# Chapter 8
# Immune Checkpoint Inhibitors-Induced Hepatitis

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**Abstract** Immune checkpoint inhibitors (ICIs) have been increasingly used for multiple cancer types in the past decade. ICIs include CTLA-4 inhibitors (e.g., ipilimumab) and the PD-1 and PD-L1 inhibitors (e.g., nivolumab and pembrolizumab). Hepatotoxicity is not uncommon secondary to ICI treatment. It can occur 8–12 weeks after the initiation of ICI and presents with elevation of aspartate transaminase and alanine transaminase. ICI-induced hepatitis is usually asymptomatic but may present with fever, malaise, and even death in rare cases. It is a diagnosis of exclusion after other etiologies are excluded based on medical history, laboratory evaluation, and imaging and histological findings. ICI-induced hepatitis might require discontinuation of ICI and/or treatment with immunosuppressants.

**Keywords** Immune checkpoint inhibitors · Hepatitis · Anti-CTLA-4 · Anti-PD-1/anti-PD-L1 · Corticosteroids · Transaminitis · Liver injury

## The Incidence of ICI-Induced Hepatitis

Immune checkpoint inhibitor (ICI)-induced liver injury occurs in 5–30% of patients [1, 2]. Compared with patients treated with PD-1/PD-L1-blocking antibodies, patients receiving CTLA-4-blocking antibodies are associated with higher risk of liver toxicity, which can be up to 15% [3, 4]. On the other hand, the incidence of hepatic injury associated with anti-PD-1/PD-L1 agents is 5–10%. However,

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hepatotoxicity raises up to 30% in patients treated with combination therapy with anti-CTLA-4 and anti-PD-1/PD-L1 inhibition [3–5].

The most common pattern of hepatocellular injury induced by ICI is panlobular hepatitis [5–12]. Grade 3–4 hepatitis has been reported in 1–3% of patients receiving ICI monotherapy and in 8–14% of patients treated with anti-PD-1 and anti-CTLA-4 combination [5, 7–10, 13–16].

## Clinical Presentation of ICI-Induced Hepatitis

ICI-induced hepatitis develops through an immune-mediated mechanism which manifests as either hepatocellular or cholestatic injury [14, 17–19]. The presentation of ICI-induced hepatitis remains highly heterogeneous, ranging from complete asymptomatic with mild rise in aminotransferases to death due to hepatic failure [6, 20, 21]. Certain patients with ICI-induced hepatitis could present with fever, malaise, jaundice, and changes of stool color [17, 22]. The increased level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin can be attributed to any ICI agent including CTLA-4 and PD-1/PD-L1 classes [13, 17, 20, 23].

ICI-induced hepatitis can occur at any time, but often becomes clinically evident 8–12 weeks after initiation of ICI therapy [16, 20, 24]. Patients present with delayed onset hepatitis tend to have milder disease [14, 25]. It should be noted that the sudden onset of fulminant hepatitis can occur despite patient has tolerated long-term ICI treatment [26].

## Diagnostic Tools for the Evaluation of ICI-Induced Hepatitis

CTCAE grading system for biochemical markers of hepatitis and hepatic failure is shown in Table 8.1 [27].

The exclusion of other causes of liver injury such as medications, autoimmunity, viral infection, and alcohol is the initial approach for the management of suspected ICI-induced hepatitis [13, 28]. In addition to monitoring hepatic function closely, the evaluation for other etiologies includes diagnostic laboratory and imaging studies. Liver biopsy should be considered for cases that fail the standard immunosuppressive treatments [29].

Diagnostic laboratory biochemistry can help to evaluate for viral and other autoimmunity-related causes. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) imaging findings are usually nonspecific for the diagnosis of ICI-induced hepatitis [30]. However, imaging modalities can be of value to detect other etiologies that lead to abnormal liver enzymes, e.g., liver metastatic disease and thromboembolic event [17, 31]. Radiological features of ICI-induced hepatitis include periportal edema, hepatomegaly, periportal MRI T2-hyperintensity, attenuated liver parenchyma, and enlarged periportal lymph nodes on CT and MRI in

