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Hepatotoxicity induced by immune checkpoint inhibitors

Flaviu Muresan[1], Olga Hilda Orasan[2], Angela Cozma[2], Madalina Daiana Bancos[3*], Lorena Ciumarnean[2], Mircea Vasile Milaciu[2], Tinca Codruta Pocol[2], Nicoleta Valentina Leach[2], Teodora Gabriela Alexescu[2], Ovidiu Vasile Fabian[1], George Ciulei[2], Mirela Georgiana Perne[2]

[1] *Iuliu Hatieganu University of Medicine and Pharmacy, 4th Surgical Department, Cluj-Napoca, Romania*
[2] *Iuliu Hatieganu University of Medicine and Pharmacy, 4th Medical Department, Cluj-Napoca, Romania*
[3] *Iuliu Hatieganu University of Medicine and Pharmacy, Hematology Department, Cluj-Napoca, Romania*

ABSTRACT

Immune checkpoint inhibitors (ICIs) are an effective immunotherapeutic approach for cancers affecting the lung, skin, kidney, mammary gland, or certain hematologic malignancies. Regarding the prognosis of these oncological conditions, treatments with ICIs open new therapeutic perspectives with benefits for both patients and healthcare providers. A drawback of immune checkpoint inhibition is the occurrence of immune-related adverse events that can involve a wide range of organs, such as the liver. Given widespread usage of immunotherapy, the number of patients who suffer from this unwanted condition has increased. Hepatopathy induced by ICIs can be severe and can even lead to death. Detecting liver toxicity in ICIs regiments requires a close monitorization of patients during and after the treatment. Such hepatopathies often involve discontinuation of immune checkpoint inhibitors and administration of corticosteroids. In conclusion, hepatopathies induced by immune checkpoint inhibitors require a comprehensive understanding for effective management, both to protect the patient's life during therapy and to ensure longer survival after cessation of treatment.

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[*]**Corresponding author:**

Madalina Daiana Bancos,

Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Department of Hematology, 34-36 Republicii Street, Cluj-Napoca, 400015, Romania

E-mail: madalinabancos@yahoo.com

Introduction

The tumor cells hold the ability to elude the immune system's self-defense. They secure their survival and proliferation by expressing immune checkpoint molecules [1].

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies used to stimulate the immune system to target and destroy malignant cells. The classes of ICIs frequently employed in clinical settings include anti-programmed cell death 1 (anti-PD-1), anti-programmed cell death ligand 1/2 (anti-PD-L1/2), and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4). The study of immunotherapy is actively ongoing with attempts to discover new classes of ICIs, such as anti-lymphocyte activation gene 3 (anti-LAG3), anti-B and T cell lymphocyte attenuator (anti-BTLA), anti-V-domain Ig suppressor of T cell activation (anti-VISTA), anti-T cell immunoglobulin and mucin domain 3 (anti-TIM-3), and anti-CD47 [1]. Researchers are also turning their attention to other molecules involved in immunity, such as killer immunoglobulin-like receptors (KIRs), CD137 (4-1BB), CD112R, signaling lymphocytic activation molecule family receptors (SFRs), signal regulatory protein alpha (SIRPa), Clever-1, SIGLEC-15, SIGLEC-10, and T cell immunoglobulin and ITIM domain (TIGIT) [2,3]. PD-1/PD-L1 inhibitors delay the phenomenon of T cell exhaustion caused by prolonged exposure to high concentrations of tumor antigen within or around the tumor. CTLA-4 inhibitors act during the early development of T cells, facilitating their activation and proliferation in lymphoid organs [1].

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The heightened usage of ICIs in the onco-hematologic domain is due to a superior and sustained therapeutic response, accompanied by a safety profile surpassing that of chemotherapy or high-risk surgeries [4]. According to a report by the American Association for Cancer Research, by 2023, eleven immune checkpoint inhibitors have received FDA approval for use in multiple types of cancer [5]. A significant challenge associated with the deployment of this oncological treatment is the emergence of immune-related adverse events (irAEs).

