

Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma

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Abstract

Immune checkpoint inhibitors (ICPIs) have reshaped cancer therapy. These molecules enhance T cell activation through various mechanisms and may help revert the exhausted phenotype of tumor-infiltrating lymphocytes. However, the disruption of the key role that checkpoint molecules have in immune homeostasis may result in auto-immune complications. A broad range of immune-related adverse events (irAEs) involve almost every organ but mostly affect the skin, digestive system, lung, endocrine glands, nervous system, kidney, blood cells, and musculo-skeletal system. They are usually manageable but can be life-threatening. The incidence of irAEs is not very different in patients with hepatocellular carcinoma (HCC) compared to other tumor types although there is a trend towards a higher incidence of hepatic irAEs. HCC usually develops on a background of cirrhosis with associated systemic manifestations. Extrahepatic organ dysfunction in cirrhosis may cause signs and symptoms that overlap with those from irAEs or increase their severity. Available guidelines for the management of irAEs have not specifically considered the assessment of toxicities in the context of patients with liver cancer and cirrhosis. This review addresses the toxicity profile of ICPIs in patients with HCC focusing on the challenges that the underlying liver disease poses to their diagnosis and management. Challenges include late recognition, inadequate work-up and delayed treatment, over-diagnosis and inappropriate interruption of ICPIs, complications caused by immunosuppressive therapy, and increased cost. A specific algorithm for the management of liver irAEs is provided.

Introduction

Immune checkpoint molecules regulate the immune response, preventing inappropriate immune activation and allowing self-tolerance [1]. However, they also provide a mechanism by which tumors evade immune surveillance, and inhibitory checkpoint molecules have become major targets for anticancer therapy. Antibodies against cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death-protein 1 (PD-1) or its ligand (PD-L1) block their negative signals and enhance T cell activation. These immune checkpoint inhibitors (ICPIs) have transformed the treatment of several cancer types. CTLA-4 is the target of ipilimumab and tremelimumab while PD-1 is the target of nivolumab and pembrolizumab, and PD-L1 is the target of durvalumab, atezolizumab and avelumab.

ICPIs have shown signs of activity against HCC. They result in 15-20% of objective remissions that are durable and associated with prolonged survival. Based on result from single-arm phase 2 trials [2,3], nivolumab and pembrolizumab have been approved by US and other regulatory agencies to treat patients who progress or are intolerant to sorafenib. Phase 3 trials comparing pembrolizumab versus best supportive care in the second line setting [4] and nivolumab versus sorafenib as first line systemic therapy [5] have nevertheless failed to confirm a superiority in terms of overall survival, despite clear trends for improved outcomes in both trials. Based on these and other data, a number of phase 3 trials testing combinations of ICPIs with tyrosine-kinase inhibitors (TKIs), antiangiogenic antibodies or other ICPIs are now underway [6].

Because of their fundamental role in maintaining immune homeostasis, blockade of inhibitory checkpoint molecules results in a broad range of immune-related adverse events (irAEs) resulting from impaired self-tolerance and may involve almost every organ. irAEs are frequent when ICPIs are used as single agents and usually manageable but can be life-threatening. With PD-1 or PD-L1 [PD-(L)1] inhibitors, the development of irAEs is unrelated to the dose at 27% for all grades and 6% for grade 3 or higher [7]. With CTLA-4 inhibitors, the overall incidence fluctuates according to the dose and is higher at 72 % for all grades and 24 % for grade 3 or higher [8]. Although direct comparisons are not available, metaanalyses indicate that rash and colitis are significantly more frequent during CTLA-4 blockade, and suggest that there are no major differences between agents within each target checkpoint [7][8][9]. Median time to onset is typically shorter for CTLA-4 than for PD-(L)1 inhibitors [10]. In a recent metaanalysis, 42 fatal irAEs were recorded among 6528 patients treated with an ICPI (0.64%) and ipilimumab-induced colitis was the most common cause of fatal irAE [9]. None of these metaanalyses, however, includes patients with liver cancer. Although T cell infiltration and activation are assumed as to be the primary events, the mechanisms of irAEs are largely unknown. This is partly because empiric therapy is often started and tissue biopsies are seldom obtained. It is interesting to note, however, that among patients with autoimmune diseases treated with a PD-(L)1 inhibitor, exacerbation of the autoimmune condition occurred rarely and the incidence of irAEs was similar to clinical trials where patients with autoimmune diseases were excluded [11].

Hepatocellular carcinoma (HCC) usually develops on a background of chronic liver disease [12] which itself may give rise to systemic manifestations. Multiple organs may show signs of dysfunction [13] and cause signs and symptoms that can overlap with those from irAEs and may increase their severity. Scientific societies such as the Society for Immunotherapy in Cancer (SITC), the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) have provided general guidelines for the management of irAEs [14] [15] [16]. However, they have not specifically considered the assessment of toxicities in the context of patients with liver cancer and cirrhosis where careful interpretation is required to differentiate irAEs from liver-related events. In this review, we will address the toxicity profile of ICPIs in patients with HCC focusing on the challenges that the underlying liver disease poses to their diagnosis and management.

The challenges of immune related-toxicities in patients with HCC

Cirrhosis is a disease with multiple causes characterized by diffuse fibrosis, disruption of the intrahepatic venous flow, portal hypertension and liver failure. If the cause is not successfully treated, it progresses in a non-linear course leading to hepatic and extrahepatic complications. A relatively long period of silent disease (compensated cirrhosis) leads to a second period of frequent complications (decompensated cirrhosis) including ascites, variceal hemorrhage or hepatic encephalopathy, and carries a poor prognosis [17]. In parallel with the progressive deterioration of liver structure and function, other organs frequently develop secondary dysfunction. Rather than following a gradual worsening of their general condition towards liver insufficiency, patients suffer from acute complications frequently triggered by a precipitating event. Additionally, cirrhosis disturbs the

liver's homeostatic immune function. The term cirrhosis-associated immune dysfunction defines an acquired alteration of innate and acquired immunity that leads to both systemic inflammation and immunodeficiency [18], and results in increased mortality. Systemic inflammation results from persistent immune cell stimulation and enhanced production of pro-inflammatory cytokines while immunodeficiency is due to derangement of local immunity of liver and of systemic immune cells.

Many extrahepatic disorders associated with cirrhosis cause symptoms that may not be easy to distinguish from irAEs and can synergize in deteriorating organ function. The most important ones are summarized in Figure 1. Similarly, almost any organ can be affected by irAEs. In general, the incidence of irAEs is not very different in HCC patients compared to other tumor types like melanoma as shown in Table 1. Overall, the reported incidence of irAEs for PD-1 inhibitors nivolumab and pembrolizumab is 10-20% in HCC and above 30% in other tumors.

Individually, there is a trend towards a higher incidence of hepatic irAEs and a lower incidence of pneumonitis in HCC.

irAEs vary in clinical significance and impact on patient safety and survival. Clinical impact depends on the organ involved, the severity of the toxicity, and response to treatment. For those that may be life threatening, early recognition and treatment is key to a successful outcome. In the cirrhotic patient, this may be a difficult task when symptoms of a given irAE overlap with those of a cirrhosis-related disorder. Baseline evaluation should take this into account (Table 2). On the one hand, late recognition may delay treatment and worsen the prognosis. On the other,

overdiagnosis of irAEs may result in inappropriate interruption of effective anti-cancer therapy, complications caused by immunosuppressive therapy, unnecessary interventions and increased cost. This is particularly true if the treating physician is not familiar with the management of cirrhosis. Corticosteroids as immunosuppressors may have more relevant consequences in cirrhotics than in other patients, although this issue has not been adequately confirmed. Importantly, the use of the PD-1 inhibitor nivolumab in patients with moderate liver dysfunction (Child-Pugh B class) is not associated with an increased rate of irAEs [19].

The most important questions that should be answered when dealing with a potential or established irAE are; how frequently to monitor, when to hospitalize, when to withhold or permanently discontinue ICPIs, when to initiate and how to escalate immunosuppression. General recommendations for the management of irAEs in HCC patients are provided in Table 3. It is very important to keep in mind that early engagement with other specialties according to target organ is recommended. Resuming ICPIs after an irAE is a difficult decision, particularly if the patient is free from tumor progression. Among 93 patients with different tumor types who experienced moderate to severe irAE (46% grade 2, 39% grade 3, 15% grade 4) including hepatitis (18%), skin events (15%), pneumonitis (14%), and colitis (12%), 40 were re-challenged with the same anti-PD(L)-1 agent and the same or a different irAE occurred in 22 patients (55%) [20]. A shorter time to the initial irAE was linked to the occurrence of a second irAE but the second irAEs were not found to be more severe than the first.

Toxicities by target organ

In a large metaanalysis in which no HCC trial was included, the most frequent target organs for irAEs during CTLA-4 inhibition were the skin (44 %) and the gastrointestinal tract (35 %). Endocrine glands and the liver were involved in 6% and 5%, respectively. Other events, including the nervous and muscle-skeletal systems, blood and eyes were rarely involved [8]. Skin, endocrine, and hepatic irAEs were high grade in less than 5 %, compared to 11% for gastrointestinal events. In another metaanalysis including nearly 3,000 treated patients, the most frequent target organs for irAEs during PD-(L)1 inhibition were the skin (pruritus 10%, rash 11%), the gastrointestinal tract (diarrhea 11%) and the thyroid (hypothyroidism 7%) [7]. The liver was involved less frequently (increased AST or ALT 4%, hepatitis 1%). Overall grade 3 or 4 irAEs occurred in less than 2 % of patients.

