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Review Article

Hepatotoxicity of immune check point inhibitors: Approach and management

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ABSTRACT

Therapeutic reversal of immune tolerance following immune checkpoint inhibitors (ICPI) administration, has proven effective in prolonging survival of patients with a variety of solid and liquid tumors, often however at the expenses of discrete toxicities known as immune-related adverse events (AEs). Such reactions result from activation of the immune system and often present with generalized symptoms including fatigue or fever and, in some patients, may cause organ-specific damage. Skin, gut, endocrine, lung and musculoskeletal are the most frequent targets of ICPI toxicity whereas, cardiovascular, hematologic, renal, neurologic and ophthalmologic AEs occur much less frequently. While the majority of AEs are mild to moderate, serious, occasionally life-threatening reactions have been reported, including severe colitis, pneumonitis, encephalitis, toxic epidermal necrolysis, myocarditis, and diabetic ketoacidosis, with a death toll of 2%. Hepatocellular carcinoma (HCC) is becoming an attractive area for immunotherapy. Owing to the fact that the association of HCC with cirrhosis may jeopardize tolerability of ICPI therapy, attention has been paid to identifying, preventing, and treating the AEs associated with ICPI, with a focus on liver safety. Though in most studies AEs resolved with interruption of treatment and short course of steroids, identification of predictive biomarkers of response might help sparing patients from potentially life-threatening toxicity in the absence of clinical benefit.

1. Introduction

The advent of immunotherapy with monoclonal antibodies directed against regulatory immune checkpoint molecules that inhibit T cell activation, has dramatically changed the therapeutic landscape of cancer [1,2]. The revolution started in 2011 following the approval of ipilimumab, a fully human IgG1 antibody that blocks the cytotoxic T lymphocyte-antigen-4 (CTLA-4), a checkpoint inhibitor of T cell activation, that proved to confer significant survival benefits to patients with advanced melanoma [3]. Subsequently, pembrolizumab and nivolumab, both engineered IgG4 antibodies that block the protein programmed death 1 (PD-1), were approved for use in patients with advanced melanoma [4,5] and non-small cell lung carcinoma [6–8], the same drugs being later approved for treatment of mismatch repair deficient/microsatellite instability high cancers that have progressed following treatment with chemotherapy.

While these drugs opened the way to the first 'tissue-agnostic', biomarker driven approvals, the first combination of ICPI endowed with distinct mechanisms of anticancer action, ipilimumab and nivolumab, were also approved, again for use in advanced melanoma [9,10]. In the end, the gold rush of immunotherapy trials translated into scientific progress with the approval of new ICPI directed against the protein programmed death-ligand 1 (PD-L1) atezolizumab, durvalumab and avelumab, for the treatment of different types of cancer.

Last year nivolumab and pembrolizumab received conditional approval by the United States (US) Food and Drug Administration (FDA) as second line treatment of hepatocellular carcinoma (HCC), a disease where the immunosuppressive milieu typical of progressive chronic liver diseases profoundly modulates tumor growth by facilitating immune evasion [11]. However, it has been recently announced that the second-line phase 3 trial of pembrolizumab versus placebo (Keynote-240) did not reach its co-primary endpoint of overall and progression-free survival (Merck Press Release Feb 2019). While approximately 60 clinical trials of immune therapeutic agents are registered for this indication, a number of discrete

