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The treatment of severe hepatitis B virus reactivation after chemotherapy

Xing Li, Yan-Fang Xing, Qu Lin, Min Dong, Xiang-Bo Wan and Xiang-Yuan Wu

We read with great interest the Review by Harrys Torres and Marta Davila (Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat. Rev. Clin. Oncol.* **9**, 156–166; 2012) on the reactivation of the hepatitis B virus (HBV) that occurs in patients with cancer after they undergo chemotherapy.[1] Although the Review provided a broad overview of the reactivation of HBV, the authors did not touch on the rescue treatments for acute exacerbations of hepatitis B. According to previous studies on this specific issue,[2] and our case series report,[3] the mortality of patients with HBV reactivation can be as high as 20–50%.[2,3] However, there has been no adequate research on rescue treatments for the acute exacerbations of hepatitis B, which can seriously affect the survival of patients with this condition.

Antiviral prophylaxis with nucleotide analogues, such as lamivudine, has been shown to be effective in preventing HBV reactivation in patients receiving chemotherapy.[1] However, HBV reactivation cannot be completely eliminated.[3] According to some reports, HBV reactivation can be induced by discontinuing antiviral agents or viral breakthrough.[2,4] Viral breakthrough that occurs during nucleotide analogue treatment is generally caused by poor adherence to therapy or selection of drug-resistant HBV variants. The possibility of drug resistance differs for each nucleotide analogue; lamivudine, telbivudine and adefovir present the highest rates of resistance whereas entecavir and tenofovir each have a high barrier to resistance. Moreover, reactivation of HBV can range from asymptomatic, self-limiting, anicteric hepatitis to severe, potentially fatal, progressive decompensated hepatitis.[1,5] Indeed, for patients with confirmed HBV reactivation that was triggered by discontinuation of prophylaxis, nucleotide analogues with potent HBV inhibition (such as entecavir and tenofovir) should be given as rescue antiviral therapy before alanine aminotransferase elevation occurs to decrease the risk of developing liver failure. Given that the 1-year cumulative rate of resistance to lamivudine can be as high as 24%, both viral breakthrough and further HBV reactivation will likely occur in patients on this regimen. Thus, in compliant patients on prophylactic lamivudine who present with HBV reactivation, the HBV should be challenged with additional drugs that do not have cross-resistance potential (such as adefovir) rather than drugs with similar resistance profiles (such as entecavir) to mitigate multidrug resistance. The only efficient rescue strategy to treat HBV reactivation caused by viral breakthrough is co-adminstration of antivirals that do not cross-resist.[6] Above all, rescue antiviral therapy should be commenced upon diagnosis of HBV reactivation and before alanine aminotransferase elevation to reduce the risk of developing acute liver failure.

Meanwhile, appropriate intensive care is critical in the management of patients with severe HBV reactivation after chemotherapy, especially for those who have developed acute liver failure.[7] However, nonspecific therapies such as rescue antiviral therapy commenced after a diagnosis of acute liver failure are of unproven benefit for patients who did not receive rescue nucleotide analogues before alanine aminotransferase elevation. Indeed, to the best of our knowledge, our article is the only primary research report focused on the prognosis and treatment of severe HBV reactivation after immunochemotherapy.[3] According to our results, rescue antiviral therapy that provides rapid reduction of viraemia might improve survival. This finding was partially supported by research on the severe acute exacerbation of chronic HBV infection, which also demonstrated that antiviral therapy might help the prognosis of patients with acute liver failure.[8,9] However, the efficacy of rescue antiviral therapy remains to be characterized in large-scale clinical trials.

Furthermore, whether the cumulative rate of resistance to lamivudine in patients with chronic HBV infection following chemotherapy is comparable to that of immunocompetent patients remains unclear. And, there is no clinical evidence indicating the superiority of lamivudine over other nucleotide analogues as prophylactic antivirals. Thus, agents with low incidences of resistance, such as entecavir and tenofovir, might be better than lamivudine as first-line prophylactic therapy. The work on prophylactic antiviral therapy to prevent HBV reactivation needs to be refined with the help of hepatologists.

*Department of Medical Oncology, The Third Affiliated Hospital of Sun Yat-sen University, 600 Tianhe Road, Guangzhou 510630, China (**X. Li, Q. Lin, M. Dong, X.-B. Wan, X.-W. Wu**). Department of Nephrology, The Third Affiliated Hospital of Guangzhou Medical College, 63 Duobao Road, Guangzhou 510150, China (**Y.-F. Xing**).*
Correspondence to: X.-Y. Wu
wuxiangy@mail.sysu.edu.cn

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Competing interests
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