

HBV Chronic Hepatitis during Chemotherapy - an Immune Controlled Disease

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Introduction

Infection with hepatitis B virus (HBV) remains one of the major causes of acute and chronic liver disease. According to WHO statistics, there are between 350 and 400 million people chronically infected with HBV worldwide [1].

Re-emergence of HBV infection means the return of the active necro-inflammatory liver disease in a known inactive HBsAg carrier or in a person with cured HBV acute infection [2]. The restart of viral activity is confirmed by the increase in serum HBV DNA levels, which marks the transition from the inactive HBsAg carrier (with low or undetectable viral load) phase, to active viral multiplication phase, described sometimes by HBeAg reversion associated with antiHBe antibodies clearance and even the presence of antiHBc IgM antibodies. HBV re-emergence might take place during immunosuppressive treatment or immediately after, with an increased risk of occurrence at its start or end [3].

Considering that cancer is a disease more and more frequently diagnosed in daily medical practice and that it has an aggressive treatment, immunosuppressive and cytotoxic, it is imperative to know that all patients with detectable HBsAg or cured HBV acute infection have an increased risk of liver disease re-emergence due to chemotherapy.

In most cases, HBV infection re-emergence is followed by an asymptomatic increase in aminotransferase levels, and sometimes by hepatitis with jaundice, hepatic failure or death [1, 2].

The highest re-emergence rate is encountered in patients with detectable HBsAg, blood cell neoplasms (leukemia, lymphoma) and bone marrow transplant (around 70%). The rates are also increased in patients with other neoplasms (breast cancer, liver cell carcinoma), up to 40% [3-7]. The

risk of hepatitis relapse due to immunosuppressive treatment in patients with non-detectable HBsAg and detectable antiHBc antibodies is by far lower (3.3%) as compared with patients with detectable HBsAg [8, 9].

Nevertheless, the re-emergence risk is not entirely known, as patients on chemotherapy and immunosuppressive treatment are not usually tested for HBV infection; therefore, the prophylactic antiviral treatment is underused, resulting in an increased hepatic morbidity and mortality.

Pathogenesis

Defining the four phases of the natural history of chronic HBV infection: immune tolerance phase, immune clearance phase, inactive HBsAg carrier state and re-emergence phase [10] has led to a better understanding of mechanisms explaining the re-emergence of HBV infection due to immunosuppressive and cytotoxic treatment.

Hepatitis B virus has a DNA embedded in the host cell genome, where it is converted to a stable form of covalently closed circular DNA (cccDNA), used to transcribe messenger and pregenome RNA. This cccDNA can be found in 5 to 50 copies/ hepatocyte and represents the most enduring site to the antiviral treatment and the host immunological response [10, 11]. This way, the virus remains within the liver for decades at low levels despite of undetectable serum HBV DNA and the presence of antiHBs antibodies. We can say that the notion of “cure” does not imply viral clearance but only immunological control.

The re-emergence of chronic HBV infection due to immunosuppressive and cytotoxic treatment requires alteration of the existing balance between the host's immunological response and viral replication [1, 10, 12].

Secondary liver injury after HBV re-emergence is a two-step process.

1. At first, during chemotherapy, the viral replication amplifies, with an increase in DNA polymerase activity, increase of serum HBV DNA and antiHBe antibodies levels, the reappearance of HBsAg and decrease of antiHBs antibodies level, resulting in liver infection spreading.

2. During the immunological reconstruction following

Received: 15.07.2008 Accepted: 10.09.2008

J Gastrointest Liver Dis

December 2008 Vol.17 No 4, 445-449

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the end of cytotoxic treatment, there is a massive and rapid destruction of infected hepatocytes, immune mediated, clinically manifested by aminotransferase level increase and hepatitis, liver failure and death [1, 12].

The severity of viral replication during the immunosuppressive treatment and the degree of liver injury at the end seem to depend on immunosuppressive and cytotoxic treatment efficacy [13].

It has been noted that the HBV re-emergence may also occur during the immunosuppression phase, suggesting a possible role of direct viral cytopathic effect in pathogenesis.

Risk factors

Virtually all HBsAg carriers or subjects with serological markers of cured HBV infection (non-detectable HBsAg, detectable antiHBc antibodies) undergoing an aggressive immunosuppressive and cytotoxic treatment have an increased risk of re-emergence of viral infection with marked consequences on initial disease and survival. Patients with cancer (leukemia, lymphoma, breast cancer, liver cell carcinoma or other solid tumors) are in the high-risk group, together with patients with long term treatment with glucocorticoids or biological therapy such as monoclonal antibodies (infliximab, rituximab).

The risk of viral re-emergence is heterogeneous and is determined by the patient's clinical and biological status, the disease type and the administered therapy [3]. Existing studies did not clearly define the cause of the variability: due to tumor's evolution or due to different chemotherapy regimens [3].

A multivariate risk factors analysis showed that the most significant predictive factor for HBV re-emergence is the HBV DNA level before the start of cytotoxic or immunosuppressive therapy [3]. Even though the viral load is not correlated to the risk of hepatitis during chemotherapy, a high viral load at the start of treatment is predictive for re-emergence of viral infection after the end of the prophylactic antiviral treatment [14].

Other risk factors were identified: positive viral serological markers for HBsAg and HBeAg, male gender, young age, the existence of pre-core mutations before lamivudine treatment, chemotherapy using glucocorticoids, rituximab and highly myelosuppressive cytotoxic regimens (anthracyclins, vincristin) [3] (Table I).