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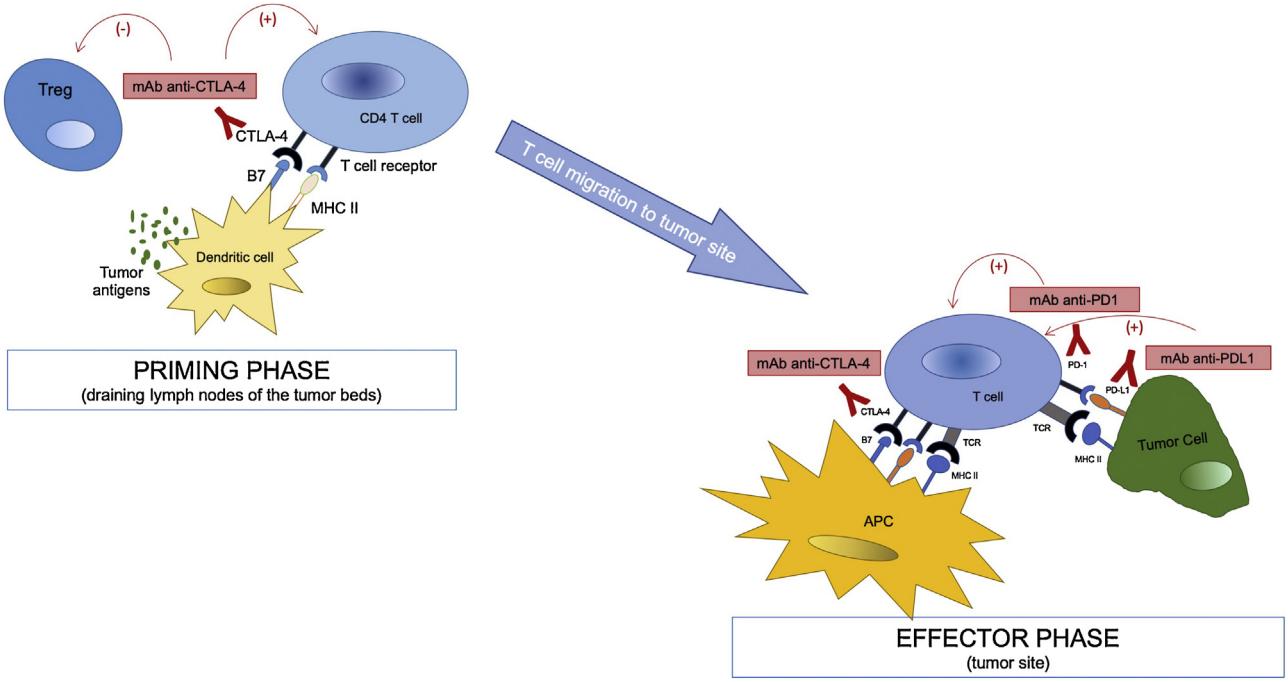

Fig. 1. Mechanisms of immune checkpoint inhibitors (ICPI) induced T cell activation. ICPI increase T cell responses and restore potent antitumor immune responses that are suppressed in cancer, with the goal of inducing tumor response. ICPI are surface molecules present on both immune cells and tumor cells and include among others cytotoxic T-lymphocyte antigen 4 (CTLA-4, target for ipilimumab), programmed cell death 1 (PD-1, target for pembrolizumab and nivolumab) and programmed cell death ligand 1 (PD-L1, target for atezolizumab, avelumab and durvalumab), which are all involved in intrinsic downregulation of immunity.

immune-related adverse events (AEs) caused by non-specific activation of the immune system emerged that may potentially affect almost any organ, including the liver. The fact that HCC is becoming an attractive area for immunotherapy with ICPI and that the frequent co-presence of cirrhosis associated with liver cancer may work against tolerability of anticancer therapy, has turned the attention to identifying, preventing, and treating the AEs associated with ICPI, with a focus on liver safety. This is even more so since the therapeutic algorithm of metastatic cancer is moving ahead to embrace combinations of different ICPIs and of ICPI with a tyrosine kinase inhibitor (TKI).

2. Mechanisms of action of the immune check point inhibitors

Immune check points like CTLA-4, PD-1, and PD-L1 are pillars of complex mechanisms that maintain self-tolerance and assist with immune response (Fig. 1). Binding of CTLA-4 and PD-1/PD-L1 to cancer cell or tumor microenvironmental ligands leads to T cell attenuation, which enables the tumor cells to avoid immune-mediated destruction [1,2], an event that can be reversed by drugs that specifically block immune check point pathways.

Under physiological conditions (i.e. in the absence of treatment with ICPIs), T-cells are primed by tumor antigens presented by antigen-presenting dendritic cells (DC) in the draining lymph nodes of the tumor beds. CTLA-4, expressed on T-helper cells and T-killer cells mediates an inhibitory signal that competes with stimulation by the CD-28 accessory molecule when ligated with B-7 on DCs. Further, CTLA-4 signaling enhances the inhibitory function of T-regulatory cells (T-regs). Activated T-cells then migrate to the tumor sites where their recognition of tumor antigens upregulates PDL-1 on the tumor cells. Increasing PDL-1 ligation of PD-1 receptors on T-killer cells determine cellular "exhaustion". These actions inhibit T-cell activation against tumor antigens but also to self-antigens. Treatment with ICPI stimulate T-cell responses to tumors; anti-CTLA- 4 antibodies enhance T-cell mediated immune responses principally at the priming stage by blocking the inhibitory signal while anti-PD-1 and anti-PDL-1 antibodies reactivate exhausted T-cells.