In the following sections we will describe in detail the most important irAEs, the disorders affecting the same organ that are associated with chronic liver disease, and the diagnostic clues specific to HCC patients. We will provide specific recommendations for the management of such irAEs in HCC patients, which largely mirror the management of irAEs in patients with other malignancies. irAEs are evaluated for severity and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v. 5.0)[21]. Grading in this review will refer to these criteria unless otherwise specified.

Skin rash, inflammatory dermatitis and other cutaneous adverse reactions

Cutaneous AEs are the most common AEs reported in clinical trials of ICPIs and can occur within two weeks of starting therapy, or as late as a year. There is a wide range of clinical manifestations of skin toxicity but rash and pruritus are the most common. In non-HCC patients, rash occurs in 20-30% of those receiving CTLA-4 inhibitors, 10-20% those receiving PD-1 inhibitors and 30-40% of those receiving a combination of both [7,22–24]. Similarly, pruritus occurs in 30-35% of those receiving CTLA-4 inhibitors, around 20% those receiving PD-1 inhibitors and 35% of those receiving a combination. Less common AEs include dry skin, erythema, alopecia and vitiligo, although the later has mainly been reported in those treated for melanoma. Erythema multiforme, psoriasis, urticaria and rosacea occur in less than 1% and more serious and potentially life-threatening side effects such as toxic epidermal necrolysis, Stevens-Johnson syndrome and DRESS (drug rash with eosinophilia and systemic symptoms) are rare with an incidence of less than 0.1%. Skin irAEs are grade 3 or higher in less than 2% of patients. Histologic characterization of the cutaneous toxicities is not available.

Data regarding skin toxicity from ICPIs in HCC so far is largely consistent with that seen in other tumor types (Table 1). In the dose escalation cohort of single agent nivolumab, there was no clear dose-response relationship for rash or pruritus [2]. Rash occurred in 15-30% of those receiving nivolumab, 8-10% of those receiving pembrolizumab and 17-29% of those receiving a combination of nivolumab and ipilimumab. Similarly, pruritus occurred in 20-27% of those receiving nivolumab, 12-18% of those receiving pembrolizumab and 30-45% of those receiving a combination. Skin irAEs were grade 3 or higher in less than 1% of patients with monotherapies and 4% with the combination. Data from single-agent

tremelimumab is more limited but grade 1 or 2 rash was reported in 65%, and grade 3 in 5% of those treated within a small phase 2 trial. This incidence is higher than seen in other tumor types but caution is warranted in view of small numbers of patients included [25]. Among 40 patients included in the phase I trial combining durvalumab and tremelimumab, pruritus and rash were reported in 22.5% and 12.5% but none had grade 3-4 skin toxicity [26].

Skin disorders associated with chronic liver disease

There is wide spectrum of cutaneous manifestations of chronic liver disease [27]. Pruritus is a common (>15%) complaint in patients with HCV infection even in the absence of overt cholestasis [28]. Bile salts possibly mediate pruritus by interacting with other pruritogens. Polyarteritis nodosa and cryoglobulinemia are associated with both HBV and HCV infection, while porphyria cutanea tarda has been observed in patients with hepatitis C, alcoholic liver disease and hemochromatosis. More than 40% of patients with HCV produce cryoglobulins and 15% develop cryoglobulinemia vasculitis [28]. Lichen planus is also seen in a range of chronic liver diseases but is particularly associated with HCV infection. As an autoimmune condition, primary biliary cirrhosis can occur in the context of other autoimmune conditions including Sjogren's syndrome, CREST syndrome, morphea and lichen planus. All these conditions can cause dermatologic symptoms or lesions.

General management

In the absence of a pre-existing skin disorder, any dermatologic problem should be considered an irAE. However, when evaluating skin conditions in patients with

HCC treated with ICPIs, it is important to bear in mind the many cutaneous manifestations of chronic liver disease and engage with the dermatology team to ensure appropriate management. Alternative causes of skin conditions should also be considered including infection, other drug reaction, and underlying systemic disease. The interpretation of skin toxicity is becoming more challenging as combinations of PD1 inhibitors and TKIs emerge. TKIs used for HCC include sorafenib, lenvatinib, regorafenib and cabozantinib, all of which are associated with skin toxicity. However, the type adverse effect and time course can help distinguish between ICPI and TKI related events. For TKIs, the onset of rash is usually within weeks of starting and palmar-plantar erythema is the most common AE, reported by 52% and 27% for sorafenib and lenvatinib respectively [29]. This compares with around 2% for PD1 inhibitors. Additionally, the relatively short half-life of TKIs results in rapid resolution of skin toxicity over the course of days which contrasts with weeks or months that may be required for resolution of ICPI-related toxicity.

A full evaluation of the extent of cutaneous involvement and systemic effects should be documented. Topical emollients and topical mild steroids (i.e., triamcinolone 0.1%) along with antihistamines are the mainstay of treatment of mild grade 1 or 2 reactions and ICPIs can be continued. For more symptomatic grade 2 or 3 reactions, a biopsy should be considered. In addition to topical therapy, oral prednisolone at a dose of 0.5 to 1mg/kg should be initiated or, for more serious symptoms, methyl prednisolone 1-2 mg/kg should be used. ICPIs can be resumed on resolution to grade 1 if appropriate. For grade 4 or potentially life threatening cutaneous toxicity, ICPIs should be permanently discontinued and the

patient admitted under close supervision of a dermatologist. Methyl prednisolone 1-2 mg/kg should be started and weaned slowly according to response [16] [14].

Diarrhea and colitis

Diarrhea is one of the more common adverse events associated with ICPIs and may occur with or without underlying colitis. Diarrhea is defined as an increase in stool frequency above the patient's baseline whereas colitis is characterized by a constellation of diarrhea, abdominal pain, with radiographic or endoscopic findings of colonic inflammation; colitis may also manifest with bleeding per rectum [30]. The most frequent histopathologic finding is acute colitis with crypt abscesses and frequent epithelial apoptotic bodies while the remaining cases resemble lymphocytic colitis [31]. Severe colitis may result in life-threatening colonic perforation and peritonitis [32]. Diarrhea occurs in 30-50% of patients receiving CTLA-4 inhibitors, 10-25% of those receiving PD-(L)1 inhibitors and 43% of those under a combination [7,22-24]. Colitis occurs in 10-12% of patients receiving CTLA-4 inhibitors, 1-2% of those receiving PD-(L)1 inhibitors and 14% of those receiving a combination. Grade 3 or higher events are reported in 7-8% of patients under CTLA-4 blockade, 0.5-1.5% of those under PD-(L)1 blockade and 8-9% of those under dual blockade.

The incidence of diarrhea with anti PD-1 agents in HCC is consistent with that reported in other tumor types. Diarrhea occurs in 11% of patients receiving pembrolizumab, 14% of those receiving nivolumab and 12-24% of those under a combination of nivolumab and ipilimumab and 12% of those under a combination of durvalumab and tremelimumab (table 1). As expected, the incidence was higher

with tremelimumab with a 30% rate of grade 1 and 2 diarrhea and 5% grade 3 diarrhea [25]. Grade 3 or higher events are reported in 1% of those under PD-(L)1 blockade and 2-4% of those under dual blockade. Similar trends are observed for the more restrictive definition of colitis, which is mostly grade 3. Around 1% for PD-(L)1 inhibitors and 2 to 6% for dual CTLA-4 and PD-(L)1 blockade.

Diarrhea associated with chronic liver disease

Patients with chronic liver disease and cirrhosis are at risk of multiple forms of intestinal dysfunction that may manifest in the form of altered bowel habits and diarrhea [33]. Some of these conditions may be overlooked or mistaken for immune therapy induced colitis. The first such condition is small intestinal bacterial overgrowth syndrome (SIBO), which is characterized by an increase in the number or alteration in the type of bacteria in the upper gastrointestinal tract. The gold standard for diagnosis is proximal jejunal aspiration revealing $\geq 10^5$ bacteria (i.e. colony-forming units) per mL [34] . However, hydrogen glucose breath test is preferred in clinical practice due to its lower cost, non-invasiveness and adequate sensitivity and specificity (62% and 78 %, respectively).

Manifestations of SIBO can mirror irritable bowel syndrome with a variety of symptoms that include abdominal bloating, abdominal pain, and diarrhea. SIBO is present in as many as 50 to 60% of patients with cirrhosis [35] [36]. One of the main reasons for the development of SIBO in cirrhotic patients is intestinal dysmotility[37]. Concurrent medical problems such as diabetes mellitus and autonomic neuropathy contribute to intestinal dysmotility and the development of SIBO [38] [39].

HCC-associated diarrhea is a vague entity that is seen in clinical practice but is poorly studied. In a small cohort series, 47.8% of patients with HCC had at least one episode of diarrhea in the 3 months prior to diagnosis versus 8.7% of the control subjects [40]. The diarrhea appeared to vary significantly in severity and chronicity, but the patients with HCC and diarrhea had worse liver function than those with HCC and no diarrhea. In another series, diarrhea was reported in 21% of 211 patients with HCC reviewed retrospectively [41]. Diarrhea in the setting of HCC is likely to be multifactorial. Case reports have described paraneoplastic diarrhea related to VIP and prostaglandin production [42] [43].

Chronic pancreatitis may ultimately cause exocrine pancreatic dysfunction with steatorrhea [44]. Clinical studies have reported a range of 6 to 16% for the coincidence of chronic pancreatitis in patients with liver cirrhosis [45]. Coexistence of both conditions is most likely in the setting of alcohol-related liver disease.

