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Management of hepatitis B in the era of checkpoint inhibition

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ABSTRACT

Hepatitis B virus (HBV) is a major global health concern, affecting more than 350 million people worldwide. Its management in the setting of cancer treatment can be problematic, particularly with the use of immunological treatment modalities, but also with chemotherapy. Immunological perturbations by chemo or immunotherapy have the potential to permit viral hepatitis reactivation and acute hepatic failure. HBV management algorithms have evolved, based on host tumor factors, viral serological factors, and the specific antitumor agents planned. As new agents enter the antitumor armamentarium, their impact on HBV infection needs to be defined. Zhang *et al* provide data on the utility of antiviral therapy in the management of HBV antigen positive patients receiving checkpoint inhibitors (CPIs) in preventing hepatitis reactivation, and offers guidance for such management in endemic areas, suggesting that prophylaxis is highly effective in preventing reactivation. This is pertinent to Western cancer therapy also, as a recent study has documented the silent existence of positive hepatitis antigenemia among newly diagnosed cancer patients. Whereas antigen and viral DNA screening is standard of care in Asia and Western Pacific oncology practice, evaluation for latent hepatitis may become a necessary part of management worldwide as CPIs continue to expand their role.

Worldwide, more than 350 million people have chronic hepatitis B virus (HBV) infection, with about 75% located in Southeast Asia and the Western Pacific.[1] Observations regarding HBV reactivation following perturbations of the immune system continue as a major research area in hepatology.[2 3] This is a subject critical to oncology, stem cell and solid organ transplantation, inflammatory diseases, and autoimmunity.[2 3] In oncology, evaluations have identified components leading to reactivation to include host tumor type (and relationship to viral etiology), viral serological status, the class of drug planned, and the duration of immune-perturbing therapy. In all of these clinical settings, components leading to reactivation include viral replication with direct viral cytotoxicity as well as immune reactivation following immune suppression leading to immune-mediated hepatic injury.[2 3]

As new immune-modulatory therapeutics enter the clinical arena, further assessment related to chronic viral infection is necessary. Building on guidelines from the American Gastroenterological Association,[4] the American Society of Clinical Oncology (ASCO) has published provisional clinical opinions outlining the scenarios for viral screening prior to cancer therapy.[5] Both reports define patient-related risk factors for latent HBV infection, and therapies associated with high risk of HBV reactivation.[4 5] This should have further wide dissemination to the oncology community. Differences in screening recommendations continue to be discussed.[2–5]

The field of immune-mediated cancer treatment has been greatly expanded by the development and use of checkpoint inhibitors (CPIs) as antitumor therapy. Importantly, the spectrum of malignant diseases that has demonstrated response to anti-PD-1 directed agents and to the combination of anti-PD-1 and anti-CTLA-4 directed agents, as well as combinations of anti-PD-1 agents and antiangiogenesis directed agents continues to broaden the potential use of these approaches. Some of these tumors are associated with viral-mediated oncogenesis, which may enhance susceptibility to viral-mediated or immune-mediated injury. Numerous trials are ongoing globally to further develop this area of clinical and translational research.

In endemic geographic areas, cancer patients with chronic hepatitis viral infection are routinely managed with antiviral prophylaxis and treatment. Such patients were initially excluded from early clinical trials, particularly of immune-mediated therapy. Nevertheless, as CPIs have gained approval and availability, their use in this patient population has increased with the concomitant use of antiviral management, as has been done with other immunological agents such as anti-CD20 agents, among others. As of 2017, there were no reports of CPI related HBV reactivation.[3] One case report was noted in 2018.[6] Loomba and Liang comment that the mechanism of CPIs should perhaps not induce

reactivation,[3] but given that enhanced cellular immune response is a component of HBV reactivation, CPI-related reactivation is still a potential concern. The exact mechanism of the complex interactions with this class of drugs and chronic HBV is yet to be fully elucidated.

Now, in this issue, Zhang *et al* report a large retrospective safety evaluation of cancer patients (multiple tumor types) with HBV surface antigen expression, undergoing PD-1 inhibition therapy, to assess the rate of HBV reactivation.[7] Their study involved 114 patients with known HBV infection and with serial measurements of HBV serological and viremic status. Diagnoses included 24% hepatocellular carcinoma (HCC), 8% lymphoma, and 68% others (including many tumor types known responsive to CPIs). One-third of patients had detectable HBV DNA and all such patients received antiviral prophylaxis during CPI treatment. None developed HBV reactivation. Importantly, of HBV surface antigen positive patients with undetectable HBV DNA, only 70% received prophylactic antiviral therapy, and among those without antiviral prophylaxis, six developed HBV reactivation during CPI treatment. All six subsequently achieved undetectable HBV DNA levels after a median of 3.5 weeks of antiviral therapy. There was no significant correlation with tumor type and HBV reactivation. The primary risk factor for reactivation was lack of antiviral prophylaxis.