A multicenter observational study showed that in lung cancer patients treated with ICIs, there was a 26.9% incidence of irAEs of all grades, where 5.8% were grade 3-5 irAEs. The most commonly affected organs, in order of frequency, were the thyroid, lungs, skin, and liver [6]. In a recently published study, an incidence of 22.1% was recorded for experiencing at least one irAE among 140 United States veterans who had received a minimum of one dose of ICIs. Hepatic conditions were identified as the second most prevalent adverse effect [7]. Consequently, the widespread use of ICIs and the frequent involvement of the liver as an adverse event during ICI treatment underscore the necessity for a comprehensive understanding of the management of this severe medical condition.

This review addresses epidemiological data, mechanism of action, histological aspects, clinical and paraclinical findings and treatment regarding liver toxicity following the use of immune checkpoint inhibitors.

Discussions

Epidemiology and risk factors

Hepatopathies are one of the leading irAEs, with 5.3-8.8% of patients receiving at least one ICI experiencing hepatic toxicity of any grade [6–8]. A study of Romanski et al. on 521 melanoma patients documented a 6.8% incidence of hepatitis of any grade according to the Common Terminology Criteria for Adverse Events (CTCAE) classification, with a higher occurrence rate for mild hepatitis (grade 1 = 28.1%) compared to severe cases (grade ≥3 = 4.4%) [9].

Risk factors for hepatotoxicity involve combined treatments, female gender, low ALP and high ALT levels on making the malignancy diagnosis [8]. ICI dose and anti-CTLA-4 regiments increase the ICI-induced liver toxicity [8–10]. Age-related data are controversial. Atallah et al. [8] found no significant age-related differences, while Zhang et al. [11] reported a higher incidence in the young (<55 years). Anti-CTLA-4 ICIs were found to be positively correlated with hepatotoxicity severity [12]. Liver toxicity is higher in melanoma patients treated with combination therapy [8]. The Eastern Cooperative Oncology Group (ECOG) status does not affect incidence [6,7]. Romanski et al. suggested a potential link between antibiotic use and hepatopathies developed over the next 7 days after finishing the antibiotic course [9]. Patients with viral hepatitis do not exhibit an increased risk for ICI-related hepatopathies [13], and the likelihood of reactivation of hepatitis B or C viral infections is low to negligible [14,15]. The relationship between immune hepatitis and irAEs requires further investigation to understand the underlying mechanisms and potential clinical implications [16].

Mechanism of action

The immune checkpoints are proteins on the cell membrane that modulate lymphocyte activity to prevent exaggerated reactions to self-antigens. This leads especially to the inhibition of the T lymphocytes' function. Programmed cell death 1 (PD-1) is an immune checkpoint found on the surface of T cells, but also on B lymphocytes and Natural Killer cells (NK cells). It interacts with programmed cell death ligand 1 (PD-L1) or programmed cell death ligand 2 (PD-L2) present on various cell types, including tumor cells. This interaction leads to the exhaustion of peripheral T effector cells, their transformation into regulatory T lymphocytes (Tregs) and to the prevention of cancer cell apoptosis. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another immune checkpoint of T lymphocytes, exhibiting a higher affinity than CD28 for the CD80 and CD86 receptors of the antigen-presenting cells (APCs), thereby inhibiting the function of T lymphocytes. The lymphocyte activation gene 3 (LAG3) encodes an immunomodulatory molecule present on different types of lymphocytes, such as CD4/CD8+ T and B cells or NK lymphocytes. The LAG3 protein plays a role in the immune response by inhibiting the proliferation and differentiation of T cells and by stimulating the function of regulatory T lymphocytes. LAG 3 is frequently expressed alongside PD-1 and CTLA-4 (Table 1) [1,17,18].

