ICI; (3) Check LFTs weekly; and (4) Investigate for other causes of hepatitis	(1) Continue ICI; (2) Monitor LFTs more closely; and (3) Investigate for other causes of hepatitis	If irAEs are excluded (unlikely or unrelated) continue therapy with close follow-up. Start symptomatic treatment
Grade 2	(1) Withhold ICI; (2) Investigate for other causes of hepatitis; (3) Start prednisone 0.5–1 mg/kg/d of prednisone Po until LFTs improve to < Grade 1 then wean steroids; and (4) Consider restarting when on less than equivalent of prednisone 7.5 mg/d	(1) Withhold ICI; (2) Investigate for other causes of hepatitis; (3) Start prednisone 0.5–1 mg/kg/d Po (or equivalent) with a 4-wk taper; (4) Monitor LFTs twice a week; (5) Liver biopsy optional; and (6) Resume ICI when steroids tapered to 10 mg/d and liver enzymes are grade 1 level or better	(1) Withhold ICI; (2) Investigate for other causes of hepatitis; (3) Monitor LFTs every 3 d and if no improvement start prednisone 0.5–1 mg/kg/d Po (or equivalent); and (4) Resume ICI when LFTs grade 1 level while on less than prednisolone 10 mg/d (taper over a month)	(1) Withhold ICI; (2) Investigate for other causes of hepatitis; (3) Recheck LFTs/INR every 3 d; (4) If LFTs increase on subsequent check after stopping checkpoint inhibitor, start oral prednisolone 1 mg/kg/d; (5) Once LFTs return to grade 1, start weaning steroids; and (6) Resume ICI when liver enzymes are grade 1 level or better while on less than prednisolone 10 mg/d	(1) Withhold ICI; (2) Monitor LFTs every 3 d; (3) Investigate for other causes of hepatitis; (4) Consider corticosteroid therapy for patients who are symptomatic or worsening LFTs; and (5) Resume ICI treatment once corticosteroid treatment is complete and tapered over 4 wk	(1) Skip dose and monitor liver parameters, INR and albumin twice weekly; (2) Start symptomatic treatment; (3) If abnormal liver parameters persist longer than 2 wk, start immunosuppression and discontinue the drug; and (4) Upon improvement immunotherapy could be resumed after corticosteroid tapering
Grade 3	(1) Permanently cease ICI; (2) Start prednisone at 1–2 mg/kg/d Po (or equivalent); (3) Consider imaging and liver biopsy while assessing for alternative causes of hepatitis	(1) Permanently cease ICI; (2) Monitor complete metabolic panel every 1–2 d; (3) Start prednisone at 1–2 mg/kg/d (or equivalent); (4) If refractory to steroids, consider adding MMF. Once LFTs improve, taper over 4 wk; and (5) Consider liver biopsy	(1) Permanently discontinue medication; (2) Consider hospitalization and start IV 1–2 mg/kg/d methylprednisolone; (3) If no improvement in 3 d consider adding secondary agent; (4) Monitor LFTs daily/every other day; (5) Once LFTs improve will need to wean steroids over 4–6 wk; and (6) Do not offer infliximab	(1) Withhold ICI; (2) Investigate for other causes of hepatitis; (3) Recheck LFTs/INR daily; (4) Consider hospitalization; (5) Start prednisolone 1 mg/kg/d Po if ALT/AST < 400 U/L and normal bilirubin/albumin/INR OR start IV methylprednisolone 2 mg/kg/d if ALT/AST > 400 U/L or elevated bilirubin/INR or decreased albumin; (6) Once LFTs improve to grade 2, can switch to PO steroids and wean over 4 wk; (7) Consider rechallenge at discretion of consultant; (8) If no improvement on steroids, consider adding mycophenolate and/or tacrolimus; and (9) Do not offer infliximab	(1) Permanently discontinue treatment; (2) Investigate for other causes of hepatitis; (3) Consider liver biopsy; (4) Hospitalize patient if unwell; (5) Urgent administration of start IV 1–2 mg/kg/d methylprednisolone For 3 d, following high dose oral prednisolone; and (6) If no improvement on steroids, urgent referral to a gastroenterologist to prescribe other steroid-sparing agents	(1) Discontinue immunotherapy and monitor liver parameters. Consider permanent discontinuation of immunotherapy; (2) Start corticosteroids (methylprednisolone or equivalent) at a dose of 1–2 mg/kg/d depending on severity; (3) If there is no response to corticosteroids within 2–3 d, MMF should be added at 1000 mg twice daily; (4) Further immunosuppression: MMF, cyclosporine, tacrolimus, anti-thymocyte antibodies; and (5) Infliximab is not recommended
Grade 4	(1) Permanently cease ICI; (2) Start prednisone at 1–2 mg/kg/d Po (or equivalent); and (3) Consider imaging and liver biopsy while assessing for alternative causes of hepatitis	(1) Permanently cease ICI; (2) Start prednisone at 1–2 mg/kg/d Po (or equivalent); (3) Monitor complete metabolic panel every 1–2 d; (4) If refractory to steroids, consider adding MMF. LFTs improve, taper over 4 wk; and (5) Consider liver biopsy	(1) Permanently discontinue medication; (2) Consider hospitalization and start IV 2 mg/kg/d methylprednisolone; (3) Add MMF if no improvement in 72 h; (4) Consider transfer to tertiary center with hepatology consultation if no improvement; (5) Do not offer infliximab; and (6) If LFTs improve, will need steroid wean over 4–6 wk	(1) Permanently discontinue medication; (2) Consider hospitalization and start IV methylprednisolone 2 mg/kg/d; (3) Formal hepatology consultation; (4) Consider liver biopsy; (5) If no improvement on IV steroids, add MMF and/or tacrolimus; (6) Do not offer infliximab; and (7) Once LFTs improve to > grade 2, can switch to oral steroids and wean over 4 wk	(1) Permanently discontinue treatment; (2) Investigate for other causes of hepatitis; (3) Consider liver biopsy; (4) Hospitalize patient if unwell; (5) Urgent administration of start IV 1–2 mg/kg/d Methylprednisolone. For 3 d, following high dose oral prednisolone; and (6) If no improvement on steroids, urgent referral to a gastroenterologist to prescribe other steroid-sparing agents	

