ISSN: 2640-7477

Review Article

Journal of Gastroenterology & Digestive Systems

Navigating the Hepatic Hurdles of Immune Checkpoint Inhibition

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Submitted: 2023, Oct 31; **Accepted:** 2023, Nov 09; **Published:** 2023, Nov 20

Citation: Patel, A. (2023). Navigating the Hepatic Hurdles of Immune Checkpoint Inhibition. *J Gastro & Digestive Systems, 7*(2), 54-57.

Abstract

The introduction of immune checkpoint inhibitors (ICIs) has revolutionized cancer therapy, offering promising outcomes in various malignancies. However, the use of these agents is associated with a spectrum of immune-related adverse events (irAEs), including liver complications commonly referred to as ICI-induced hepatitis. This review article aims to provide a comprehensive overview of the epidemiology, pathophysiology, clinical manifestations, diagnosis, and management strategies for ICI-induced hepatitis. We also discuss the histopathological features that distinguish this condition from other liver diseases like autoimmune hepatitis. Additionally, the article explores existing guidelines and recommendations for managing ICI-induced hepatitis. As the application of ICIs continues to expand, understanding the nuances of associated hepatic complications becomes increasingly critical for clinicians involved in cancer care. Therefore, this review serves as a timely resource for oncologists, gastroenterologists, and other healthcare professionals engaged in the management of patients undergoing ICI therapy.

Keywords: Immune Checkpoint Inhibitors, Hepatic Adverse Events, ICI-induced Hepatitis, Immune-Related Adverse Events

1. Introduction

The therapeutic landscape of oncology has been dramatically reshaped by the introduction of immune checkpoint inhibitors (ICIs), offering remarkable efficacy across a diverse range of malignancies [1,2]. These ground-breaking agents modulate immune response by targeting inhibitory pathways like PD-1/PD-L1 and CTLA-4, thereby boosting the immune system's ability to combat cancer cells [3,4]. Despite their transformative impact, ICIs are not without challenges; they can cause a spectrum of immune-related adverse events (irAEs), affecting multiple organ systems, including the liver [5,6].

Immune checkpoint inhibitor-induced hepatitis is an emerging concern that warrants focused investigation due to its clinical implications and potential to influence patient outcomes [6]. The condition most commonly manifests as isolated elevations in liver transaminases but can vary in severity, up to and including fulminant hepatic failure [7]. Early identification and appropriate management are critical components of mitigating the risks associated with ICI-induced hepatitis [8,9].

This review aims to provide overview of the epidemiology of ICI-induced hepatitis, exploring its clinical manifestations, diagnostic criteria, and management strategies. It will further delve into the histopathological features that distinguish ICI-induced hepatitis from other hepatic disorders like autoimmune hepatitis (AIH) [10]. Additionally, the review will discuss existing guidelines and recommendations that standardize the clinical management of this irAE [3,11].

1.1. Epidemiology of Immune Checkpoint Related Hepatitis

Understanding the epidemiology of ICI-induced hepatitis is crucial for gauging its impact and implementing effective management strategies. The incidence of ICI-induced hepatitis varies widely, ranging from 0.5% to 30%, depending on factors such as the type of ICIs, the underlying cancer, and individual patient characteristics [10]. This variability suggests that the true incidence may be underreported and underdiagnosed.

Common malignancies treated with ICIs that present a risk for hepatitis include melanoma, lung cancer, and hepatocellular carcinoma [12,13]. Risk factors for the onset of ICI-induced hepatitis include the type and dosage of the ICI, treatment duration, and pre-existing liver conditions [13]. Patients with pre-existing liver diseases like viral or autoimmune hepatitis are particularly vulnerable to this adverse event [13]. Additionally, the risk escalates when ICIs are used in combination with other immunomodulatory agents [13].

1.2. Pathophysiology of Immune-Checkpoint Induced Hepatitis

ICIs, pivotal in cancer therapy, have a darker side: they can instigate immune-related adverse events, including liver-specific conditions like hepatitis [10]. The crux of ICI-induced hepatitis

lies in the disruption of immune homeostasis. ICIs target and block inhibitory checkpoints like CTLA-4 and PD-1, thereby augmenting T-cell activation against tumors. This process, however, also sets off a chain of events that disrupt self-tolerance, unleashing autoreactive T cells that cause hepatitis [14].