General management

Patients should be evaluated for symptoms of diarrhea and colitis regularly while receiving ICPIs. It is critical that a good history be obtained prior to initiation of checkpoint inhibitor therapy to establish an accurate baseline and be able to determine whether patients have worsening of their diarrhea on treatment. If patients report new onset diarrhea or worsening of existing diarrhea, a work-up to rule out non-immune causes should be performed and include infectious etiologies as well as non-colitis immune mediated toxicities such as hyperthyroidism. Furthermore, a careful review of medications that could contribute to diarrhea

should be conducted, especially for patients who have been started recently on lactulose and may need an adjustment of the dose.

In the absence of alternative etiologies, the assumption should be that the patient has immune mediated diarrhea and/or colitis. The diagnosis is frequently made on the basis of clinical symptoms and signs, but colonoscopy remains the gold standard and is helpful for assessment of severity, prognostication and confirmation of diagnosis [46]. Endoscopic evaluation should not delay initiation of appropriate therapy as discussed below, and is more critical in cases of lack of response to therapy or before infliximab initiation.

For grade 1 diarrhea (< 4 stools/day over baseline), treatment continuation is reasonable with close monitoring; if the diarrhea persists or worsens, interruption of ICPIs is warranted until resolution of diarrhea. For grade 2 diarrhea or colitis, treatment with the ICPIs should be withheld; if the symptoms persist for about 3 days or longer, oral corticosteroids should be initiated at 0.5 to 1 mg/Kg. For grade 3 symptoms, hospitalization should be considered for maintaining hydration and expedited work-up; checkpoint inhibitor therapy should be withheld and corticosteroids initiated at the dose of 1-2 mg/Kg, preferably intravenously. If there is no improvement within 3 days, additional immunosuppressive therapy with drugs such as infliximab is indicated. For grade 4 events, in addition to the above therapy, ICPIs should be discontinued permanently. In a recently published retrospective review, the earlier introduction with selective immunosuppressive therapy such as infliximab was associated with fewer hospitalizations, less frequent steroid failure, and a shorter duration of symptoms [47].

Limited data are available regarding the resumption of ICPIs after an episode of immune mediated diarrhea and/or colitis. Guidelines indicate that ICPIs can be attempted again in the case of grade 1 to 3 toxicity after resolution of symptoms to grade 0-1 and once the dose of steroids is at the equivalent of 10 mg of prednisone or less per day. In a large multicenter retrospective review, it was noted that 30% of patients who had experienced immune mediated diarrhea/colitis were treated again with an ICPI; upon repeat exposure to ICPI therapy, 34% of patients experienced immune mediated diarrhea/colitis with the majority of the events being grade 2 diarrhea or grade 1 colitis. On multivariate analysis, prior treatment with anti PD-(L)1 antibody, higher grade of diarrhea at the initial diagnosis of immune mediated diarrhea/colitis, the need for immunosuppressive therapy, and longer duration of symptoms were all associated with a higher risk of recurrence of immune mediated diarrhea/colitis upon repeat exposure [48].

Hepatitis

The term hepatitis or immune-related hepatitis is commonly used to describe any alteration in liver tests induced by ICPIs. However, a histopathologic correlate is only available for the more intense grade ≥ 3 cases. Both the laboratory profile and the pathological features are different according to the ICPI. PD-(L)1 inhibitors typically cause only elevations in transaminases (AST/ALT) while CTLA4 inhibitors may also result in cholestasis with increased alkaline phosphatase, GGT or bilirubin, and mixed patterns may be observed with combinations. Histology related to anti-CTLA-4 agents is granulomatous hepatitis including fibrin ring

granulomas and central vein endotheliitis while PD-(L)1 inhibitors are characterized by lobular hepatitis [49].

Hepatitis tends to be asymptomatic even in severe cases and warrants regular examination of liver tests in all treated patients. It appears usually 4 to 12 weeks after initiation of therapy but may appear at later stages too. CTLA-4 and PD-1 blockade may very exceptionally cause rapidly progressing hepatic failure [50] [51]. In non-HCC patients, hepatitis of any grade and grade ≥ 3 occur in 4-6% and 1-2% respectively of patients treated with CTLA-4 or PD-1 inhibitors, and in 15-20% and 5-15% of patients treated with the combination of both [7,22-24].

The incidence of hepatitis is slightly higher in HCC patients than in other tumor types. Increased AST occurred in 9-10% of patients receiving nivolumab, 9-14% of those receiving pembrolizumab, 13-20% of those receiving nivolumab plus ipilimumab, and 17.5% of those receiving durvalumab plus tremelimumab. This difference can be explained at least in part by baseline alterations in liver function tests and the fact that tumor progression inside the liver may also induce changes in laboratory values that can be regarded as hepatitis. In the phase 2 trial with pembrolizumab, immune-related hepatitis was reported if one of the following changes in liver tests appeared and other possible etiologies were excluded, i) AST or ALT values change from $< 2 \times \text{ULN}$ baseline to $\geq 5 \times \text{ULN}$; or from $\geq 2 \times \text{ULN}$ at baseline to $> 3 \times$ the baseline level; or reach $> 500 \text{ U/L}$ regardless of baseline level; or ii) total bilirubin values change from $< 1.5 \text{ mg/dL}$ at baseline to $> 2.0 \text{ mg/dL}$; or from $\geq 1.5 \text{ mg/dL}$ to $\geq 2 \times$ the baseline level; or reach $> 3.0 \text{ mg/dL}$ regardless of baseline level [3]. With these strict criteria, the incidence of immune-related

hepatitis was 3%. In line with this observation, nivolumab at doses 1-10 mg/kg caused hepatitis in only 1 out of 30 patients with chronic hepatitis C and no HCC [52]. Hepatitis grade ≥ 3 occurred in less than 2% of patients under anti-PD-(L)1 agents but in up to 20% of those receiving the highest dose of ipilimumab in combination with nivolumab [53].

Hepatitis associated with chronic liver disease

HCC is usually the result of a chronic liver disease due to HCV or HBV chronic infection, alcoholic or non-alcoholic steatohepatitis, and others. Therefore, most HCC develop in a liver that hosts chronic inflammation and progressive liver fibrosis [12]. Additionally, patients with chronic HBC or HCV infection show T cell responses against viral antigens [54]. Actually, T cell exhaustion is one of the main mechanisms resulting in chronic viral infection [55]. Reinvigoration of antiviral immunity is associated with hepatitis flares in patients chronically infected with HBV and HCV [56]. This is particularly true for hepatitis B and every clinical trial has excluded patients who were not under effective antiviral therapy with direct antiviral agents. In early trials with PD-1 agents, a cutoff values were 100 UI/mL of HBV-DNA was applied while in more recent trials these values have the value has been raised to 500 UI/mL. No cases of clinically relevant hepatitis flares have been reported. We ignore if patients with higher viral loads can be treated safely and the recommendation is not to treat until evidence of safety is provided. Some clinical trials have requested that patients with negative hepatitis B surface antigen (HBsAg) but positive anti-core antibodies (anti-HBc) should be treated with antiviral agents preemptively although it is highly unlikely that this would be needed based on the information available at this point. Opposite to HBV, there

have been no restrictions to the enrolment of patients with HCV infection into clinical trials based on the amount of circulating HCV viral load. Indeed, transient decreases in HCV-RNA have been reported with nivolumab [2] and significant decreases were observed with tremelimumab [25].

General management

Besides being chronically inflamed, the liver is most frequently involved in tumor spread at the advanced stage because it is also the most frequent site of recurrence after resection or percutaneous ablation. Therefore, HCC patients generally show altered liver tests that may confound the diagnosis of ICPI-induced hepatitis.

Exceptions are patients with low liver tumor burden and eradicated HCV infection, effectively treated HBV infection, or a healthy liver. Subsequent increases in liver tests should raise the suspicion of an irAEs but may also be due to spontaneous fluctuations, tumor progression inside the liver or other causes. In fact, in controlled trials in the second line setting the incidence of any grade increased AST among placebo-treated patients ranged from 10 to 20% [57–59]. Therefore, timing and tumor response are important in adjudication of causality. To avoid premature interruption of ICPIs, stopping rules were adapted accordingly in clinical trials. Any physician using ICPIs in HCC patient has to be familiar with these rules and modified grading of liver AE. A set of specific recommendations is summarized in Figure 2.

Flares may occur in patients with HCV or HBV infection. In HBV infection, they are associated with an increase in viral load and HBV-DNA should be measured in moderate to severe hepatitis occurring in HBsAg or anti-HBc positive patients. The

role of pre-existing CMV infection has not been studied but CMV reactivation has been reported as a cause of hepatitis in patients under ipilimumab [60]. Newly acquired viral hepatitis may also appear. Other etiologies should be ruled out as in non-HCC patients, in particular drug toxicities.

Besides monitoring transaminases, it is important to request alkaline phosphatase as well as bilirubin, albumin and prothrombin to evaluate synthetic liver function. If hepatitis becomes more intense, an ultrasound or CT scan is mandatory to rule out biliary obstruction (that may raise transaminases before bilirubin) and tumor progression (particularly in the form of portal or hepatic vein invasion), and to early detect ascites. Cirrhosis at any stage is associated with portal hypertension and reduced liver functional reserve. The consequences of liver toxicities by ICPIs may consequently be more severe in HCC patients. Consultation with a hepatologist is strongly recommended for any hepatitis grade 2 or higher.

