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INVITED COMMENTARY

New treatment-induced adverse effects we need to learn as modern hepatologists

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In this issue, Nishida and Kudo have written a review article entitled, "Liver damage related to immune check point inhibitors." [1]. As we know, any medical treatment, whether medical or surgical, can exert an adverse effect at any level. Classically, for example, in the field of hepatology, it is well known that microvesicular steatosis is related to the administration of aspirin, resulting in so-called Rye's syndrome, of which the essential pathogenesis is mitochondria damage in the hepatocytes. In the age of interferon, the hypothyroidism induced by interferon administration is a well-known iatrogenic disease that frequently needs medical treatment. Moreover, even liver transplantation is consistently required for drug-induced acute liver failure worldwide. Most recently, molecular targeting drugs also induce varieties of hepatic injury while treating hepatocellular carcinoma (HCC) [2, 3]. Thus, sometimes it is ironical that we may induce new diseases during treatment in patients who completely rely on us. However, there are no concrete methods to prevent iatrogenic adverse effects with the development of new drugs to overcome their target diseases. Fortunately, during drug development, especially in phase III trials, most drug-related adverse effects are revealed. Thus we are aware of their existence before the introduction of clinical practice. For example, treatment-related hyperbilirubinemia is reported in the use of protease inhibitors in directly acting anti-viral (DAA) treatments for hepatitis C virus (HCV). In addition, lenvatinib, a multikinase inhibitor for treating HCC, is reportedly related to the exacerbation of hepatic function [2, 4]. These new adverse effects were not mentioned in the textbook in the curriculum of medical school. As medical professionals, all of us have learned, experienced, and managed these upcoming unwelcome diseases in the clinical setting.

Immune check point inhibitors (ICPIs), as results from recent application of immuno-oncology (IO) drug developments, are expected to be the mainstay of anti-cancer treatments. They could be used as a part of monotherapy, although one of their strength is combined use with other curative therapies, such as surgery, locoregional therapy, or systemic molecular targeting therapies [5]. With these combinations, our patients are expected to have significantly better survival rates in the very near future. However, we then expect to encounter new treatment-related adverse effects with these new treatments. ICPIs, such as nivolumab and pembrolizumab, have been approved or are expected to be approved in most countries for treating HCC. With their use, anti-tumor effects, including overall survival and progression-free survival [6, 7], improve dramatically. This is the benefit of this treatment.

The limitation of this ICPIs therapy includes induction of new treatment-related adverse effects [8, 9]. The augmentation of the host immune system could be predicted to increase autoimmune phenomena, such as chronic thyroiditis, skin lesion, interstitial pneumonia, inflammatory bowel disease, and autoimmune hepatitis. These adverse effects have been reported in clinical trials [6]. Fortunately, these adverse effects could be manageable by themselves in most cases [10, 11]. With the discontinuation of ICPI treatments or the addition of immune-suppressive agents in some serious cases, most adverse effects can be controlled. However, we need to be careful while dealing with adverse effects because ICPIs could be the only potential treatment option for most patients. Discontinuation of ICPIs could lead to mortality in these patients. Thus, the best treatment option is the continuation of IO treatment with safe management of adverse effects [11]. In clinical trials, every patient needs

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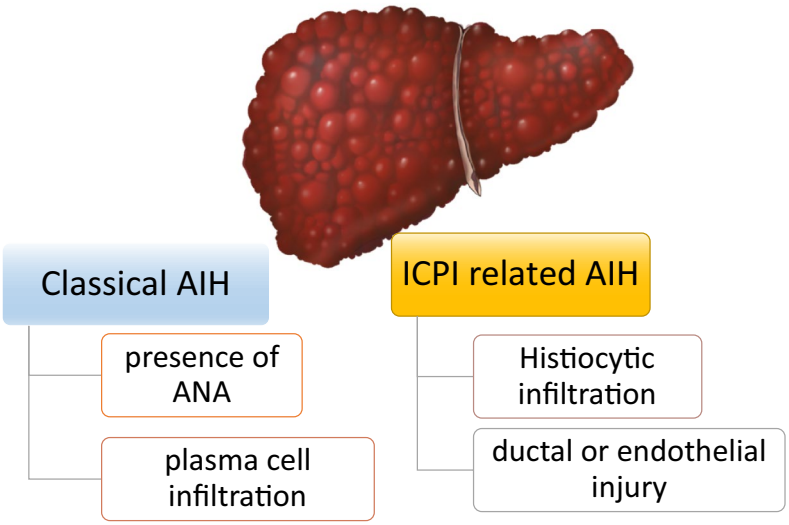

Fig. 1 The different clinico-pathological features of classical and ICPI-related AIH

AIH: autoimmune hepatitis, ANA: anti-nuclear antibody, ICPI: immune checkpoint inhibitor

to be handled as per a strict protocol. However, in the real world, we need to find optimal ways to manage individual patients. In Nishida's review, the hepatic adverse effects of several ICPIs were introduced [1, 12]. The first one is the hepatotoxicity of ICPIs themselves. Especially in patients with HCC, majority have profound chronic liver disease, most commonly, liver cirrhosis. Before the clinical trials, it was believed that ICPI could abandon the immunological tolerance toward chronic viral infections, such as HBV or HCV, which might induce the acute exacerbation of viral hepatitis by the activation of the immune reaction of the host. If these uncontrolled immunoreactions occur in cirrhotic patients, it could possibly result in a fatal outcome. However, fortunately, this has not been observed with early clinical trial of ICPI so far. All the patients treated with nivolumab demonstrated similar hepatic adverse effects in both severity and frequency, as well as treatment responses between viral and non-viral cirrhosis. In the other ICPI clinical trial, a similar observation was made. Thus, uncontrolled attacks to viral infected hepatocytes, which could result in hepatic failure, have not been reported so far.