These drugs are currently utilized to treat a variety of malignancies and have demonstrated durable clinical activities in a subset of cancer patients.

While new inhibitory pathways and drugs blocking LAG-3, TIM-3, TIGIT, VISTA, or B7/H3 are being investigated [12], the list of potential targets of cancer treatment has further expanded to embrace such agonists of stimulatory checkpoint pathways as OX40, ICOS, GITR, 4-1BB, CD40, and molecules targeting tumor microenvironment components like IDO or TLR [13]. As the potential of immunotherapy to harness the patient's immune system to fight cancer is being investigated in more than 1000 clinical trials, a major challenge of immunotherapy remains however the identification of the right patient to treat, based on the presence of biomarkers that may predict a response to a given regimen.

In a study of 956 HCC patients, 25% clustered within a coordinated pro-inflammatory gene expression profile, with increased PD-1/PD-L1 expression in association with molecular abnormalities suggestive of exhausted immune response [14].

3. Adverse events caused by immune check point inhibitors

The expression of checkpoint molecules in T-cell populations that have specificity for self-antigens largely accounts for treatment with ICPI to be associated to a variety of discrete toxicities caused by non-specific activation of the immune system. This is in fact the consequence of the T lymphocytes hyperactivation induced by ICPI which generates a specific response directed against tumor antigens, leading to anti-tumor activity in tumor tissues but also side effects in normal tissues called ön-target.. As the CD8+ cytotoxic T lymphocytes-mediated cell lysis induces the release of neoantigens, tumor antigens and auto-antigens from normal tissues, respectively, a phenomenon called ëpitope spreading", diversification of the T cell repertoire and reduced immune tolerance occur,

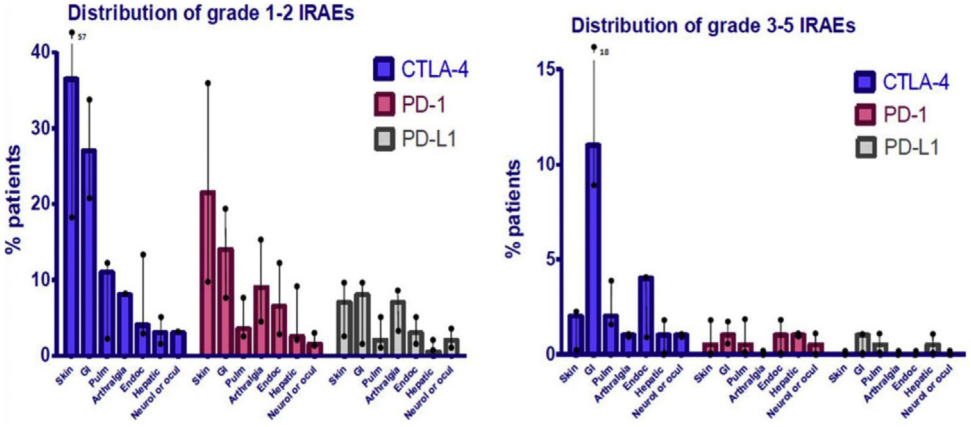

Fig. 2. Immune related adverse events (IRAEs) associated with immune checkpoint inhibitors. Distribution of grade I and II and grade III and IV IRAEs for all tumor types in the main clinical trials with anti-CTLA4, anti-PD-1 or anti-PD-L1 antibodies as single therapies. The values quoted are the median (range) IRAE rates for the set of clinical trials as a whole.

Adapted from Refs. [19] and [30].

which are exacerbated by inhibition of regulator T lymphocytes. In the end, the predominant activation of Th1 and Th17 T lymphocytes mediated by ICPI stimulates production of pro-inflammatory cytokines such as interferon-γ (IFNγ) and interleukine-17 (IL-17) (Fig. 1). While these mechanisms are responsible for the so called "off targeẗoxicities, the roles of cross-reactivity with the intestinal microbiota, hypersensitivity and the specific effect of PD-L2 remain to be determined [15].