Table 1. Immune checkpoint inhibitors by mechanism of action

Drug mechanism	Drug name
Anti-PD-1	Cemiplimab, Dostarlimab, Nivolumab, Pembrolizumab, Retifanlimab, Toripalimab
Anti-PD-L1	Atezolizumab, Avelumab Durvalumab
Anti-CTLA-4	Ipilimumab Tremelimumab
Anti-PD-1/Anti-LAG-3	Nivolumab + Relatlimab

Anti-PD-1: anti-programmed cell death 1; Anti-PD-L1: anti-programmed cell death ligand 1; Anti-CTLA-4: anti-cytotoxic T-lymphocyte-associated protein 4; Anti-LAG-3: anti-lymphocyte activation gene 3

The T lymphocytes' capacity to react to autoantigens is regulated by the inhibitory action of immune checkpoint molecules, which is essential for keeping self-tolerance.

Tumor cells overexpress these surface molecules to avoid the cytotoxic action of T lymphocytes. By blocking these immune checkpoints using ICIs, the patient's immune system is activated to attack the tumor. The healthy cells also possess these molecules [18].

Regarding their immunologically mediated mechanism, ICI-induced hepatopathies are considered a special type of drug-induced liver injury (DILI), different from idiosyncratic and intrinsic ones [19]. The liver meets a plethora of antigens due to its dual role in blood filtration and digestion. To prevent exaggerated immune reactions to these antigens, the liver exhibits immunotolerance. Key players in liver immune tolerance include liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and dendritic cells (DCs). Hepatic dendritic cells present lower levels of major histocompatibility complex-II (MHC-II) and costimulatory molecules (such as CD80/CD86) compared to dendritic cells in other locations. Moreover, these cells mainly release anti-inflammatory cytokines, leading to reduced T lymphocyte activation and the promotion of Tregs development. The liver presents endotoxin tolerance, enabling it to withstand constant exposure to bacterial components such as lipopolysaccharides (LPS). This function is helped by the secretion of anti-inflammatory cytokines, like IL-10, and TGF-beta, which play key roles in keeping the liver's immunotolerant state. Hepatic stellate cells act like APCs and promote the expansion of Tregs. Hepatocytes lack costimulatory molecules, leading to the destruction of the T cell clone previously generated upon first contact with the hepatocyte. The interaction between hepatocytes and NK cells fosters the production of IL-10. Another mechanism supporting hepatic immunotolerance involves elevated levels of PD-L1 and PD-L2 expressed on various liver cells. Consequently, the inhibition of immune checkpoint molecules triggers the activation of T cells that target a broad spectrum of antigens, including self-antigens [20].

Histopathology

A study performed by Cohen et al. in 2021 involving a cohort of 60 patients identified three patterns of ICI-induced liver injuries, namely, in descending order of frequency, the hepatitic, cholangiopathic, and steatotic patterns.

- *The hepatitis pattern* of immune checkpoint inhibitor (ICI)-induced liver injuries includes predominantly lobular inflammatory changes. These often involve centrilobular damage, followed by azonal, panlobular, and periportal involvement. The inflammatory infiltrate in lobular injury is primarily composed of histiocytes, which can sometimes organize into granulomas ranging from vague to well-formed, or into fibrin ring granulomas. Endothelialitis lesions were also reported in the involvement of both the portal vein and the central vein. Localized portal inflammation was especially seen with a mononuclear inflammatory infiltrate, with or without eosinophils, and occasionally concomitant with neutrophils.
- *The cholangitis pattern* of immune checkpoint inhibitor (ICI)-induced liver injuries features ductal and portal inflammatory lesions, with rare granulomas and no endothelialitis lesions. In biopsies examined for cholangitis, bile duct lesions and pericholangitis predominate, marked by the presence of neutrophils, with lesions primarily found in the portal areas.
- *The steatotic pattern* of immune checkpoint inhibitor (ICI)-induced liver injuries ranged from mild to severe steatosis, even progressing to fibrosis. Granulomas or endothelialitis were not observed, and if portal inflammation was present, it was mild and nonspecific.

Out of the total of 60 patients, 60% exhibited the hepatitic pattern, 26% the cholangitic pattern, 7% steatosis or steatohepatitis, and 7% presented with nonspecific changes.