In the liver, a critical organ for immune regulation, this disturbance manifests as immune-mediated injury. Activated T cells infiltrate hepatic tissues, target self-antigens, and trigger the release of pro-inflammatory cytokines like interferon-gamma and TNF-alpha, culminating in hepatocellular damage [15].

Histologically, ICI-induced hepatitis resembles, yet distinctively differs from, autoimmune hepatitis. Liver biopsies typically reveal a blend of lymphocytes, plasma cells, and eosinophils, along with signs of hepatocellular necrosis and interface hepatitis [10].

While the exact mechanisms are not fully deciphered, prevailing theories suggest a complex interplay of autoreactive T cell activation and pro-inflammatory cytokine release, with each amplifying the other, resulting in liver injury [15]. Clinically, symptoms can range from asymptomatic elevations in liver enzymes to severe dysfunction, warranting immediate cessation of ICIs and immunosuppressive treatment, often corticosteroids [10,15].

1.3. Clinical Features of Immune-Checkpoint Inhibitor-Induced Hepatitis

The clinical manifestations of ICI-induced hepatitis are diverse, ranging from asymptomatic to severe and potentially life-threatening liver dysfunction [5]. Patients may also experience non-specific symptoms like fatigue, abdominal pain, nausea, and jaundice [5]. Given the overlap of these symptoms with other liver conditions, the diagnosis of ICI-induced hepatitis can be challenging. Thus, it remains vital to include it in the differential diagnosis for any patient with liver abnormalities and relevant clinical symptoms.

In severe cases, patients can develop acute liver failure, a rare but life-threatening complication marked by hepatic encephalopathy, coagulopathy, and jaundice [16]. This severe progression necessitates immediate medical intervention and may even require liver transplantation.

Histologically, ICI-induced hepatitis often reveals a mixed inflammatory infiltrate, predominantly consisting of lymphocytes, plasma cells, and eosinophils, as well as hepatocellular necrosis and interface hepatitis. These features point toward an immune-mediated process and differentiate it from other etiologies such as viral hepatitis or autoimmune hepatitis [5].

1.4. Diagnosis of Immune Checkpoint-Related Hepatitis

Diagnosing ICI-related hepatitis is a multifaceted process that demands a comprehensive assessment of clinical presentation, laboratory findings, and histopathological evaluations. Early recognition and precise diagnosis are imperative for the initiation of timely and effective treatment measures [13].

Clinically, patients may present with non-specific symptoms, such as fatigue, jaundice, or abdominal discomfort. While the most common initial sign is an asymptomatic elevation in liver enzymes, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), it's crucial to note that the extent of enzyme elevation is not a reliable indicator of disease severity [5].

Histopathological examination offers valuable diagnostic insights, especially when the clinical picture is unclear. Biopsies can help distinguish ICI-induced hepatitis from other hepatic disorders, such as AIH or drug-induced liver injury (DILI). Characteristic histological features may include lobular hepatitis, bile duct injury, and granulomatous changes [10].

In patients with pre-existing liver conditions like chronic hepatitis B, serum markers like hepatitis B core-related antigen (HBcrAg) and hepatitis B virus RNA might offer additional diagnostic utility. These markers can be particularly useful in assessing the etiology of liver dysfunction in the context of ICI therapy [17,18].

A multidisciplinary approach, involving oncologists, gastroenterologists, and pathologists, is often recommended for accurate diagnosis and optimal management. Various diagnostic criteria and guidelines, such as those outlined by the American Gastroenterological Association (AGA), can provide a structured framework for diagnosis and treatment [19].

1.5. Management of Immune Checkpoint-Related Hepatitis

Management of ICI-related hepatitis is a challenging yet vital component of patient care in oncology. It involves a multidisciplinary approach, in which guidelines and recommendations from various medical societies serve as critical roadmaps [3,20,21].