Adverse events related to ICPI therapy were less frequent than those observed in patients receiving TKIs and were rather delayed in onset as they tend to appear beyond week 8 of therapy compared to TKI-associated AEs, that in fact were seen after week 4 of therapy, on average. Skin, gut, endocrine, lung and musculoskeletal are the most frequent targets of ICPI toxicity whereas, cardiovascular, hematologic, renal, neurologic and ophthalmologic adverse effects occur much less frequently, with some evidence of higher attack rates with the use of anti-CTLA-4 monotherapy than with anti-PD-1/PD-L1 agents (75% vs 30%) [16–18] (Fig. 2). Anti-CTLA-4 monotherapy appears to be associated with higher risk of grade 3 AEs compared to PD-1/PD-L1 agents (43% vs. $\leq$ 20%), and, although the relationship between AEs and dose/exposure remains to be fully established, the incidence of ICPI associated toxicities appears to be dose-dependent, with greater toxicity at higher dose levels [16].

Noticeably, obtaining accurate data on incidence and prevalence of AEs is hampered by significant variance in definitions of toxicity severity across disciplines as well as to the frequent overlap between mechanisms of inflammatory toxicity and those responsible for the drugs' therapeutic effects. In general, the mechanism of toxicity may vary by ICPI, and may occur in patients with durable responses to treatment, and although the majority of toxic effects are mild to moderate in severity, serious, occasionally life-threatening AEs have been reported in trials, including severe colitis, pneumonitis, encephalitis, toxic epidermal necrolysis, myocarditis, and diabetic ketoacidosis, with a death toll of 2% [19]. Most important, care givers should be aware that ICPI related toxicity can have a delayed onset and prolonged duration compared to AEs resulting from chemotherapy or other anti-cancer therapies, with chances that patients may present with toxicities even after treatment discontinuation [20,21].

4. Liver related adverse events

Immunotherapy is well tolerated in patients with chronic liver diseases, but liver toxicities may occur, requiring a specific work-up for diagnosis and management. This is even more so in the upcoming scenario of ICPI being tested in less advanced HCC as adjuvant or neoadjuvant therapy or in combination with locoregional treatment, and of treating patients with advanced cancer using combinations of different ICPIs and of ICPIs with antiangiogenics or TKIs, an approach that currently is being tested in numerous registration trials.

Using the Common Terminology Criteria for Adverse Events (CTCAE) established by the Cancer Therapy Evaluation Program of the National Cancer Institute, ICPI clinical trials have graded hepatotoxicity severity based on peak abnormalities of serum liver biochemical indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and bilirubin, measured as categorical levels of multiples of the upper limit of normal [22]. With this system, the higher grades of severity (grades 3-4) driven by elevations of ALT or AST do not necessarily require the presence of elevations of serum bilirubin or direct evidence of loss of hepatocyte function.

Meyer and colleagues recently analyzed the hepatic AEs in the CheckMate-040 trial, a phase 1/2, open-label, non-comparative, dose escalation and expansion trial that included histologically confirmed sorafenib-experienced and sorafenib-naive advanced HCC patients with or without HCV or HBV infection [23]. Nivolumab 3 mg/kg was given, regardless of PD-L1 status, every 2 weeks in the dose-expansion phase to patients in four cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressor without viral hepatitis, HCV infected, and HBV infected. Any grade ALT elevations were recorded in 12 patients representing 7.8% of the treated populations whereas grade 3–4 ALT elevation was observed in 4 patients only (2.6%) [24]. Interestingly enough, grade 3–4 AEs were not seen in any patients with hepatitis B related cancer who however had hepatitis suppressed by NUCs. Raised levels of bilirubin were reported in a very few patients (3.2%), none displaying grade 3–4 elevations. Liver-related severe AEs were reported in 4% of 154 patients exposed to nivolumab and 3% of 104 exposed to pembrolizumab compared to 10% of 32 patients treated with tremelimumab, where treatment had to be interrupted in 6%, 6.7% and 1.3% of patients, respectively; in patients with other than liver sites cancer, the rate of ICPI associated AEs was 3.5% [24]. A recent meta-analysis of published data highlighted that CTLA-4 inhibitors seem to be related to a higher rate of all-grade and high-grade hepatotoxicity compared with PD-1 inhibitors [25].

