Acute Liver Failure Related to Chemotherapy

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ABSTRACT

Hepatitis B virus (HBV) reactivation is a serious but preventable complication of immunosuppression. Chemotherapy in patients with lymphoma without specific anti-HBV prophylaxis leads to significant impairment of liver function and results in an overall liver-related mortality of greater than 5%. Prevention is a better approach than intervention at the time of reactivation. The cause of death is usually HBV-related fulminant liver failure.

We reported a case of a male patient aged 42 years old who was present with acute liver failure related to chemotherapy for treatment of gastric lymphoma. He was later known as having chronic carrier hepatitis B, with high elevated transaminases and hyperbilirubinemia and signs of decompensated liver. The patient was admitted to High Care Unit for best supportive care but his condition was deteriorating and eventually died even though he had been already given antiviral agent.

Key words: HBV reactivation, chemotherapy, liver failure.

INTRODUCTION

Acute Liver Failure can be precipitated by several conditions, one of them is chemotherapy which leads to reactivation of hepatitis B virus (HBV) in chronic Hepatitis B. This issue should be highlighted because HBV reactivation is common following chemotherapy and is associated with a high mortality despite prompt antiviral treatment.1 The prevalence of HBV infection in patients with haematological malignancies is increased compared to the general population worldwide. Even though there is no exact incidence, this condition can be prevented, especially for chemotherapy candidates.2

Chemotherapy-induced immune suppression may lead to increased HBV replication. Immune reconstitution within the weeks and months following recovery from chemotherapy may be associated with a flare up of hepatitis B manifested by hepatocellular injury. Current recommendations emphasize the screening for HBV infection in all haematology patients,
particularly prior to chemotherapy. Here we report a male patient with acute liver failure due to reactivation of hepatitis B related to chemotherapy.

CASE ILLUSTRATION

A male, 42 years old, was brought to the hospital unconsciousness. From the history, 6 months earlier he was diagnosed as gastric lymphoma and underwent chemotherapy 3 cycles of CHOP regimen every 3 weeks. At the 4th cycle the regimen was switched to R-CHOP because of low response of previous regimen. One week later, he felt nausea and often vomiting and 2 days before admission, he got jaundice, icteric skin, fever, and tea-colored urine. There was history of alcohol consumption and blood transfusion. On physical examination, he had delirious, tachycardia (110 bpm), tachypne (28x/mins), icteric skin and sclera, hepatomegaly (3 cm below arcus costarum, 2 cm below processus xiphoideus), and edema. Laboratory result showed high level of transaminase (AST/ALT: 1295/1051), hyperbilirubinemia (14.4/2.5/11.9), elevated LDH (1137), hypoalbuminemia (2.6), and prolonged PT/aPTT (61.4”/98.2”). His chest X-ray and ECG were normal. We inserted the NGT and revealed 400 cc dark colored fluid. He was admitted to High Care Unit.

He was diagnosed with hepatic encephalopathy with differential diagnosis of intracranial lymphoma infiltration, fulminant hepatitis due to chemotherapy with differential diagnosis of acute hepatitis infection, haematemesis due to stress ulcer, and gastric lymphoma post R-CHOP.

He was treated with L-ornithine L-aspartate (LOLA) inj., antiviral 3TC 1x100 mg & adefovir once daily, PPI inj., sucralfat syr, lactulac syr, vitamin K inj., SNMC inj., replaced FFP, and best supportive care. On day 3 of follow up, he was still unconscious, haematemesis was ceased, AST/ALT was lowered (684/529), bilirubin was elevated (23/11/12), and prolonged PT/aPTT (44”/56”). On day 5, AST/ALT was lowered (319/491), bilirubin was highly elevated (28/14/14), and he died eventually due to fulminant liver failure.

DISCUSSION

In this report, we present a case of liver failure due to chemotherapy. Patients with haematological malignancies deserve special attention regarding their hepatitis B status for several reasons. First, in endemic countries, the incidence of HBV reactivation is increased in this group compared with normal subjects. Yet, overt and occult HBV infections often missed at a stage when pre-emptive antiviral treatment may prevent HBV reactivation.

Secondly, HBV reactivation is a common sequella of chemotherapy occurring in 21–53% of HBsAg carriers and when left undetected, may carry a poor prognosis.

Thirdly, even when full recovery is achieved, reactivation may reduce survival because it may require interruption of chemotherapy as scheduled.

This patient had a history of blood transfusion, presuming whether the transmission is vertical or through blood and eventhough we do not know the exact serology profile but his HBsAg revealed positive so at least we concluded that this patient was in chronic carrier of hepatitis B because there was no symptom of acute infection.