Hepatitis does not always deserve immediate steroid therapy. Transaminases often return to baseline levels despite continuing ICPIs or after delaying the dose, even when transaminases are moderately elevated [49] [25]. Repeated testing within one week and ruling out exposure to hepatotoxic drugs or substances is recommended for grade 1/2 elevations and the decision to start steroids can be based on progressive elevation or when hypertransaminasemia is associated with increased bilirubin (direct bilirubin predominantly) or liver decompensation. When transaminases decline or return to baseline levels, hepatitis may not necessarily recur if ICPIs are reintroduced [49] [25]. The dose of steroids can be adjusted individually. Lower doses of oral prednisone may be enough for grade 2

to 3 elevations in transaminases that do not progress after one week, while higher doses are more appropriate in case of further increase. IV pulses of corticosteroids or the addition of a second immunosuppressive drug like mycophenolate mofetil (MMF)(1 g twice daily) should be reserved for refractory cases. Anti-thymocyte globulin therapy was used in one case of ipilimumab-associated steroid-resistant hepatitis leading to hepatic failure with a favorable outcome [50].

Although HBV hepatitis flares have not been reported with the current restrictions to therapy based on viral load, if a viral flare is observed or suspected, the decision to start steroids, change the antiviral agent, or do both has to be taken individually after consultation with the hepatologist. If a delay in obtaining viral serologies, viral load or liver ultrasound results is expected, steroids should be started pending confirmation for moderate hepatitis or if hepatitis is associated with liver decompensation. Whether obtaining a liver biopsy to confirm diagnosis is useful is unknown. A standardized histologic evaluation may identify hallmarks that differentiate autoimmune hepatitis from drug-induced liver injury [61]. Whether this may be helpful in patients under ICPIs is something that deserves to be explored prospectively. When steroids are given in doses equal or higher than 1 mg/kg/day, prescribing antibiotics to prevent opportunistic infections should be considered. Infliximab is contraindicated due to potential hepatotoxicity.

Pneumonitis

Pneumonitis is a rare but threatening toxicity of ICPIs. The clinical presentation is variable, with initial symptoms including cough, fever and shortness of breath.

Acute respiratory failure may ensue rapidly. The time from ICPI initiation to

pneumonitis is unpredictable, ranging from 9 days to over 1 year [62] [63]. Over 75% of patients show mild to moderate pneumonitis. However, pneumonitis worsens in a subset of patients despite steroids and immunosuppressors, resulting in death from pneumonitis or complications of infection [62] [64]. In retrospective series, chronic smoking is associated with a slightly higher risk of deterioration [62]. In the overall cancer population, it occurs at a rate of 2-3% with PD-(L)1 inhibitors, and the incidence increases to 7% in combination with CTLA4 inhibitors [7,22–24]. The incidence of grade ≥ 3 pneumonitis is below 2%. A histological correlate for the imaging signs of pneumonitis is lacking.

The incidence of pneumonitis is extremely low in HCC patients receiving single-agent ICPIs; around 1% in patients receiving nivolumab and pembrolizumab with virtually no grade 3 or higher severity (table 1). For combination of CTLA4 and PD-(L)1 inhibitors, pneumonitis occurred in 10% of patients receiving nivolumab plus ipilimumab (and only in the high ipilimumab combination) and 2.5% of those receiving durvalumab plus tremelimumab [26] [53].

Lung disorders associated with chronic liver disease

Two syndromes with different pathophysiology may mimic symptoms of immune-mediated pneumonitis: the hepatopulmonary syndrome and porto-pulmonary hypertension [65]. The former is the most common cause of respiratory insufficiency in patients with cirrhosis and is caused by intrapulmonary vascular dilatations [66]. Abnormal oxygenation as defined by an alveolar-arterial oxygen gradient >15 mmHg (>20 mmHg in older patients) is the mainstay of hepatopulmonary syndrome. It should be ruled out in any HCC patient with

cirrhosis that reports dyspnea prior to or during ICPI therapy. Pulse oximetry may identify all patients with PaO₂ <70 mmHg using an oxygen saturation cut-off <96% [67]. Arterial blood gas analysis should follow the detection of low oxygen saturation. Orthodeoxia (oxygen desaturation while lying) and platypnea may be additional complaints or findings [68]. Spirometry is typically normal while diffusion capacity of carbon dioxide is frequently decreased. Transthoracic contrast-enhanced echocardiography confirms the diagnosis. Lung perfusion scanning cannot differentiate intracardiac from intrapulmonary shunting. Chronic obstructive pulmonary disease, asthma, ascites, hepatic hydrothorax or more rarely idiopathic pulmonary fibrosis, can also cause or exacerbate dyspnea in cirrhotics.

Porto-pulmonary hypertension is featured by increased pulmonary vascular resistance in patients with portal hypertension in the absence of any other causative factor such as mitral stenosis or left ventricular failure [65]. The pathophysiology is poorly understood but genetic factors and a dysregulation of vasoactive and inflammatory mediators are likely involved [69]. It is not related to the degree of portal hypertension or liver dysfunction. Increased pulmonary arterial pressure can be suspected by transthoracic echocardiography and confirmed by right heart catheterization

General management

Early detection is the key to improve prognosis of pneumonitis hence clinicians should have a low threshold of arranging investigations in patients with suspicious symptoms. Pulse oximetry at rest and after 1-minute walking can be useful for

screening minimally symptomatic patients. Chest X-ray is usually the first investigation if pulse oximetry is not available but high-resolution computed tomography should be ordered if the suspicion is high even when x-ray is normal. Radiological findings include ground glass opacities, organizing pneumonia-like appearance and interstitial pneumonitis [62] [70]. An abnormal chest X-ray or CT excludes the hepatopulmonary syndrome and may diagnose concurrent chronic respiratory conditions such as emphysema or bronchiectasis. Lung function tests are not specific but may help in ruling out other disorders.

Early multidisciplinary input from respiratory and/or infectious disease specialists is recommended to help in the diagnostic work-up and to rule out infection by bronchoscopy. Additional investigations such as work-up for virus, mycoplasma or legionella may be considered in the context of clinical picture and local epidemiology. Biopsy of involved lung tissue is not necessary unless there is diagnostic doubt. With the criteria mentioned above, immune pneumonitis may be usually distinguished from other disorders.

Management depends on the severity of symptoms. For asymptomatic patients with radiographic changes only (grade 1), IPCIs should be delayed and patients should be monitored closely for early symptoms every 2-3 days. For grade 2 pneumonitis with mild to moderate symptoms, hospitalization and consultation of respiratory and infectious disease physicians is indicated. Urgent investigations should be arranged but oral prednisolone at 1 mg/kg/day and antibiotics should be started immediately. If there is no improvement in the next 2-3 days, patients should be managed as per grade 3 to 4 disease (severe symptoms or evidence of

hypoxia/respiratory distress). IV methylprednisolone should be started promptly at 1-2 mg/kg/day, and ICU/respiratory support has to be considered. The addition of further immunosuppressive therapy, including infliximab (5 mg/kg which can be repeated after 2 weeks if needed) or MMF (1 g twice daily), may be considered if there is no improvement. Re-administration of ICPIs may be considered in patients recovering from grade 1-2 pneumonitis while ICPIs should be stopped permanently in case of grade 3-4 pneumonitis.

Thyroiditis

Thyroid irAEs are most often asymptomatic and may present in the form of hyper- or hypothyroidism, or a full-blown thyroiditis. Hypothyroidism preceded or not by hyperthyroidism is the most common event. Signs of hypothyroidism include fatigue, weight gain, bradycardia, slow bowel transit while those of hyperthyroidism may comprise fatigue, nervousness, weight loss, and palpitations. Diagnosis is based on thyroid hormones compared with pre-ICPI values [71]. The rate of irAEs varies according to the treatment received. Any thyroid abnormality occurs in 39% of cases following PD-1 inhibitors, 23.0% following ipilimumab, and 50% following combination treatment in several indications [72]. The incidence of hypothyroidism is 5-7% with CTLA-4 inhibitors, 7-11% with PD-(L)1 inhibitors, and 10% with combination of both [7,22-24]. The rate of thyroid irAEs in HCC patients at 5% is similar to other tumor types. The pathogenesis of immune-mediated thyroiditis is largely unknown and anti-thyroid antibodies only develop in a minority of patients. Inflammation is frequently identified in patients with thyroid dysfunction by FDG-PET scan or Tc99m-scintigraphy [73].

Thyroid disorders associated with chronic liver disease

Alterations in thyroid hormone regulation and metabolism are frequently observed in cirrhosis. Peripheral conversion of thyroxine (T4) to triiodothyronine (T3) is reduced in patients with cirrhosis since the liver is one of the major sites of conversion [74]. Therefore, cirrhotics show higher free T4 and reduced free T3 values than normal subjects, and the decrease in T3 correlates closely with the degree of liver dysfunction. On the other hand, patients with fatty liver disease have higher TSH levels than normal subjects and a higher rate of subclinical hypothyroidism [75].

General management

The management of immune-related thyroid dysfunction is well established in patients with other tumors. In HCC patients, the main difference relies in the complexity of establishing a clinical diagnosis when the symptoms may mimic usual symptoms in cirrhosis complications. Slight isolated changes in thyroid hormones should also be considered as linked to the underlying liver disease. Signs and symptoms of hypothyroidism in cirrhotics include fatigue, myalgia, muscle cramps, or increased transaminases [76]. Ascites and jaundice are rarely the first symptoms.

If a patient under ICPIs is screened regularly for TSH and free T4, thyroid dysfunction is detected when the patient is asymptomatic. When analyzing the results of TSH and T4 it is important to ensure that there is no iodine saturation related to contrast medium injection. Hypothyroidism does not require stopping ICPIs. In hyperthyroidism, ICPIs should only be interrupted in patients who are

unwell. When symptoms develop or hormone changes are progressive, consultation with the endocrinologist is recommended. There is no need to start specific treatment when the patient is asymptomatic. For symptomatic hypothyroidism, thyroid replacement therapy can be started at a dose of 25–50 µg. For hyperthyroidism, beta-blockers are indicated if symptomatic (e.g., atenolol 25–50 mg/day in order to maintain a heart rate below 90 bpm. Graves' disease should be managed per standard guidelines as in patients with no liver disease under the supervision of an endocrinologist.