In 2017, the Society for Immunotherapy of Cancer (SITC) released the guidelines for the management of toxicity of immunotherapy for cancer, where hepatitis was listed as an asymp-

tomatic adverse event of ICPI administration. Typically, hepatitis is characterized by elevated ALT or AST, with or without raised bilirubin, with transaminase elevation taking place approximately 6–14 weeks after starting ICPI treatment, is almost invariably asymptomatic, and only a minority of patients present with fever [17]. The incidence of any-grade hepatic enzyme disturbance with ipilimumab is dose dependent, with 3 mg/kg monotherapy it is less than 4% whereas it raises up to 15% when the drug is dosed at 10 mg/kg. Incidence of hepatitis in patients treated with anti-PD-1 ICPIs is less, approximately 5%, but this rises to 30% when patients are treated with the combination of ipilimumab and nivolumab. More recently, in a comprehensive clinical and pathological analysis of the hepatic AEs associated with ICPI targeting 536 patients treated in France with anti-PD-1/PD-L1 or CTLA-4 immunotherapies for non-hepatic tumors, 3.5% of patients were found to have had severe hepatitis [26]. After exclusion of all known hepatotropic viruses, metabolic hepatotoxins and autoimmune hepatitis, the diagnosis of immune mediated liver toxicity was established in 13 patients whereas one patient lacked liver histology, one had viral hepatitis E, and one had hepatic infiltration by tumor. Interestingly, the nine patients exposed to anti-PD-1/PD-L1 were significantly older (69 years vs. 52 years) than the seven patients who received anti-CTLA-A monoclonals, without any gender disparity. The incubation period of hepatitis was rather short, as biochemical abnormalities developed in a mean period of five weeks after the first dose of immunotherapy, with patients receiving a median of two injections (range 1–36) during the study period. Another interesting finding of this survey was the histological pattern of hepatitis that differed by the type of immune checkpoint inhibitor involved: granulomatous hepatitis, including fibrin ring granulomas and central vein endothelitis was preferentially seen in patients receiving anti-CTLA-4 therapy compared to lobular hepatitis that was more often associated to anti-PD-1/PD-L1 monoclonals. Importantly, the outcome of hepatitis was universally benign as no patient developed hepatic failure. While six patients spontaneously recovered from hepatitis requiring no treatment, seven were treated with oral corticosteroids at doses of 0.5–1 mg/kg/day, two were maintained on 0.2 mg/kg/day corticosteroids and one patient required pulses and 2.5 mg/kg/day of corticosteroids, with the addition of a second immunosuppressive drug. In three patients, immunotherapy was reintroduced without recurrence of liver dysfunction. Thus, this multicenter survey in France provided evidence of the rare occurrence and the benign course of acute liver injury induced by ICPI therapy of metastatic cancer, the diagnosis requiring thorough clinical, laboratory and histological investigations to exclude other causes of hepatitis.

5. Rare liver related adverse events

Nodular regenerative hyperplasia of the liver (NRH), a benign transformation of hepatic parenchyma that may cause portal hypertension, was reported in 35-year-old male (with no history of liver disease) with melanoma who was admitted to hospital with anasarca and ascites ensued three weeks after starting pembrolizumab [27]. Portal hypertension was documented by a portal pressure gradient of 16 mm Hg (normal, <7) on *trans*-jugular liver catheterization whereas the accompanying liver biopsy revealed mild sinusoidal dilatation and congestion without significant lobular or portal inflammation and fibrosis. Characteristically, the reticulin staining revealed nodular transformation with compressed and atrophic hepatocytes between nodules and portal vein stenosis, and the immune histochemical staining for CD34 showed aberrant capillarization in periportal sinusoids. NRH has been associated to diverse drugs with a potential to cause endothelial injury and to lead to obstruction or obliteration of the microscopic branches of the portal veins. At variance with immunosuppressive therapy of hepatitis caused by ICPIs, pembrolizumab associated NRH required treatment with withdrawal of immunotherapy followed by placement of an intrahepatic portosystemic shunt (TIPSS) which resulted in a reduction of the mean portosystemic gradient to 4 mm.

Table 1
Recommendations on the management of suspected ICPI-induced liver injury. Modified from [29,31].