Grading of severity is according to common terminology criteria for adverse events. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FDA: United States Food and Drug Administration; ICI: Immune checkpoint inhibitor; INR: International normalized ratio; irAEs: Immune-related adverse events; IV: Intravenous; LFTs: Liver function tests; MMF: Mycophenolate mofetil; PO: Per oral.

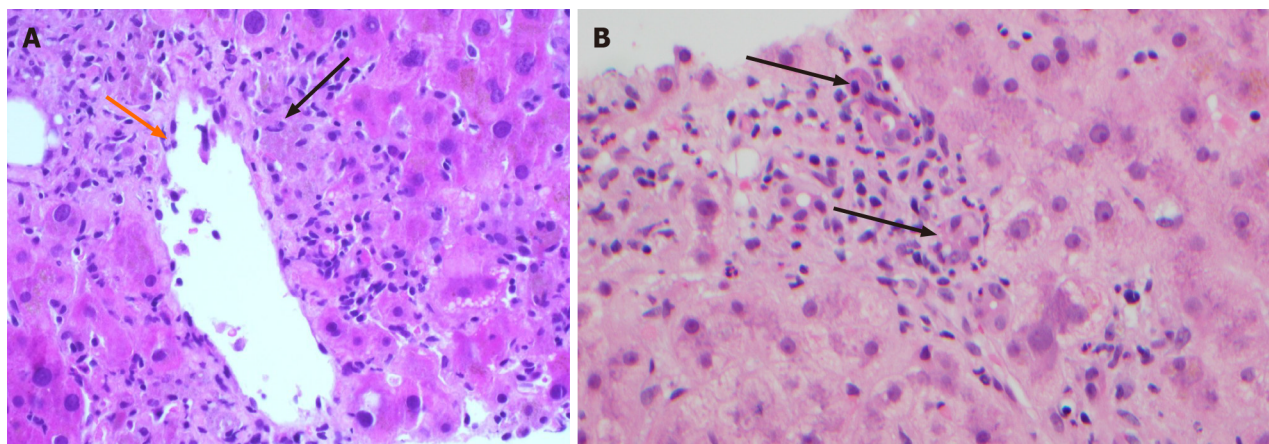


Figure 1 Histopathological changes of inhibitor-related hepatotoxicity. A: Prominent perivenulitis (black arrow) with endothelialitis (orange arrow) in a case of ipilimumab related hepatotoxicity (hematoxylin and eosin, 400 ×); B: Lymphocytic cholangitis with prominent duct damage secondary to nivolumab (black arrows; hematoxylin and eosin, 400 ×).