Hypophysitis and adrenal insufficiency

The most relevant pituitary gland and adrenal gland disorders triggered by immunotherapy are hypophysitis and primary adrenal insufficiency. Hypophysitis appears clinically with headache and fatigue and more rarely with visual changes like diplopia. More often, it is suspected in an asymptomatic patient under ICPIs when laboratory tests show central hypothyroidism (a low TSH and low free T4). Central adrenal insufficiency is also observed in most patients and anterior panhypopituitarism (adrenal insufficiency, hypothyroidism and hypogonadism) occur in around 50% of patients with hypophysitis [77]. Pituitary enlargement and other radiological features can usually be observed on MRI.

Hypophysitis is exceedingly rare with PD-1 inhibitors and fairly uncommon during CTLA-4 blockade [7,22–24]. Incidence with ipilimumab shows a trend to dose dependency, from ≤ 10% at a dose of 3 mg/kg to 17% at 10 mg/kg. After dual CTLA-4 and PD-1 blockade, the incidence is similar at 13%. The median time from

starting ipilimumab to diagnosis of hypophysitis is 8–9 weeks but this complication may appear at any time during ICPI therapy.

Primary adrenal dysfunction appears with fatigue, dizziness, low blood pressure and orthostatic hypotension, muscle aches, nausea or vomiting. Symptoms may develop slowly and insidiously. If left untreated, hypoglycemia, dehydration, and disorientation may develop. The rate of adrenal dysfunction with tremelimumab, pembrolizumab and nivolumab is 0% [25], 2% [3], and 1% [2], respectively.

Adrenal dysfunction may occur at any time during or even after ICPIs.

Immune-related pituitary and adrenal irAEs have been described at very low frequencies in HCC patients (Table 1). Hypophysitis was not reported in nivolumab or pembrolizumab trials while adrenal insufficiency occurred in 0.5% to 3% of patients during pembrolizumab therapy. However, the limited number of patients evaluated does not rule out the risk of developing this potential irAE. Importantly, this irAE can occur several months after discontinuing an ICPI [78].

Hypopituitarism and adrenal disorders associated with chronic liver disease

The dysfunction of the hypothalamic-pituitary-adrenal axis in patients with liver disease has been extensively described and worsens in parallel with the severity of cirrhosis [79]. Relative adrenal insufficiency is well described [80] but mainly in decompensated cirrhotics who are not candidates for immunotherapy. Data available for patients with compensated cirrhosis or advanced fibrosis is very scarce. Among patients admitted due to complications, the prevalence was comparable (20% to 30%) in Child-Pugh A, B and C [81] and similar in a small

group of 10 ambulatory patients. The impact of liver diseases on sex hormone production is also very well established. The prevalence of hypogonadism in cirrhotics ranges from 20% to 65% [82]. Response of luteinizing hormone after gonadotropin-releasing hormone stimulation is altered only in Child-Pugh B and C patients.

General management

As mentioned, some symptoms of cirrhosis overlap with those of thyroid dysfunction or adrenal insufficiency. For this reason, the main recommendation in HCC patients is to assume an active role in its early identification. Patient under ICPIs can be screened regularly for TSH and free T4 (v.g. every 4-6 weeks). The finding of central hypothyroidism demands a complete hormone testing including adrenocorticotrophic hormone (ACTH), corticotropin-releasing hormone (CRH), cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and prolactin. For the initial screening of a symptomatic patient in whom hypophysitis or adrenal insufficiency is suspected, at least serum levels of TSH, free T4, ACTH, cortisol, sodium and potassium should be measured. An ACTH stimulation test is warranted if ACTH or cortisol levels are abnormal or the suspicion is strong. If hypopituitarism is detected, a pituitary MRI is recommended. When interpreting the results of the tests, the peculiarities of the cirrhotic patients should be taken into account.

There are no specific recommendations for the management in cirrhotic patients. For patients with very mild or no symptoms, intervention is not needed but early consultation with the endocrinologist is highly recommended. In symptomatic

patients, when hypophysitis is confirmed by hormones and MRI, corticosteroids should be started (prednisone 1-2 mg/kg/day or equivalent) as well as hormone replacement (central adrenal insufficiency: hydrocortisone 100 mg IV as a starting dose; central hypothyroidism: levothyroxine 1 mg/kg). Patients with severe symptoms should be admitted for evaluation and work-up. Patients with suspicion of an adrenal crisis (severe dehydration, hypotension, shock) should be managed in the intensive care unit. Sepsis has to be ruled out and the crisis be managed per standard guidelines.

Nephritis

Renal dysfunction during ICPI therapy was initially considered a rare event occurring in <1% of patients [83]. Later it became clear that the incidence of renal toxicity might be higher at 9.9 to 29% [84], particularly when ipilimumab and nivolumab are used in combination or sequentially [85]. In a system-based review of 139 case reports or series, acute kidney injury (AKI) occurred in 16 cases (11.5%) [86]. In the first clinical trial of CTLA-4 blockade with tremelimumab in patients with HCC and chronic HCV infection, acute renal failure was reported in 3 out of 15 patients and was considered to be related to underlying cirrhosis, not to ICPIs [25]. AKI was reported in one out of 262 HCC patients treated with nivolumab [2]. Although the incidence of AKI appears to be lower in HCC than in other tumors, it should be pointed out that the rate of kidney-related AEs in other tumor types was initially underestimated and then increased as data became more mature. Similar underreporting is at least possible in HCC patients, in whom the attribution of causality may be challenging. Underlying kidney disease of a non-

immune cause is not a reason to exclude patients from ICPIs, which appears to be safe even in patients with baseline renal function impairment.

AKI occurs earlier with CTLA-4 inhibitors (after 2-3 months) than with PD-1 inhibitors (after 3–10 months) [84]. In a series of 13 biopsy-proven cases, AKI developed 21 to 245 days after ICPI (median 91 days), median peak serum creatinine was 4.5 mg/dl (interquartile range, 3.6-7.3), and four patients required hemodialysis [87]. Acute tubulo-interstitial nephritis was the histopathological lesion in 12 patients, sometimes with granulomatous features. Ten out of these 12 patients were treated with corticosteroids with complete or partial improvement in renal function in 2 and 7 patients, respectively. In contrast, renal function did not improve in the two patients not given corticosteroids. Lupus-like immune complex glomerulonephritis has been described in a patient with nephrotic syndrome and preserved renal function under treatment with ipilimumab [88].

Renal disorders associated with chronic liver disease

Impaired kidney function is frequently observed during the natural course of chronic liver disease and needs to be distinguished from ICPI-related toxicity [89]. Viral hepatitis may produce renal disorders. Epidemiological studies have shown a relationship between HBV infection and the development of proteinuria and impaired kidney function. The presence of immune complexes in the kidney suggests an immune-complex basis for the disease [90] while histology may show membranous nephropathy. On the other hand, extra-hepatic manifestations of HCV infection include various types of renal diseases. The most common are essential mixed cryoglobulinemia leading to membranoproliferative glomerulonephritis,

membranoproliferative glomerulonephritis without cryoglobulinemia, and membranous glomerulonephritis [91].

Disturbances in the circulatory function frequently result in renal failure in cirrhotics. The presumed mechanism is increased production or activity of vasodilators triggered by portal hypertension [89]. The decline in renal perfusion reduces glomerular filtration rate and sodium excretion. Diagnosis of hepato-renal failure is suggested by a progressive rise in serum creatinine, a very low rate of sodium excretion (urine sodium concentration < 10 mEq/L) and oliguria. Urine sediment is often normal and there is no or minimal proteinuria. Precipitating factors include bacterial infection or gastrointestinal bleeding. Fluid depletion by large volume paracentesis or diuretics may also contribute to renal dysfunction.

General management

Any increase in creatinine levels during ICPI therapy should be considered a potential irAE. However, all other causes of renal failure have to be ruled out before assuming it is an irAE. Early renal consultation is recommended and a kidney biopsy should be performed if ICPI-related nephritis is considered the most likely event. The risk of post-interventional bleeding needs to be addressed in patients with poor liver function and coagulopathy. If biopsy shows podocytopathy or acute interstitial nephritis, ICPIs should be discontinued and a course of corticosteroids installed. Prednisone 1 mg/kg tapered over a period of 1–2 months is a possible option. Close monitoring of the serum creatinine is recommended. Resumption of ICPIs can be considered once nephritis has resolved. Potentially

nephrotoxic drugs such as non-steroidal anti-inflammatory drugs should always be avoided [84].

Neurological toxicity

Clinical manifestations of neurological toxicity include a broad spectrum that involves central as well as peripheral nervous systems, including myasthenia gravis, peripheral neuropathy, Guillain-Barre syndrome, autonomic neuropathy, aseptic meningitis, encephalitis and transverse myelitis [92] [93] [94]. The overall incidence of neurological irAEs is 3.8% and 6.1% among patients treated with CTLA4 and PD-1 inhibitors, respectively [95]. The incidence increases to 12% in patients undergoing combination of CTLA-4 and PD-1 inhibitors [95]. The severity of most neurological irAEs is mild to moderate, with grade 3 or above events observed in lower than 1% of patients [95]. In HCC, grade 3 or higher encephalopathy occurred in 3 out of 20 patients during treatment with tremelimumab but all events were attributed to underlying cirrhosis [25]. For PD-1 inhibitors, grade ≥ 3 events ranged from 0 to 1.9% [2] [3].