A correlation was seen between the liver function test pattern and the histopathological features for both the hepatitis and cholangitis patterns [21].

Diagnosis

The grading of irAE severity in hepatic toxicity can be performed using either the Common Terminology Criteria for Adverse Events (CTCAE) or the Expert Working Group (EWG) definitions for Drug-Induced Liver Injury (DILI). The CTCAE is the most widely used criteria in clinical practice and trials, but the first version was drafted before immunotherapy became a part of cancer treatment protocols. Hepatic impairment severity is higher under the CTCAE system compared to DILI. There is a discrepancy between clinical severity and CTCAE criteria, with the latter tending to overestimate severity [8]. Figure 1 is CTCAE Version 5, the latest version in use, which was updated in 2017 [22]. (Table 2)

The clinical presentation can vary from asymptomatic cases to severe liver failure or hepatic encephalopathy. Most patients have no symptoms, showing only signs of hepatocellular injury on routine examinations. Other manifestations may include nausea, vomiting, abdominal pain, jaundice, fever, weakness, fatigue, and in more severe cases, ascites and coagulopathies [23].

The onset of ICI-induced hepatitis typically occurs around 3 months after starting ICI treatment, but can manifest at any time during or after the treatment [24]. The likelihood of occurrence diminishes over time. According to Zhang et al. within the first 100 days of initiating anti-PD-1 and CTLA-4 therapy in melanoma patients the incidence of hepatic involvement was 59%, 35.9% being CTCAE grade 3-4 [11]. Anti-CTLA-4-based regiments present an earlier onset [9]. The risk of liver injury decreases after 4.5 months in patients undergoing combination therapy [8].

When hepatotoxicity is suspected, the RUCAM (Roussel Uclaf Causality Assessment Method) scale is applied to assess the possibility of ICI-related liver injury. A percentage of 19% of suspected cases of ICI-induced hepatopathies had another cause, according to causality assessment [8]. Immune checkpoint inhibitors induced hepatopathy is a diagnosis of exclusion. The first step involves ruling out other causes of liver injury such as viral, autoimmune etiologies, metastasis, hepatic vein thrombosis, biliary obstruction, alcohol consumption, and drug-induced hepatitis from administration of another therapeutic agents [25].

Table 2. Immune-related adverse events severity in hepatic toxicity

Adverse event	Grade I	Grade II	Grade III	Grade IV	Grade V
ALP	Increase up to 2,5 X base value	Increase between 2,5-5 X base value	Increase between 5-20 X base value	Increase > 20 X base value	
ALT	Increase up to 3 X base value	Increase between 3-5 X base value	Increase between 5-20 X base value	Increase > 20 X base value	
AST	Increase up to 3 X base value	Increase between 3-5 X base value	Increase between 5-20 X base value	Increase > 20 X base value	
Blood bilirubin	Increase up to 1,5 X base value	Increase between 1,5-3 X base value	Increase between 3-10 X base value	Increase > 10 X base value	
GGT	Increase up to 2,5 X base value	Increase between 2,5-5 X base value	Increase between 5-20 X base value	Increase > 20 X base value	
Hepatic failure			Asterixis Mild encephalopathy Limiting selfcare	Life-threatening consequences Moderate/severe encephalopathy, coma	Death
Portal hypertension		Decreased portal vein flow	Reverse portal vein flow associated with varices and/or ascites	Life-threatening Consequences Urgent intervention needed	Death

ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transpeptidase.

The guidelines from the European Society of Medical Oncology and the American Society of Clinical Oncology suggest performing a blood assessment of ALT, AST and bilirubin levels before every ICI administration during the treatment. If the liver functional test (LFT) corresponds to CTCAE grade 1 of hepatotoxicity, monitoring should be undertaken 1-2 times a week, and daily for severe cases [26,27].