The second hepatic treatment-related adverse effect of ICPIs is autoimmune hepatitis. Nishida has described the clinical and pathological characteristic features of classical autoimmune hepatitis and IO-related liver damage (Fig. 1). Among them, the ICPI-related hepatic injury seems to have more complex pathological features, including ductal injury and endothelial injury. More importantly, the infiltrating cells are different from those of classical AIH, and plasma cell infiltration is rare, while histiocytic infiltration is predominant. Thus, the profound nature of the pathogenesis of ICPI-related AIH remains unclear. These findings were reported by other recent report analyzing 536 cases with ICPI treatments [13]. Interestingly, the characteristic features of anti-PD-1/PD-L1 are different from those of CTLA-4 immunotherapies; the former consists of mixed type of lobular hepatitis, whereas the latter demonstrates fibrin ring granulomas and central vein endothelitis [13]. One of the most debating issue about the management of hepatotoxicity with ICPIs is its managements. Most agree that in common terminology criteria for adverse events (CTCAE) grade 1 (G1) could be manageable with close monitoring, and in G2 holding ICPI temporally. However, in G3 or higher, the use of systemic immunosuppressive drug is debatable [11, 13, 14]. Thus, the actual management in CTCAE G3 or higher cases are remaining in future consensus. Current algorithm for monitoring hepato-toxicities in patients under ICPI treatment is summarized in Fig. 2. However, we should be aware of that these management option is not evidence-based. Thus, the use of hepato-protective drugs remains to

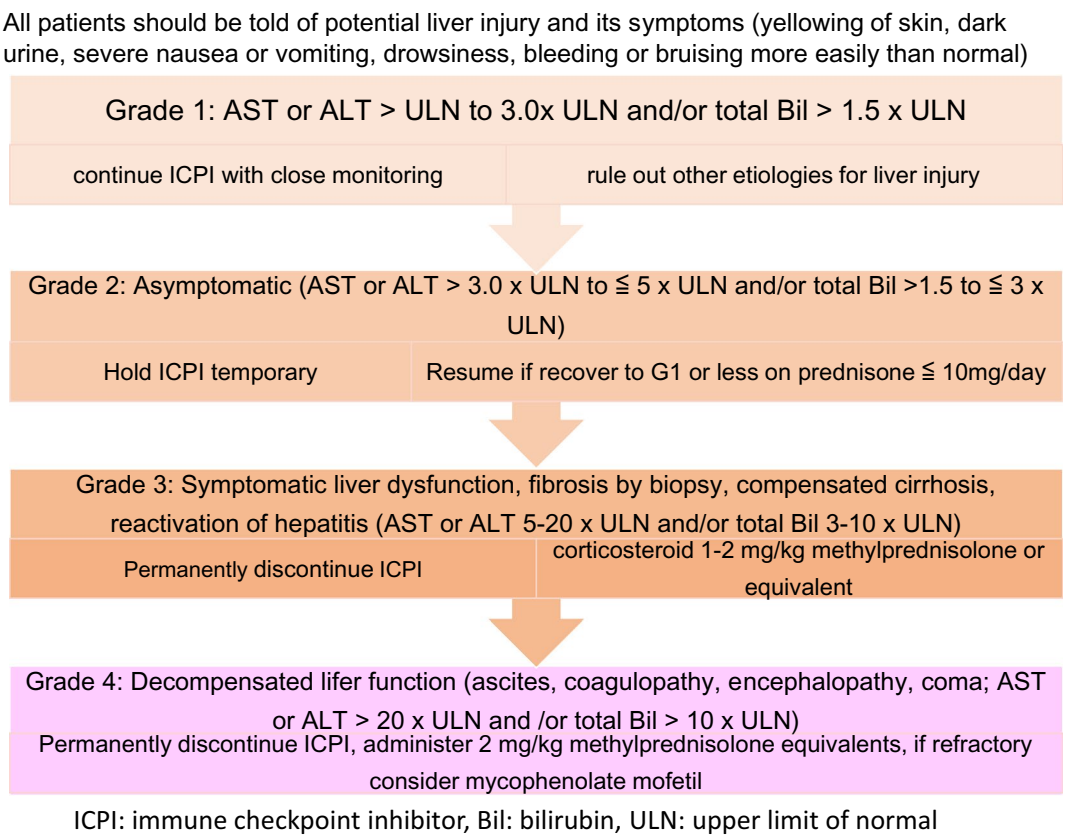

Fig. 2 Management of hepato-toxicities of patients under IPCI treatment. Adapted and modified from [11]

be experimental. While the number of patients treated with ICPIs is estimated to increase dramatically in the upcoming couple of years, we need to be aware of these unfamiliar new diseases in our patients who are undergoing these challenging treatments for their survival.

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