Neurological disorders associated with chronic liver disease

Central and peripheral nervous system signs and symptoms are common in patients with cirrhosis. Hepatic encephalopathy is the most frequent disorder. Its clinical expression comprises a variety of signs and symptoms including cognitive defects (from mild inattentiveness to dementia), altered conscious state (from sleepiness to coma) or impaired neuromuscular function (asterixis and hyperreflexia). [96]. On the other hand, up to 2% of patients with cirrhosis develop

chronic acquired hepatocerebral degeneration, that includes neuropsychiatric changes and movement disorders such as tremor, dysarthria, ataxia, parkinsonism, and others. [97]. Cognitive dysfunction is the rule, but it may be difficult to identify. Both entities are typically associated with large portocollateral shunting and may occur in an HCC patient with normal liver function. Superimposed mechanisms include brain accumulation of toxic compounds such as ammonia, lactate or manganese; altered permeability of the blood-brain barrier; or inflammation due to circulating cytokines. Some other neurological complications are linked exclusively to specific disorders, like alcoholism and Wernicke encephalopathy. Finally, impaired autonomic function is often found in individuals with chronic HCV infection, even in the absence of cirrhosis [98].

General management

Corresponding investigations vary according to the clinical pictures. In general, it is necessary to exclude alternative etiologies for related neurological symptoms. For example, MRI brain is indicated to rule out brain or leptomeningeal metastases when there are CNS symptoms. For clinical presentation of encephalopathy in patients with hepatic tumors, detailed history on drinking and diet could help rule out differential diagnoses of Wernicke encephalopathy and porto-systemic encephalopathy, and electroencephalography may also be required to rule out subclinical seizure activity. Serum ammonia levels should also be measured to exclude hepatic encephalopathy. Other less common possibilities such as autoimmune encephalitis or paraneoplastic syndrome may also be ruled out by clarifying onset of confusion or headache in relation to malignancy and immunotherapy as well as checking paraneoplastic autoantibodies [93] [94]. For

patients with peripheral sensory or motor neuropathy, nerve conduction studies and/or electromyography is required for work-up of peripheral sensory or motor neuropathy. After ruling out space-occupying lesions, obtaining cerebral spinal fluid is frequently an important work-up procedure for evaluation of the protein, glucose, cell count, cytology, bacterial and herpes simplex viral infection. In case of autonomic neuropathy, apart from ICPI-related, it is also possibly related to HCV infection. HCV RNA, liver tests (especially ALT and AST) and serum cryoglobulins could help distinguish between the two diagnoses, and it has been reported that antiviral therapy may potentially reverse the autonomic neuropathy [98] [99]. In all neurological toxicities, consultation with neurologist specialists is recommended especially when there is grade 2 or higher neurological toxicity.

In general, the threshold of withholding ICPIs is low when there are symptoms suggestive of Guillain-Barre syndrome or myasthenia gravis due to potentially life-threatening respiratory compromise. In patients with mild but progressive symptoms, steroid treatment and additional measures such as intravenous immunoglobulin or plasma plasmapheresis should be considered as early as possible, when appropriate. Although steroids are generally not indicated in idiopathic Guillain-Barre syndrome, it may still be considered in addition to intravenous immunoglobulin. For encephalitis and aseptic meningitis, steroids should be administered early with consideration of concurrent antiviral for herpes simplex virus infection and antibiotics to cover bacterial infection. Hepatic function and ammonia level should always be monitored even in patients with established neurological diagnoses. There are currently no data to guide the resumption of ICPIs following recovery from neurological toxicity. In general, for

grade 3-4 neurological complications, ICPIs should be discontinued permanently, and even for patients who recover from mild Grade 1-2 toxicity, extreme caution should be exercised before resumption of ICPIs, with detailed discussion of benefits and risks with patients.

Blood and bone marrow toxicity

Hematologic irAEs are uncommon and include hemolytic anemia, red cell aplasia, bone marrow failure, hemophilia A, hemophagocytic lymphohistiocytosis, macrophage activation syndrome, and hematological cytopenias affecting one or more hematological cell lines [100]. In addition, non-clinically relevant increases in any white blood cells (neutrophils, lymphocytes, monocytes and eosinophils) may also be observed during treatment with ICPIs. Data on incidence of hematologic irAEs in clinical trials in HCC patients scarce. Anemia was reported in 4% of patients receiving pembrolizumab [3] and 8% of those receiving nivolumab [2] and it was grade 3 in 2% of patients. As it occurs with other irAEs, the pathogenesis of hematologic irAEs is largely unknown although autoantibody production may be an underlying mechanism since platelet-associated autoantibodies are frequently detected in patients with thrombocytopenia [101].

Hematologic disorders associated with chronic liver disease

Cytopenias are common in chronic liver diseases. Portal hypertension may produce congestive splenomegaly with increased intrasplenic sequestration and destruction of blood cells, particularly when associated with portal vein thrombosis or tumor invasion by HCC. Alcoholic patients may show a direct toxic

effect of alcohol on blood cell precursors in the bone marrow. In other cases, the mechanisms are particular to each cytopenia.

Thrombocytopenia is the most frequent disorder, occurring in almost 78% of patients with compensated cirrhosis [102]. Spontaneous bleeding is very rare but a platelet count $\leq 60,000/\mu\text{L}$ is associated with a 5% rate of bleeding events after liver biopsy [103]. Besides hypersplenism and alcohol toxicity, decreased activity of thrombopoietin and antiplatelet antibodies may contribute to the development of thrombocytopenia in chronic liver disease [104]. Anemia of diverse etiology occurs in almost 75% of patients with chronic liver disease [105]. Asymptomatic cirrhotics with gastric or esophageal varices or portal hypertensive gastropathy may have a slow chronic loss of blood into the gut and develop anemia due to iron deficiency while vitamin B12 and folate deficiency due to reduced diet intake or intestinal malabsorption emerge commonly in cirrhosis.

General management

Cytopenia during ICPI therapy should be specifically evaluated for autoimmune causes if they are progressive or reach a clinically significant level. Relative changes in cell count are more important than absolute levels to raise the suspicion of an ongoing irAE while the need for specific therapies like transfusion or growth factors set the time for in-depth testing. Causal attribution is complicated by the fact that both cirrhosis and malignant disease may also cause cytopenias. A high proportion of around 40% of patients with cancer have anemia at diagnosis and an additional 30% develop anemia as disease progresses [106]. Different mechanisms may lead to anemia in cancer patients. They include an

impaired proliferative response of the bone marrow to erythropoietin stimulation due to overproduction of inflammatory cytokines, inappropriately low production of erythropoietin by the kidney, shortened erythrocyte survival, and impaired iron utilization [107]. Extensive tumor burden and bone marrow metastasis may also cause microangiopathic hemolytic anemia and leukoerythroblastosis [108].

The development or worsening of pre-existing anemia should trigger an evaluation for common causes and a peripheral smear, reticulocyte count, ferritin, iron and transferrin saturation index, haptoglobin and Coombs test should be ordered. If occult GI bleeding is suspected, upper and eventually endoscopy could be considered. If anemia requires transfusion and the source cannot be identified, bone marrow biopsy may be indicated to rule out red cell aplasia. Likewise, in the absence of a precipitating factor such as non-malignant portal vein thrombosis or progression of malignant portal vein thrombus, the development or worsening of pre-existing thrombocytopenia warrants the search for platelet-bound IgG. If platelet count falls below 60,000/ μ L or is associated with any bleeding event, bone marrow biopsy may be indicated to rule out myelodysplasia or bone marrow metastasis. Any patient with an unexplained severe or rapidly progressing cytopenia should be referred to a hematologist for evaluation.

Musculoskeletal toxicity

Musculoskeletal symptoms occur in up to 40% patients and seem to be more common with PD-(L)1 inhibitors rather than CTLA4. The most common adverse events are arthropathies, polymyalgia-like syndrome and myositis but vasculitis and temporal arteritis have also been reported. Arthritis can present as a

symmetrical polyarthritis associated with synovitis, or oligoarthritis limited to a few large joints. Reactive arthritis with conjunctivitis and uveitis has also been described. Grades 1/2 and 3 myalgia was reported in 6% and 1% of HCC patients treated with pembrolizumab [3] in a phase 2 trial but none was reported in the phase 3 trial [4]. Incidence of grade 1/2 arthralgia in these trials were 5% and 2.5% respectively and myasthenia syndrome and myositis occurred in 0.5% and 1% in the phase 2 trial only. One of 21 patients treated with tremelimumab had grade 2 arthralgia but no musculoskeletal events have been reported for nivolumab [2], nor to date from the combination trials of ipilimumab plus nivolumab [53] or durvalumab plus tremelimumab [26]. Currently, there is no evidence to suggest that patients with HCC have higher rates of musculoskeletal toxicity and if anything, the incidence is rather less than expected.

Musculoskeletal disorders in chronic liver disease

Up to 50% of patients with autoimmune hepatitis have other autoimmune conditions such as rheumatoid arthritis but this condition is generally regarded as a contraindication to ICPIs. Both hepatitis B and C infection are associated with extrahepatic manifestations including arthritis, sicca syndrome and polyarteritis nodosa [109]. Arthritis during acute HBV infection characteristically presents with symmetric polyarthritis and is associated with immune complexes containing the HBV antigens and antibodies in the serum and synovial fluid [110]. HCV has also been linked to the development of symmetrical small joint polyarthritis although it is typically not erosive or deforming. Although 85% are positive for rheumatoid factor, anti-cyclic citrullinated peptide (CCP) is found in less than 6% [111]. The incidence of HCV related arthritis seems to have been overestimated in the past

and is in the region of 1% [112]. Alcohol is associated with both acute and chronic myopathy, with acute myopathy presenting in up to 2% alcoholics [113]. Acute alcohol myopathy is characterized by rhabdomyolysis and results in a symmetrical proximal polymyopathy. Elevated serum creatine kinase (CK) and myoglobin may be found. Chronic alcohol myopathy typically manifests with progressive weakness over weeks or months and is present in up to 50% patients with cirrhosis [114].