In case of suspicion of ICI-induced liver toxicity, it is recommended to perform a complete blood count, coagulation profile, and to analyze serum levels of AST, ALT, ALP, GGT, and Bilirubin. Hepatitis viral markers A, B, C, +/- E are performed to exclude newly diagnosed or recurrent viral hepatitis. Testing for EBV and CMV infection is recommended. In case of suspicion of autoimmune liver disease, serological testing for specific antibodies is indicated [25].

Clinical patterns of ICI-induced hepatopathies are hepatocellular (38%), cholestatic (37%) and mixed (25%). Patients who take combination therapy of ICI have a greater chance to develop hepatocellular clinical pattern, and those with anti-PD-(L)1 are more likely to present a cholestatic pattern. The hepatocellular model is associated with CTCAE grade 4 and with anti-CTLA-4 treatment [12] (Figure 1).

As medical imaging tests, abdominal ultrasonography should be performed for differential diagnosis, such as biliary obstruction or thrombosis. It can demonstrate the presence of hepatomegaly, periportal edema, or periportal lymphadenopathy. CT scan with contrast is more appropriate for investigating hepatic metastasis, especially if more than 4 weeks have passed since the last CT scan performed. MRI is an alternative to CT and ERCP has special indications for use [28].

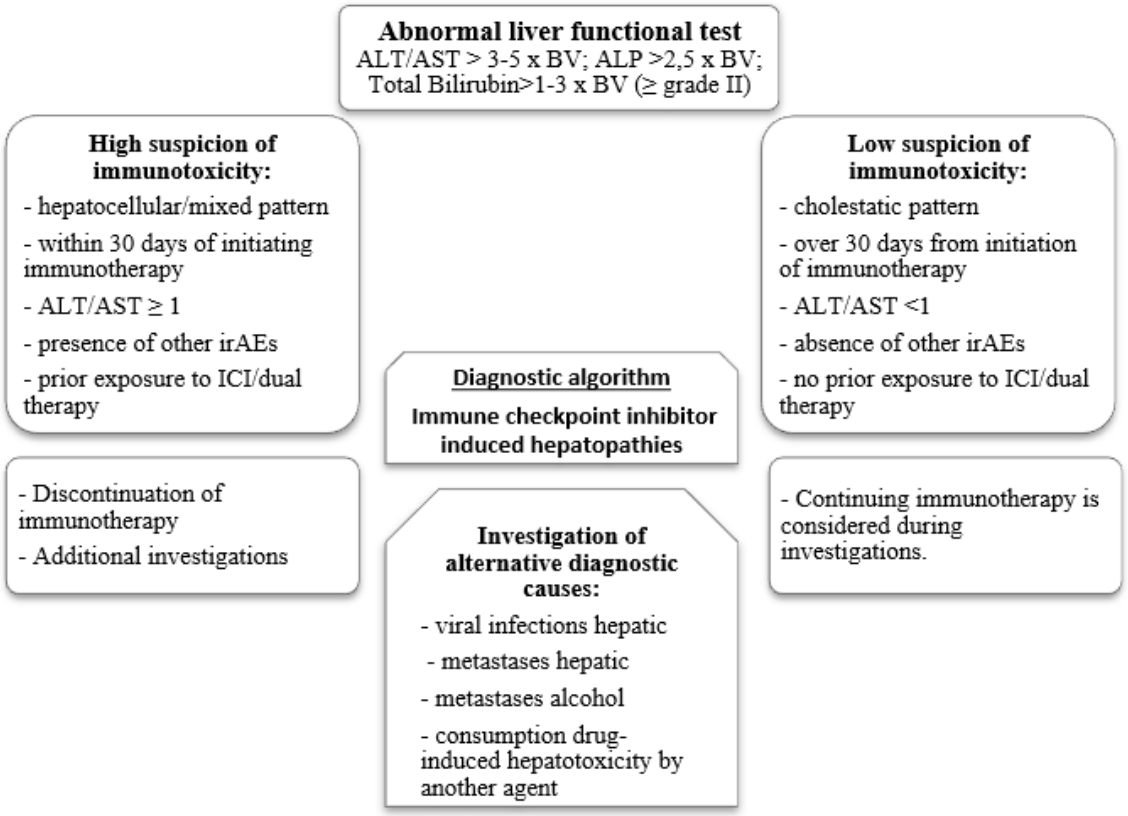

Figure 1. Diagnostic algorithm in Immune checkpoint inhibitor induced hepatopathies (ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BV: Base Value).