His condition with gastric lymphoma since 6 month earlier led to the decision to give chemotherapy with 3 cycles of CHOP regimen, containing immunosupresant agent, with unknown hepatitis B status at that time. Later on, for the 4th cycle the regimen was switched to R-CHOP because of low response.
Chemotherapy is the mainstay for treatment of most hematologic malignancies. When immunosuppressive agents are given to chronic HBV carriers, there is an increased risk of liver-related mortality and morbidity. Lymphoma patients who are HBsAg-(+) are noted to have a higher risk of HBV reactivation after chemotherapy than other cancer patients. This may be related to the relatively more immunosuppressive chemotherapeutic drugs and also the intrinsic immunosuppressive effect of lymphoma.6

Modern therapy for lymphoid malignancies often includes the use of monoclonal antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52). These agents are highly immunosuppressive, and their use has been associated with HBV reactivation.7

Rituximab is an anti-CD20 humanized chimeric monoclonal antibody. Rituximab plus CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) is now a standard treatment of diffuse large B-cell lymphoma. The addition of rituximab significantly increases response rates. There are also improvements in survival and the chance of cure. Without antiviral prophylaxis, treatment of HBsAg-(+) lymphoma with CHOP chemotherapy alone is associated with an approximately 50% risk of HBV reactivation.8

Direct hepatotoxicity of chemotherapy agents have been noted, as rituximab and vincristine are associated with hepatocellular injury, cyclophosphamide and doxorubicin with veno-occlusive disease (VOD) and hepatocellular injury, and prednisolone with hepatomegaly (rare association).7 This patient might have direct hepatotoxicity of chemotherapy also due to its regimens.

We did not have data on the HBV-DNA levels of this patient due to financial reason. Currently, no uniform diagnostic criteria are available for HBV reactivation. It has been defined as an increase of HBV viral replication in chronic HBV infection.1 HBV reactivation can be confirmed by an increase in serum HBV DNA level to more than 1 log higher than that of the baseline, an absolute increase exceeding 6 log10 copies/mL, or HBV DNA turning from negative to positive.8

One week after receiving chemotherapy, he developed acute liver failure leading to decompensated liver, with increased of transaminase level and progressive hyperbilirubinemia. His condition deteriorated despite best supportive care, assuming fulminant hepatitis due to reactivation of HBV and later on he died ever after antiviral treatment.

Pathogenesis of HBV reactivation remains unclear but it has been known that HBV is non-cytopathic; therefore, its clinical condition depends on viral immune response through cytolytic process. Any use of chemotherapy and strong immunosuppression agent will lead to suppression of immune response; therefore, viral load will increase and when the agent is stopped, there will be great immune response recovery and massive cytolitic in infected hepatocytes, leading liver failure.10

Lamivudine, a nucleoside analog, is an effective treatment in controlling viral replication and is therefore potentially useful for the treatment of HBV reactivation. Preemptive anti-HBV therapy should be given to all at-risk patients, and the benefit of this approach has been clearly shown for HBsAg-positive patients receiving chemotherapy or HSC transplants.10

At this time, it remains uncertain whether any of these newer agents should be routinely used instead of lamivudine as first-line preemptive anti-HBV treatment or be reserved for second-line therapy. Further clinical trials would be useful to define their precise roles. Other newer nucleoside analogues, such as adefovir, entecavir, telbivudine, and tenofovir, have a different drug resistance profile. Adefovir gives a low incidence of drug resistance and is active against lamivudine-resistant HBV infection.11

The optimal duration of anti-HBV treatment remains uncertain. Preemptive treatment should be given for about 2 weeks before receiving chemotherapy and needs to be continued for at least 3 months (range 3-12 months) after the cessation of chemotherapy. For patients receiving conventional chemotherapy, lamivudine therapy until 6 months after cessation of chemotherapy has been recommended. A longer duration of lamivudine of 12 months or longer may be necessary for patients receiving monoclonal antibodies (rituximab or alemtuzumab), or HSC transplants because of the late immune-recovery of these patients. In addition, patients with high baseline HBV DNA before chemotherapy may also need more prolonged lamivudine. Late HBV reactivation has been observed as the results of
Despite lamivudine, the mortality rate of HBV reactivation remains high. This is possibly due to the delay in starting lamivudine while the hepatic viral load is already high and massive immune-mediated hepatic damage had already occurred.

Initial screening is based on serological tests for anti-HBc antibodies, HBsAg and anti-HBs antibodies. There are some algorithms published, for example as seen in Figure 2.

Prognostic of HBV reactivation related to chemotherapy is poor and related to long-term declining of liver function. Extended anti-HBV prophylaxis can improve survival rate by 2.4% in HBsAg-positive patients, if 1,000 HBsAg-positive lymphoma patients receive prophylaxis, one will die from hepatitis B virus reactivation versus 25/1,000 if no prophylaxis is administered. Survival rate of patients with antiviral treatment undergoing MARS or liver transplantation is variable individually but most reports show better prognosis for early antiviral treatment.

CONCLUSION

HBV reactivation is a serious but preventable complication of immunosuppression. At-risk patients must be identified promptly and surveillance for HBV status should be an integral part of the care of the haematology patient. Preemptive anti-HBV therapy should be given to all at-risk patients. By implementing good medical practice, virtually all patients could be prevented from reactivating HBV, in view of the potentially serious consequences which lead to high mortality rate.

REFERENCES


Figure 2. Guidelines for prevention of hepatitis B virus reactivation in haemato-oncologic patients: patients management according to status of hepatitis B virus markers.