General management

Investigations should be conducted to rule out other differential diagnoses which such as rheumatoid arthritis, gout, pseudogout and septic arthritis. Blood tests including erythrocyte sedimentation rate (ESR), C reactive protein (CRP), antinuclear antibody (ANA), rheumatoid factor (RF), anti-CCP should be done along with X-rays of the effected joints. HLA B27 should be tested if there is spinal involvement and expert rheumatology advice sought in the presence of synovitis. Polymyalgia-like syndrome is associated with muscle pain and stiffness and needs to be distinguished from fibromyalgia and statin-induced myopathy. ESR and CRP will be elevated but CK is not significantly raised. By contrast, myositis is rare but potentially fatal and characterized by weakness rather than pain and is associated with markedly elevated CK. Additional investigations should include ESR, CRP, ANA, RF, anti-CCP. Troponin, ECG and echocardiography should also be considered since myocarditis can occur concurrently. Electromyogram and muscle biopsy may be indicated in selected cases. To date there is no evidence that ICPI cause reactivation of HCV or HBV and new onset arthritis in a chronic HBV or HCV patient treated with ICPI should be assumed to be drug-related in the first instance.

Grade 1 inflammatory arthritis or polymyalgia-like syndrome can be managed symptomatically with paracetamol or non-steroidal anti-inflammatory drugs (NSAID), and ICPI can be continued. If activities of daily living are limited by muscle pain or stiffness or by joint inflammation (grade 2), ICPI should be withheld and systemic corticosteroids should be started at an equivalent dose of 10-20 mg/day prednisolone. Severe functional limitation or joint destruction (grade 3/4) warrants higher dose oral prednisolone 0.5-1 mg/kg, again with slow taper. If symptoms worsen or fail to improve, or the dose of prednisolone cannot be reduced to ≤ 10 mg/day after 3 months, disease-modifying antirheumatic drugs (DMARD) such as methotrexate, TNF- α or IL-6 inhibitors may be added.

For myositis, mild weakness without elevated CK, can be managed with simple painkillers and ICPI continued. If the CK is elevated or function limited, prednisolone should be started and ICPI held until the CK is normal and the dose of prednisolone is less than 10 mg/day. Severe weakness limiting self-care (grade 3-4) warrants higher dose steroid equivalent to 1-2 mg/kg prednisolone and ICPI discontinued permanently if there is evidence of cardiac involvement. Hospital admission and referral to rheumatology or neurology may be needed and the addition of further immunosuppressive agents such as methotrexate, azathioprine, MMF may be needed if CK fails to return to normal. Plasmapheresis or intravenous immunoglobulin can be considered.

Cardiac toxicity

Cardiovascular complications from ICPI include myocarditis, pericarditis, myocardial fibrosis, cardiomyopathy, heart failure, dysrhythmias and cardiac arrest. Histological examination has revealed lymphocytic infiltration of myocardium and conduction system [115]. Cardiac adverse events can be life threatening and require early recognition and prompt intervention. The onset ranges from two to 32 weeks with a median of 10 weeks [116], and can present with a range of symptoms including chest pain, palpitations, breathlessness, edema, effusions, fatigue, malaise or weakness. Cardiac complications are estimated to occur in less than 0.1% patients but are more common in those patients receiving combination (PD1/CTLA4) therapy (0.27%) compared with single agent ICPI (0.06%) [16]. To date the number of HCC patients reported to have experienced cardiac toxicity is very low. One patient of 104 treated with pembrolizumab [3] was reported to have grade 3 cardiac failure but no other cardiac events have so far been reported among 262 patients treated with single agent nivolumab [2], nor for the 148 patients treated with combination nivolumab and ipilimumab [53], nor the 40 patients treated with durvalumab and tremelimumab [26]. Outside of clinical trials, there has been one case report of a man with HCC who developed bradychardia due to sick sinus syndrome. This was found to be secondary to immune mediated adrenal insufficiency rather than myositis and resolved with glucocorticoid supplementation [117].

Cardiac complications of chronic liver disease.

Chronic liver disease is associated with a range of cardiac complications. Cirrhotic cardiomyopathy has been recognized as a distinct entity in which there is diastolic dysfunction, decreased cardiac output and prolonged QT interval which can

predispose to dysrhythmias [118]. Patients with liver disease secondary to fatty liver disease and diabetes have pre-existing risk factors for cardiac disease including coronary heart disease and ventricular failure, and high levels of alcohol intake are associated with a higher risk of atrial fibrillation [119]. Hepatitis B infection has also been associated with myocarditis [120]. Because of the prevalence of coincident cardiac disease in patients with chronic liver disease, it is prudent to perform baseline investigations including chest X-ray, ECG and troponin along with BNP and echocardiography in selected patients.

General Management

Investigations should include electrocardiogram (ECG), chest X-ray, troponin, CK, brain natriuretic peptide (BNP) and echocardiogram. Troponin is elevated in over 94% cases of myocarditis and a third will have ECG changes [121]. Early involvement of cardiology is recommended and selected patients may require cardiac catheterization or cardiac MRI. ICPIs should be permanently discontinued in the event of a cardiac adverse event of any grade. The equivalent of 1-2 mg/kg prednisolone should be administered and the patient should be admitted for monitoring and cardiology review. In the absence of a rapid response, the dose of steroid should be escalated to 1 g per day and the addition of MMF, tacrolimus or anti-thymocyte globulin should be considered in the absence of a response to steroids. Standard cardiac medications may be required for management of ventricular dysfunction or dysrhythmia. Infliximab is contraindicated at high doses in patients with moderate-severe heart failure and should be avoided under these circumstances [14].

Table 1. Immune-related adverse events in patients with HCC (incidence is presented as percentage of patients)

Checkpoint inhibited		CTLA-4		PD-1			PD(L)-1 & CTLA-4			
Source study		Sangro	Duffy	Checkmate 040	Checkmate 040 (Child B cohort)	Keynote 224 & 240	Checkmate 040			AZ 022
Reference		[25]	[122]	[123]	[19]	[3] [4]	[53]			[26]
Agent(s)		Tremelimumab		Nivolumab		Pembrolizumab	Nivolumab + Ipilimumab			Durvalumab + Tremelimumab
Dose		15 mg/kg q3m	3.5 & 10 mg/kg q4w	various doses	240 mg q2w	200 mg/kg q3w	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg q3w	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg q3w	Nivolumab 3 mg/kg q2w + Ipilimumab 1 mg/kg q6w	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg q4w
n		21	32	262	49	104 & 279	50	49	49	40
Discontinuation due to toxicity		0	13	3.4	4	5.0-17.2	nr	nr	nr	7.5
Treatment-Related AE	All grades	nr	nr	77.0	51	60.9-73	94	71	79	60
	Grade ≥3	nr	nr	18	nr	18.6-26	53	29	31	20
irAE	All grades	nr [§]	nr	18	nr	10-18.3	29	22	17	nr
	Grade ≥3	nr [§]	nr	1	nr	0-7.2	4	4	0	nr
Rash	All grades	65	16*	18	nr	8-10	29	22	17	12.5
	Grade ≥3	15	3	1	r	0-1	4	4	0	0
Pruritus	All grades	nr	9*	20	12	12-18	45	33	29	22.5
	Grade ≥3	nr	3	1	0	0-0	4	0	0	0
Diarrhea	All grades	30	nr	14	nr	11	24	12	17	12.5
	Grade ≥3	5	nr	1	nr	0	4	2	2	2.5
Colitis	All grades	nr	6*	nr	nr	1.4	10	2	2	2.5
	Grade ≥3	nr	0	nr	nr	0.8	6	2	2	2.5
AST	All grades	70	34*	9.9	10	14	20	20	13	17.5
	Grade ≥3	45	22	5.3	6	7	16	8	4	10
ALT	All grades	55	19*	9.5	10	9	16	14	8	20
	Grade ≥3	25	9	3.4	4	4	8	6	0	5

Hepatitis	All grades	nr	nr	0.6*	nr	1.8-3	20	12	6	nr
	Grade ≥3	nr	nr	0.6*	nr	1.4	20	10	6	nr
Pneumonitis	All grades	nr	nr	1.3*	nr	2.2	10	0	0	2.5
	Grade ≥3	nr	nr	0.6*	nr	0.4	6	0	0	2.5
Adrenal insuf	All grades	nr	3*	nr	nr	0.6-3	18	6	6	nr
	Grade ≥3	nr	3	nr	nr	0-2	4	0	0	nr
Hypothyroidism	All grades	nr	6*	nr	nr	5-6	0	0	2	nr
	Grade ≥3	nr	3	nr	nr	0-0.6	0	0	0	nr
Hypophysitis	All grades	nr	nr	nr	nr	0.4	nr	nr	nr	nr
	Grade ≥3	nr	nr	nr	nr	0	nr	nr	nr	nr

* Only AEs ≥ grade 3 were reported; § no patient received steroids

Table 2. Pre-treatment evaluation recommended for patients with hepatocellular carcinoma before starting immune checkpoint inhibitors.