Based on the severity of the hepatitis and other clinical parameters, one of the first steps in management is to decide whether to temporarily or permanently discontinue ICI therapy [3,22]. For mild cases of hepatitis, close monitoring of liver function tests may suffice. In more severe instances, corticosteroids like prednisone are often used to mitigate immune responses and control inflammation in the liver [11]. In refractory cases or for those not responding to corticosteroids, other immunosuppressive agents such as tacrolimus can be considered [22].

Histopathological evaluations can help differentiate ICI-induced hepatitis from other forms of liver diseases like autoimmune hepatitis or drug-induced liver injury, thereby informing treatment strategies [10]. In patients with liver metastases, there may be an elevated risk of developing ICI-induced hepatitis, thus necessitating additional monitoring [23].

Alternative treatments are considered when standard approaches fail. For example, infliximab, a drug commonly used to treat inflammatory bowel diseases, has been employed successfully for the management of refractory ICI-induced hepatitis [24].

Several guidelines provide a framework for healthcare professionals. For example, the American Society of Clinical On-

cology (ASCO) offers comprehensive guidelines on managing immune-related adverse events, including hepatitis [20]. Similarly, the Japanese Society of Gastroenterology provides evidence-based recommendations that can be applied to managing liver diseases, including ICI-induced hepatitis [21].

1.6. Future Research

Future research in the field of ICI-related hepatitis holds great potential for improving our understanding of the underlying mechanisms, risk factors, and optimal management strategies. Here are some potential research ideas for further investigation:

1. Mechanisms of immune-related hepatitis: Further studies are needed to elucidate the precise mechanisms by which ICIs induce hepatitis. This research could involve exploring the role of specific immune checkpoint molecules, such as PD-1, CTLA-4, LAG-3, and TIM-3, in the development of immune-related hepatitis [10].
2. Biomarkers for predicting immune-related hepatitis: Identifying reliable biomarkers that can predict the development of immune-related hepatitis would be valuable for patient management. Future research could focus on identifying specific genetic, immunological, or serological markers that can help identify patients at higher risk of developing hepatitis following ICI therapy [11].
3. Differentiation of immune-related hepatitis from other liver diseases: Immune-related hepatitis can present with similar clinical and histological features as other liver diseases, such as autoimmune hepatitis or idiosyncratic drug-induced liver injury. Future research could aim to identify specific histological or molecular markers that can differentiate immune-related hepatitis from other liver diseases, aiding in accurate diagnosis and appropriate management [10].
4. Optimal management strategies: Although corticosteroids are commonly used to manage immune-related hepatitis, there is a need for further research to determine the optimal dosing, duration, and timing of corticosteroid therapy. Additionally, the role of other immunosuppressive agents, such as tacrolimus or infliximab, in the management of refractory cases of immune-related hepatitis could be explored [10,11].
5. Long-term outcomes and follow-up: Long-term follow-up studies are needed to assess the impact of immune-related hepatitis on patient outcomes and survival. Research could focus on evaluating the long-term liver function, recurrence rates of hepatitis, and the potential for chronic liver disease following immune-related hepatitis [11].
6. Combination therapies and novel treatment approaches: Investigating the potential of combination therapies, such as combining ICIs with other immunomodulatory agents or targeted therapies, could be an interesting avenue for future research. Additionally, exploring novel treatment approaches, such as immune checkpoint inhibitors with modified dosing schedules or alternative routes of administration, may help optimize the balance between efficacy and toxicity [11].

2. Conclusion

The advent of ICIs has revolutionized oncology but brings with it the challenge of managing immune-related adverse events like hepatitis. Understanding the epidemiology, pathophysiology, and clinical manifestations of ICI-induced hepatitis is crucial for timely diagnosis and effective management. While corticosteroids remain the cornerstone of treatment, a multi-disciplinary approach involving oncologists, gastroenterologists, and pathologists is often necessary for optimal patient outcomes. Future research should focus on elucidating underlying mechanisms, identifying predictive biomarkers, and optimizing management strategies to improve both the safety and efficacy of ICIs in cancer treatment.

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