**Table 8.1** Hepatobiliary disorders

| Grade | | | | | |
|---|---|---|---|---|---|
| Adverse events | 1 | 2 | 3 | 4 | 5 |
| Hepatitis | | | | | |
| 1. ALT and AST | 1–3xULN | 3–5xULN | 5–20xULN | >20xULN | – |
| 2. Total bilirubin | 1–1.5xULN | 1.5–3xULN | 3–10xULN | >10xULN | |
| Hepatic failure | – | – | Asterixis; mild encephalopathy; limiting self-care ADL | Moderate to severe encephalopathy; coma; life-threatening consequences | Death |

severe hepatitis [17, 25, 32]. Mild hepatitis usually has normal appearance of the liver on imaging [17, 33]. ICI-induced hepatitis treatment has been reported to improve hepatomegaly and periportal lymphadenopathy on imaging [17].

Histological examination of ICI-induced hepatitis demonstrated nonspecific features of panlobular hepatitis and bile duct injury [22] including fibrin ring granulomas [34], central vein endotheliitis [20, 35], prominent sinusoidal lymphohistiocytic infiltrates, and endothelialitis involving central veins [20]. The histology of anti-PD-1/PD-L1-induced hepatitis is different from that of anti-CTLA4. PD-1/PD-L1 antibody-induced hepatitis causes lobular non-granulomatous hepatitis [16], whereas CTLA4 antibody-induced hepatitis causes granulomatous hepatitis with fibrin deposits [16]. In addition, ICI-induced hepatitis has increased numbers of $CD3^+$ and $CD8^+$ lymphocytes and decreased $CD20^+$ B cells and $CD4^+$ T cells compared with autoimmune hepatitis and drug-induced liver injury [35].

## Management and Outcomes of ICI-Induced Hepatitis

For mild cases, e.g., grade 1 hepatitis, expectant management with close laboratory monitoring is recommended [36]. ICI can be continued in these cases. For grade 2 and above hepatitis, after other apparent causes are excluded, immunosuppressants, e.g., corticosteroid should be initiated and ICI should be held. The dosage of corticosteroids that has been recommended with over 4 weeks taper range from 0.5 to 2 mg/kg/day [11, 13]. ICI can be resumed when corticosteroid has been tapered down to 10 mg/day (toxicity grade $\leq$ 1) for grade 2. Permanent discontinuation of ICI and corticosteroids treatment are recommended for grades 3 and 4 hepatitis [36]. Usually, corticosteroids lead to the normalization or improvement of liver enzymes in most patients [20, 26, 35]. Some patients might need multiple cycles of corticosteroid treatment [17]. The median time from corticosteroids initiation to resolution is approximately 8 weeks [37]. In clinical practice, spontaneous improvement of liver biochemistry following ICI cessation without any corticosteroid

therapy has been reported [16]. Patients with ICI-induced hepatitis that is refractory to high dose corticosteroids may need a trial of mycophenolate mofetil based on some case studies [6, 21]. Because of its potential hepatotoxic effect (very rare), infliximab is not recommended for the treatment of ICI-induced hepatitis [22, 24]. Antithymocyte globulin therapy was also reported as an alternative treatment in the event of corticosteroid intolerance [21].

For ICI-induced hepatitis, ICI therapy can be resumed after the resolution of transaminitis to grade 1 or below. In the event of persistent grade 3 or 4 hepatitis, it may require more than 1 month to the resolution of hepatic injury, and this can lead to permanent termination of ICI treatment. The liver function panel should be monitored as some patients may have rebound elevation of AST and ALT even after completion of corticosteroids therapy and clinical resolution [20].

## Conclusion

The high incidence of ICI-induced hepatitis has been reported in the literature considering the wide use of ICI in the past few years. ICI-induced hepatitis often occurs 8–12 weeks after the initiation of ICI. The presentation of ICI-induced hepatitis is usually asymptomatic and shares a few characteristics with viral hepatitis, displaying elevated levels of AST, ALT, and total bilirubin, but may co-present with fever, malaise, and even death in rare cases. The diagnosis of ICI-induced hepatitis is usually made after the exclusion of other etiologies of hepatitis. For the management of ICI-induced hepatitis, the discontinuation of ICI treatment and the early use of immunosuppressants, e.g., corticosteroids, can lead to quick improvement in severe cases. The ultimate goal is to maintain normal hepatic function panel while continuing ICI treatment to maximize the benefit of ICI in good responders. Future studies are still required to further improve the management of ICI-induced hepatitis.

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