Before therapy	
- Assess baseline liver parameters and lipid profile. Investigate history of alcohol consumption. - Check for potential pre-existing liver diseases, presence of liver metastases, and viral infections (HIV, HBV, HCV). - Rule out underlying autoimmune hepatitis and underlying autoimmune conditions.	
During therapy	
- Monitor liver biochemical parameters every 2 weeks during the first 8 to 12 weeks and then every 4 weeks.	
If abnormal liver parameters	
CTCAE grade of severity	General recommendations
Grade ≥2 (AST and/or ALT >3-5 ULN or total bilirubin >1.5-3 times ULN)	1. Institute corticosteroids (minimum 0.5–1.0 mg/d prednisone equivalent) 2. Withhold ICPI (do not restart until return to Grade 1 or baseline) 3. Monitor for changes in liver function: a. Recheck LTs/INR/albumin every 3 days b. Review all potential hepatotoxic medications, including herbal supplements c. Rule out alternative alcohol, viral, or autoimmune etiologies
Grade ≥3 (AST and/or ALT >5 times ULN or total bilirubin >3 times ULN)	1. Institute corticosteroids (1-2 mg/kg/d prednisone equivalent). If there is no response to corticosteroids within 2–3 days, mycophenolate mofetil should be added at 1000 mg twice daily. 2. Hospital admission if biochemical evidence of impending liver failure (bilirubin above 2.5 mg/dl and/or INR above 1.5). 3. Permanent discontinuation of ICPI 4. Withdraw hepatotoxic drugs.

CTCAE: Common Terminology Criteria for Adverse Events; ICPI: immune checkpoint inhibitor; LT: liver test; ULN: upper limit of normal.

6. Management of ICPI-related hepatotoxicity

Although clear strategies for effectively managing specific ICPI-associated hepatotoxicity remain to be defined, prospective surveillance, prompt identification, and differential diagnosis with other liver complications are mandatory. Indeed, routine laboratory assessments (including serum AST, ALT, and bilirubin) before and during ICPI are critical for early detection of ICPI associated liver damage, and are recommended by the US FDA-approved product labels [28].

Importantly, there is not a uniform definition of ICPI-induced hepatoxicity in the literature and described hepatotoxicity ranges in presentation from asymptomatic increases in aminotransferases to acute hepatitis. Liver biopsy demonstrating immune cell infiltration of the liver can aid in the diagnosis of autoimmune hepatitis but is not routinely performed nor recommended. According to the European Association for the Study of the Liver (EASL) recommen-

dations for the management of drug-induced liver injury (DILI) [29], decisions regarding corticosteroid treatment of immune-mediated liver damage associated with ICPI should be made by a multidisciplinary team involving hepatologists if DILI is severe. While this recommendation is extrapolated from individual cohort studies since no prospective studies are yet available, EASL also suggests to take into account known risk factors contributing to higher risk of liver injury before starting therapy: (i) drug, dose and combination therapies, as a higher dose of ipilimumab (10 mg/kg) was associated with more severe hepatotoxicity, as well as combination therapies [19,25]; (ii) a pre-existing autoimmune diathesis that may be unmasked by the ICPIs; (iii) a pre-existing liver disease or silent hepatic metastases [29].

Recommendations on the management of suspected ICPI-induced liver injury, are summarized in Table 1, and rely on clinical experience and the management of autoimmune hepatitis. These recommendations are similar to protocol procedures used in registrational trials and have been suggested by the American Society of Clinical Oncology and the European Society of Medical Oncology.

7. Conclusions

Monoclonal antibodies against immune check points increase T cell responses and restore potent antitumor immune responses that are suppressed in cancer. The therapeutic use of ICPI in a variety of neoplastic diseases have greatly improved response rates, response durability, and overall survival rates. ICPI, however, can induce immune-related hepatotoxicity in a substantial proportion of patients, with CTLA-4 inhibitors (ipilimumab) being more hepatotoxic than anti-PD-1 agents (nivolumab), and combination treatments carrying a greater risk. Hepatotoxicity of ICPI can be a potentially life-threatening complication when not promptly recognized and managed. Accurate assessment at baseline of liver parameters, risk factors, and associated liver diseases might greatly help to limit the liver damage. Further, prompt initiation of steroids in collaboration with the treating oncologist is essential for managing toxicity and therefore continue therapy.

This notwithstanding, further studies are needed to better understand the pathophysiology of hepatotoxicity associated with ICPIs, to identify patients at highest risk of severe outcomes, and to develop evidence-based therapies to manage toxicity in a scenario where the effect of immunosuppressive treatment on ICPI efficacy and patient survival is unknown.

Conflict of interest

Prof. Ana Lleo has served as a speaker for Abbvie, MSD, BMS, Gilead, and Intercept. Dr. Rimassa has served in Advisory Boards for ArQule, Lilly, and Incyte; she has served as a speaker for Gilead and MSD. Prof Massimo Colombo has served in Advisory committees for MSD, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman, and Intercept; he has further served as speaker for Tibotec, Roche, Novartis, Bayer, BMS, Gilead Sciences, Vertex, MSD, Janssen, and AbbVie.

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