The biopsied liver injury pattern and its histological severity exhibits no correlation with the requirement for corticosteroid, treatment or additional immunosuppression, the resolution time, or the hepatopathy's CTCAE grade [21]. Therefore, liver biopsy is recommended for grade III/IV hepatotoxicity, uncertain diagnoses, or when there is resistance or non-responsiveness to glucocorticoids [27].

Treatment

According to the guidelines, for CTCAE grade 1 ICI-induced hepatopathies close monitoring without interruption of ICI treatment is often recommended. CTCAE grade 2 implies ICI temporary interruption and administration of 0.5-1 mg/kg/day prednisone. ICI should be permanently stopped for CTCAE grade ≥3 and corticosteroid should be increased at 1-2 mg/kg/day methylprednisolone. If the clinical improvement is not seen in 2-3 days, mycophenolate mofetil (MMF), tocilizumab, tacrolimus, azathioprine, cyclosporine or anti-thymocyte globulin should be considered [26,27]. Other therapeutic approaches are infliximab or plasma exchange [15]. A two-case report documented favorable outcomes in corticoresistant/ relapsing patients treated with 2000 mg/day of MMF [29]. Immunosuppression should be taper only after clinical improvement and CTCAE severity is ≤ 1 [27] (Table 3).

Corticoresistant/refractory hepatopathies occurred in 12% of cases among 2750 patients with lung cancer [30]. According to a study conducted on 521 melanoma patients, approximately one-third of hepatitis cases recurred, predominantly of grade 3-4. The delay in initiating corticosteroid therapy showed no change in the evolution of ICI-induced hepatopathies. Patients who received >4000 mg of corticosteroids exhibited a reduced anti-tumor response compared to those who received lower doses [9]. Better outcomes with the use of lower doses of corticosteroids were also observed by Hountondji et al. [12].

Out of 117 patients with hepatitis, ICI treatment was resumed in 51 patients, most of them receiving the same type of ICI along with corticosteroid administration. Among these, hepatitis reappeared in 23.5% of cases, with 33.3% being grade 2, 41.7% grade 3, and 25% grade 4. There was no correlation between the recurrence of hepatitis after resuming ICI treatment and the type of treatment or clinical pattern. Patients who did not receive any treatment, even those with severe ICI-induced hepatopathy, had a faster clinical progression [12].

Prognosis

The majority of ICI-induced hepatopathies are corticosensitive with positive outcomes. Severe cases of hepatitis leading to patient death are rare. However, in the anti-PD-(L)1 regiment, 22% of deaths due to irAEs were attributed to hepatotoxicity. The liver involvement caused 16% of irAEs-related deaths in the ipilimumab regiments [10].

Table 3. Immune checkpoint inhibitor induced hepatopathies treatment

Grade I • asymptomatic • ALT or AST or TB > BV	***Continues ICI treatment*** • weekly blood tests
Grade II • asymptomatic • ALT or AST ≥ 3 x BV and/or TB ≥ 1,5 x BV	***Temporary interruption of ICI treatment*** • blood tests x 2/week • symptoms > 3-5 days -> Prednisone 0.5 mg/kg/day or equivalent • 4-6 weeks, reduction by 10 mg/week
Grade III • symptomatic • ALT or AST ≥ 5 x BV and/or TB ≥ 3 x BV	***Interruption of ICI treatment*** • daily blood tests • Methylprednisolone 1 mg/kg/day to 2 mg//kg/day • reduction of toxicity ≤ grade I -> equivalent dose of Prednisone • decrease by 10-20 mg/week, 6-10 weeks
Grade IV • symptomatic • ALT or AST ≥ 20 x BV and/or TBB ≥ 10 x BV	***Permanent discontinuation of ICI treatment*** • daily blood tests • Methylprednisolone 1 mg/kg/day to 2 mg//kg/day • refractory toxicity – mycophenolate mofetil 500 mg twice daily, maximum 1.5 g twice daily or Tacrolimus 1-2 mg every 12 hours, if there is no response to mycophenolate mofetil

ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TB: Total Blood Bilirubin; BV: Base Value

Conclusions

Immune checkpoint inhibitors have revolutionized oncological therapy but are burdened by multiple irAEs. The increasing trend in the use of ICIs across an extensive range of neoplasms with the frequent occurrence of hepatic toxicity in these patients underscores the importance of a thorough understanding of the management of these conditions. ICI-induced hepatopathy can be severe and can even lead to death. Detecting liver toxicity in ICIs regiments requires a close monitorization of patients during and after the treatment. Hepatic involvement is suspected in all patients receiving at least one ICI if their liver functional tests are higher than the baseline value. The treatment of hepatic toxicity in ICIs depends on the severity of irAEs.

Highlights

- ✓ The liver is frequently affected during immune checkpoint inhibitors treatment.
- ✓ Immune checkpoint inhibitors-induced hepatopathies are major immune-related adverse events, difficult to manage and a possible cause of death.

Abbreviations

ALP - alkaline phosphatase
ALT - alanine aminotransferase
APCs - antigen-presenting cells
AST - aspartate aminotransferase
BTLA - B and T cell lymphocyte attenuator
CD - cluster of differentiation
CMV – Cytomegalovirus
CT - computed tomography
CTCAE - Common Terminology Criteria for Adverse Events
CTLA-4 - cytotoxic T-lymphocyte-associated protein 4
DCs - dendritic cells
DILI - drug-induced liver injury
EBV - Epstein-Barr virus
ECOG - Eastern Cooperative Oncology Group
ERCP - endoscopic retrograde cholangiopancreatography
EWG - Expert Working Group
FDA - Food and Drug Administration
GGT - gamma-glutamyl transferase
ICIs - Immune checkpoint inhibitors
IL-10 - interleukin 10
irAEs - immune-related adverse events
KCs - Kupffer cells
KIRs - killer immunoglobulin-like receptors
LAG3 - lymphocyte activation gene 3
LFT - liver functional test
LPS - lipopolysaccharides
LSECs - liver sinusoidal endothelial cells
MHC-II - major histocompatibility complex-II
MMF - mycophenolate mofetil

MRI - magnetic resonance imaging
NK cells - Natural Killer cells
PD-1 - programmed cell death 1
PD-L1/2 - programmed cell death ligand 1/2
RUCAM - Roussel Uclaf Causality Assessment Method
SFRs - signaling lymphocytic activation molecule family receptors
SIRPa - signal regulatory protein alpha
TGF-beta - transforming growth factor beta
TIGIT - T cell immunoglobulin and ITIM domain (TIGIT)
TIM-3 - T cell immunoglobulin and mucin domain 3
Tregs - regulatory T lymphocytes
VISTA - V-domain Ig suppressor of T cell activation

Contributions

Conceptualization M.G.P., O.H.O., A.C., M.D.B. F.M.; Data curation M.G.P., F.M., M.D.B.; Formal analysis M.V.M., T.C.P., N.V.L., O.V.F.; Investigation T.G.A. O.V.F., T.C.P. F.M.; Methodology O.H.O., A.C., F.M., N.V.L.; Project administration T.G.A, L.C., T.C.P.; Resources M.D.B., G.C., O.V.F., M.G.P.; Supervision M.G.P., O.H.O., A.C.; Validation M.V.M, T.G.A. O.V.F., G.C., O.H.O., A.C.; Visualization L.C., M.V.M., G.C., T.G.A., F.M; Writing – the initial draft M.G.P., M,D.B.; Writing – revision and editing O.H.O., A.C., M.G.P.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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