<p>History</p> <ul style="list-style-type: none"> • Detailed questioning for prior decompensations of cirrhosis (ascites, edema, GI hemorrhage, jaundice or encephalopathy), including date of last gastroscopy. • Detailed questioning for any co-morbidities, in particular those of autoimmune origin or associated with cirrhosis. • History of base line bowel habits (frequency of bowel movements, usual stool consistency) • Detailed questioning for past or current use of alcohol, recreational drugs, medicines, and homeopathic or herbal medicinal products.
<p>Physical examination</p> <ul style="list-style-type: none"> • Height and weight. Heart and respiratory rates. Blood pressure. Oxygen saturation on room air at rest and after 1-min or 6-min ambulation. • Regular physical examination including skin and mucosal visual exam, thyroid palpation and search for signs of ascites, edema and encephalopathy.
<p>Blood and urine tests</p> <ul style="list-style-type: none"> • Complete blood cell count • Glucose and lipid profile (HbA1c if abnormal glucose) • Liver tests (AST, ALT, alkaline phosphatase, GGT gamma-glutamyltransferase). • Liver function tests (total bilirubin, albumin, prothrombine activity/INR). • Creatinine, urea, urinalysis. • Sodium, potassium, calcium. • TSH (free T3 and T4 if abnormal TSH). • Total creatine kinase. • HBsAg and HBcAb. If positive, HBsAb, HBeAg, HBeAb, HBV-DNA and HDV antibodies ^a. • HCVAb. If positive, HCV-RNA unless known eradication of HCV infection ^a. • HIV and CMV antibodies ^a. • Troponin. • Alpha-fetoprotein.
<p>Other tests</p> <ul style="list-style-type: none"> • ECG • Chest and abdominal CT or MRI scan
<p>Additional tests recommended in patients with suspected co-existing organ disease</p> <ul style="list-style-type: none"> • BNP and troponin if any ascites, edema or dyspnea or cardiac enlargement on chest imaging.

- Pulmonary function tests and oxygen saturation on room air at rest and after 6-min ambulation if dyspnea or lung abnormalities on chest imaging.

^a These tests should not be repeated if available within a reasonable time.

ACTH, Adrenocorticotrophic hormone; BMP, N-terminal pro B-type natriuretic peptide; CMV, Cytomegalovirus; ECG, electrocardiogram; HbA1c, Glycosylated hemoglobin; HBsAg, Hepatitis B surface antigen; HBsAb, Hepatitis B surface antibody; HBcAb, Hepatitis B core antibody; HBeAg, Hepatitis B e antigen; HBeAb, Hepatitis B e antibody; HCVAb, Hepatitis C virus antibody; HDV, Hepatitis D virus antibody; HIV, Human Immunodeficiency Virus; TSH, Thyroid-stimulating hormone; T4, Thyroxine.

Table 3. General management of non-liver immune-related toxicities in patients with hepatocellular carcinoma.

CTCAE v. 5.0 grade	Grade 1	Grade 2	Grade 3	Grade 4
Definition	Mild	Moderate	Severe	Life-threatening
ICPI modification	<ul style="list-style-type: none"> • Continue ICPI. • Consider withholding ICPI for suspected pneumonitis or myocarditis during diagnostic work-up. 	<ul style="list-style-type: none"> • Withhold ICPI until \leq grade 1 (except for hypothyroidism, adrenalitis, limited rash or sensory neuropathy). • ICPI can be resumed after completion of steroid taper. • Consider permanent discontinuation for pneumonitis, myocarditis, or peripheral neuromotor syndromes based on clinical judgment. 	<ul style="list-style-type: none"> • Permanently discontinue CTLA-4 inhibitors in any event. • Permanently discontinue PD-(L)1 inhibitors except for hypothyroidism, adrenal insufficiency, nephritis. or rash that resolve within 30 days 	<ul style="list-style-type: none"> • Permanently discontinue any ICPI.
Monitoring	<ul style="list-style-type: none"> • Monitor within 2 weeks or more frequently depending on irAE and clinical judgment. 	<ul style="list-style-type: none"> • Monitor within 1 week or more frequently depending on irAE and clinical judgment. • Refer to the specialist 	<ul style="list-style-type: none"> • Monitor every 2-3 days or more frequently depending on irAE and clinical judgment. • Refer to the specialist 	<ul style="list-style-type: none"> • Continuous monitoring during hospitalization
Medical therapy	<ul style="list-style-type: none"> • Not needed 	<ul style="list-style-type: none"> • Initiate steroids (prednisone at 0.5-1 mg/kg/day or equivalent PO or IV). • Decision to start steroids can be differed a few days for nephritis. • If it worsens, treat as grade 3. 	<ul style="list-style-type: none"> • Initiate steroids immediately (prednisone at 1-2 mg/kg/day or equivalent IV). IV route for pneumonitis, diarrhea, and others based on clinical judgment. • If no improvement, consider infliximab, particularly for pneumonitis and colitis. 	<ul style="list-style-type: none"> • Manage as grade 3.

ICPI: immune checkpoint inhibitor. irAE: immune-related adverse event.

Table 4. Potential coexisting disorders that have to be considered in the diagnostic work-up of immune-related adverse events in patients with hepatocellular carcinoma.

Organ	iRAE	Chronic liver disease	Cancer	Others
Skin	<ul style="list-style-type: none"> • Pruritus • Rash • Erythema multiforme, psoriasis, urticaria and rosácea. • Severe cutaneous adverse reactions, including Steven-Johnson Syndrome, toxic epidermal necrolysis, and DRESS 	<ul style="list-style-type: none"> • Pruritus • HCV- and HBV-related skin disorders, including lichen planus, polyarteritis nodosa, cryoglobulinemic vasculitis, and porphyria cutanea tarda. 	<ul style="list-style-type: none"> • Biliary tract obstruction due to liver nodules or hilar lymphadenopathies. 	<ul style="list-style-type: none"> • Cutaneous toxicity from other medications
GI tract	<ul style="list-style-type: none"> • Diarrhea • Colitis 	<ul style="list-style-type: none"> • Small intestine bacterial overgrowth • Chronic pancreatitis 	<ul style="list-style-type: none"> • HCC-associated diarrhea 	<ul style="list-style-type: none"> • Clostridium difficile • Antibiotic-induced dysbacteriosis • Lactulose-induced diarrhea
Liver	<ul style="list-style-type: none"> • Hepatitis • AST/ALT elevation 	<ul style="list-style-type: none"> • Flares or viral infection 	<ul style="list-style-type: none"> • Tumor progression in the liver. 	<ul style="list-style-type: none"> • Hepatotoxicity from other medications • Benign biliary obstruction
Lung	<ul style="list-style-type: none"> • Pneumonitis 	<ul style="list-style-type: none"> • Hepatopulmonary syndrome • Porto-pulmonary hypertension 	<ul style="list-style-type: none"> • Tumor progression in the lung. 	<ul style="list-style-type: none"> • Pneumonia
Thyroid	<ul style="list-style-type: none"> • Hypothyroidism • Hyperthyroidism • Graves' disease 	<ul style="list-style-type: none"> • Reduced peripheral conversion of T4 to T3. • Thyroid dysfunction. 		
Adrenal glands and hypophysis	<ul style="list-style-type: none"> • Adrenal insufficiency • Hypophysitis 	<ul style="list-style-type: none"> • Hypogonadism • Hypothalamic-pituitary dysfunction • Relative adrenal insufficiency 	<ul style="list-style-type: none"> • Bilateral adrenal metastasis. 	<ul style="list-style-type: none"> • Hyponatremia induced by diuretics

		<ul style="list-style-type: none"> • Hypogonadism 		
Kidney	<ul style="list-style-type: none"> • Nephritis 	<ul style="list-style-type: none"> • Hepatorenal syndrome • HCV-related glomerulonephritis (mixed cryoglobulinemia) • HBV-related nephropathy • IgA nephropathy 	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • Iodinated contrast agents • Renal dysfunction induced by diuretics
Nervous system	<ul style="list-style-type: none"> • Encephalitis • Aseptic meningitis • Peripheral neuropathy • Myasthenia gravis • Guillain-Barre syndrome • Autonomic neuropathy • Transverse myelitis 	<ul style="list-style-type: none"> • Porto-systemic encephalopathy (typical and atypical) • Viral-related peripheral neuropathy • Wernicke's encephalopathy • Autonomic neuropathy associated to HCV infection 	<ul style="list-style-type: none"> • Tumor progression in the brain or bone (spine). • Carcinomatous meningitis • Paraneoplastic hypercalcemia. 	<ul style="list-style-type: none"> • Opiates, psychotropic drugs
Blood and bone marrow	<ul style="list-style-type: none"> • Cytopenias • Hemolytic anemia • Red cell aplasia • Bone marrow failure • Hemophilia A • Hemophagocytic lymphohistiocytosis • Macrophage activation syndrome 	<ul style="list-style-type: none"> • Hypersplenism and bone marrow depression • Anemia due to folate or iron deficiency • Hemolytic anemia • Viral-related thrombotic thrombocytopenic purpura and aplastic anemia. • Immune thrombocytopenia associated with HCV infection. • Lymphopenia related to HCC therapies such as internal or external radiation 	<ul style="list-style-type: none"> • Tumor bleeding • Bone marrow involvement 	<ul style="list-style-type: none"> • Heparin-induced thrombocytopenia

DRESS (drug rash with eosinophilia and systemic symptoms). HCV: hepatitis C virus. HBV: hepatitis B virus.

Figure legends

Figure 1. Most common organ comorbidities associated with chronic liver diseases.

Figure 2. Management of hepatitis induced by ICPI in patients with hepatocellular carcinoma.

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