Zhang *et al* additionally evaluated the development of hepatitis in all 114 patients treated with CPIs.[7] They describe all grade hepatitis in 35 patients (30.7%), and categorized these as HBV-related hepatitis in five patients (4.4%) and immune-related hepatitis in 15 patients (13.2%). They state that other hepatotoxicity was due to disease progression in the liver (nine patients) or to cytotoxic drugs (six patients). Grade 3/4 hepatitis was noted in four each with HBV-related hepatitis and immune-related hepatitis, as well as one each due to cytotoxic drug therapy and hepatic lesion progression. Twenty of 35 patients with all grade hepatitis had complete normalization of liver enzymes after a median of 3.5 weeks of antiviral treatment. Six patients required steroids for immune-related hepatitis and none experienced HBV reactivation. These findings provide useful guidelines for the management of cancer patients with chronic viral hepatitis or viral antigen positivity who are candidates for treatment with CPIs. The Zhang data provides encouraging support that antiviral prophylaxis is effective and safe in the setting of CPI therapy, both in terms of suppression of reactivation and management of immune-related hepatitis and suggests that careful viral monitoring will allow ongoing treatment.

Limitations of the Zhang *et al* paper include the retrospective nature of the data, emphasizing safety, but not providing details regarding antitumor response among those with our without antiviral therapy. Nor was there data regarding the need for corticosteroids for CPI toxicity management among either group. Additionally, there was no quantitation of viral DNA among those already receiving antiviral prophylaxis (simply called detectable). These questions will need to be answered in prospective evaluations.

Currently, there is enthusiasm for further evaluation of CPI therapy in patients with HCC, due to early reports of responsiveness to anti-PD-1 treatment. Prospective clinical trials are ongoing, in which chronic hepatitis viral carriers are required to receive antiviral therapy. In these trials, patients with HCC are routinely screened for viral markers which are utilized to monitor the course of treatment as well as the effectiveness of antiviral therapy.[8 9] These trials will provide important prospective data on management of virally infected patients receiving CPIs. However, another important observation from the Zhang report is that the majority of patients described with positive HBV antigen undergoing PD-1 inhibition therapy had cancer diagnoses other than HCC, including nasopharyngeal, melanoma, and non-small cell lung cancer, among others. The approach in Asia is to screen all cancer patients, regardless of diagnosis, for hepatitis virus infection, given the known high prevalence. This practice remains a question in other parts of the world, although viral screening prior to anti-CD20 therapy has become more common in the West.

A recent study of more than 3000 newly diagnosed cancer patients undergoing treatment at nine academic and nine community oncology institutions affiliated with the US Southwest Oncology Group Cancer Research network reported on the prevalence of HBV, hepatitis C virus (HCV), and HIV infection among persons newly diagnosed with cancer.[10] As noted in this report, currently, in the US universal hepatitis viral screening is not routine in oncology practice. However, among the screened patients, the observed rate of prior HBV infection was 6.5% and chronic HBV was 0.6%. The observed rate of prior HCV infection was 2.4%. Importantly, eight patients with chronic HBV and 22 patients with HCV were newly diagnosed in this study. Additionally, four patients with HBV and 23 patients with HCV had no identifiable risk factors for viral infection. The authors conclude that in view of their study defining a level of unawareness of prior viral infection at the time of cancer diagnosis, screening for HBV and HCV may be warranted

In summary, Zhang *et al* demonstrates that antiviral therapy and careful viral monitoring allows safe administration of CPIs to HBV infected cancer patients and demonstrates a management approach that is readily adoptable both in Asia and in the West.[7] Additionally, Ramsey *et al* demonstrate that screening for high risk patients as defined in the recent ASCO clinical opinion report[5] is potentially a cost effective approach in the West, yielding new viral carrier diagnoses in asymptomatic cancer patients.[10] This is particularly relevant given the increasing utilization of CPIs in patients with a broad range of cancer diagnoses.

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