As aforementioned, ICH can also present as an immune-mediated cholangiopathy, especially in those receiving PD-1/PD-L1 inhibitors. In this entity, the inflammation is centred around the biliary tree with CD8+ T cell infiltration seen on liver biopsy. Characteristically has a moderate to poor response to steroid therapy[63] and the addition of ursodeoxycholic acid to immunosuppression may be helpful[64].

Ongoing monitoring and prognosis

Once a response is achieved, patients should have ongoing monitoring for clinical signs and symptoms and LFTs. The monitoring frequency (between daily to weekly) is titrated according to the severity of ICH and rate of improvement after commencing treatment[53]. Subsequent LFTs also help guide decisions regarding weaning of immunosuppression. Importantly, LFTs monitoring (fortnightly to monthly) should continue after apparent resolution of ICH and completion of immunosuppression as rebound hepatitis has been reported in up to a third of patients[65].

Although the majority of ICH patients recover and deaths due to hepatitis very rarely occur, the impact of ICH and its treatment on cancer outcomes is unclear. In a study of 491 pembrolizumab-treated patients, Tsung *et al*[39] demonstrated that development of liver injury portended worse overall survival compared to those without liver injury[39]. On sub-analysis, patients with liver injury due to 'probable' ICH exhibited significantly better survival compared to those with other causes of liver injury (*e.g.*, hepatic metastases). In contrast, corticosteroid treatment in melanoma patients with irAEs (including ICH) after CTLA-4 blockade did not impact on treatment response or survival[66,67].

As patients receiving ICI typically have advanced (incurable) malignancy, referral to palliative care services should be considered if not already done so. Palliative care services may assist clinicians and patients with managing the symptoms arising from irAEs, making treatment decisions (including when to cease therapy), and future planning. Early referral to palliative care has been shown to significantly improve patient physical and psychological symptoms, quality of life, and treatment satisfaction[68].

Restarting vs permanently ceasing ICI

The decision on whether to restart or permanently cease ICI is a difficult one. Although current guidelines recommend temporarily withholding ICI in grade 2 ICH and permanently ceasing in grade 3/4 (Table 4), the decision is often more challenging and involves weighing up the ICH (its severity and response to immunosuppression) against the advanced cancer (its current activity, response to ICI and other available treatment options). Furthermore, multiple case reports have described successful

reintroduction of ICI without ICH recurrence despite initial grade 3/4 hepatotoxicity. Other promising strategies include co-administration of budesonide (corticosteroid with high first-pass metabolism) when rechallenging with ICI[69] or resuming anti-PD-1 monotherapy in patients with severe toxicity from combination ICI therapy[70]. However, these approaches need confirmatory study before they can be widely adopted. At present, the decision to rechallenge with ICI should still be determined on a case-by-case basis through multidisciplinary discussion.

FUTURE DIRECTIONS

As the indications and frequency of ICI use expand, recognition and management of ICH will be an increasingly important issue. Current guideline recommendations are based on experience found in retrospective case series due to relatively low numbers of patients developing ICH overall (especially those who are steroid refractory). In order to strengthen the evidence base in this area, clearly both prospective large observational registries and eventually randomized controlled trials are needed. This would almost certainly involve collaborations across many centers for patient recruitment. Our rudimentary knowledge of the pathobiology behind ICH also limits our ability to predict which patients will develop it and who will respond to treatment. Therefore, efforts at the basic science level to study the genetic and immune profile of ICH patients are equally important. As our knowledge and experience increases, ICI selection may be personalized to each individual in the future not only with regards to their cancer response but also their risk of developing ICH and how best to treat it.

CONCLUSION

In summary, we have arrived at a new era of cancer therapy where ICI will form the backbone of many regimens. Uncommonly, these treatments are complicated by ICH which can be severe. After excluding key differential diagnoses, the management algorithm follows a stepwise escalation in immunosuppression. The majority of patients recover with some being able to recommence ICI therapy. Future studies are needed to boost the evidence base and hence confidence behind current treatment recommendations.

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