Although most cases of secondary hepatitis after immunosuppressive treatment occur in HBsAg positive patients, there can be cases of hepatitis, acute liver failure and death in HBsAg negative patients but with detectable antiHBc antibodies [3, 15, 16].

The use of glucocorticoids in the chemotherapy regimens for blood cancer increases the risk of re-emergence, most likely due to activation of steroid dependent DNA element responsible for viral transcription and multiplication [3, 17].

In 2003, in a prospective study including 50 patients with

Table I. Risk factors for re-emergence of HBV infection

Increased HBV DNA level ($> 10^5$ copies/ml)
Positive HBsAg and HBeAg
Highly active immunosuppressive chemotherapy regimens or therapy including glucocorticoids or rituximab for treating: <ul style="list-style-type: none"> - blood cancer - bone marrow transplant
Male gender
Young age
Pre-core or core promoter HBV mutations

non-Hodgkin lymphoma randomized 1:1 for chemotherapy with or without glucocorticoids (prednisolone), Cheng et al proved that excluding glucocorticoids from treatment significantly decreased the risk of HBV re-emergence from 73% to 38% [18]. Also, it was noticed that despite the reduction of viral infection re-emergence risk in the glucocorticoids free treatment group, the overall survival at 46 months was only 36% compared to 68% in the prednisolone treated group [18].

The introduction of new biological therapies with monoclonal antibodies (infliximab, rituximab) had an interesting impact on patients with chronic infections with HBV or cured acute HBV infection; the increase of HBV infection re-emergence risk in patients with such therapeutic regimens was clearly proven [3].

In 2004, the FDA acknowledged the association between rituximab and acute liver failure secondary to HBV infection re-emergence [3]. The clinical impact is severe, since the number of approved indications for this type of biological therapy increased significantly in the last decade. Most of the patients receiving rituximab are often undergoing chemotherapy based on glucocorticoids; therefore, a direct relationship and a relative risk of rituximab treatment for HBV infection re-emergence cannot be clearly proven at this moment [19, 20].

Symptoms and signs

This type of hepatitis has various forms, ranging from asymptomatic to liver failure and death. Severely affected patients may develop jaundice, ascites or hepatic encephalopathy [1]. The incidence of these symptoms varies in different studies: in one prospective study, half of the patients with hepatitis secondary to HBV re-emergence had jaundice and the incidence of ascites and hepatic encephalopathy was 7% and 4% in HBsAg positive and HBsAg negative patients, respectively; the mortality from liver causes ranged from 5% to 22% [1, 16].

Management of patients with high-risk of HBV re-emergence

The primary objective of prophylactic antiviral treatment in patients on chemotherapy is the prevention of cytolysis and symptomatic liver disease. The prophylactic antiviral treatment has other benefits as well: it decreases the risk of severe hepatitis, increases the adherence to the high

dosage chemotherapy, and prevents dose reductions or immunosuppressive therapy discontinuation [8].

The consequences of HBV re-emergence are severe because advanced liver failure frequently compromises the treatment options for the underlying disease, thus creating a vicious circle where liver failure contraindicates chemotherapy. Invariably, this leads to neoplasm progression and decompensation of the underlying disease (leukemia, lymphoma) due to: 1) delay in chemotherapy schedule; 2) changes in the chemotherapy regimen, and 3) adjustment of chemotherapy dosage

There is a widely accepted consensus that the ideal solution for these patients is an antiviral prophylactic treatment, mostly with lamivudine (considering the safety profile of this nucleoside, with no myelosuppressive effect in patients already exposed to an immunosuppressive and cytotoxic treatment regimen). Rare complications, including red blood cell aplasia with secondary anemia, have been described in AIDS patients receiving both zidovudine and lamivudine.

Despite the absence of serious adverse effects, there is a downside to prolonging the prophylactic treatment with lamivudine more than 12 months: the selection of resistant viral mutants YMDD (tyrosine-methionine-aspartate-aspartate), with an incidence of 12-20% in the first year [3, 21-23]. Even if lamivudine is the most studied antiviral agent, adefovir, entecavir and telbivudine can also be considered eligible for prophylactic treatment.

The AASLD 2007 practice guidelines recommend lamivudine or telbivudine for treatment under a year, while adefovir or entecavir should be considered if the prophylactic treatment is planned for more than 12 months [2]. Interferon alpha is contraindicated for prophylaxis because of the myelosuppressive effect [2].

Based on reviewing 12 prospective controlled studies including 249 patients undergoing prophylactic treatment, lamivudine was proved to be effective in preventing HBV re-emergence in patients with immunosuppressive or cytotoxic treatment, which had a re-emergence risk of 10.8% compared with 52% in the controls [3].

According to the AASLD guidelines, it is recommended to start the antiviral therapy seven days before the chemotherapy and to continue it for six months after the end of chemotherapy (Fig. 1) [3, 14].

Patients with high risk of resistance to lamivudine (previously treated patients, prophylactic treatment more than one year) should receive an antiviral agent with low risk of resistance.

The lamivudine resistance monitoring can be performed by measuring ALT and HBV DNA serum levels every three months; an increase of HBV DNA levels with more than 1 log₁₀ from nadir should be considered a sign of genotype resistance [3]. Studies on lamivudine resistance management showed that replacing lamivudine with, or just adding adefovir dipivoxil once YMDD mutations occur, is safe and efficient and should be preferred to a switch on entecavir, a drug that can promote new viral DNA mutations by crossed

resistance mechanisms [3, 24-27].

An HBV DNA level 1 log₁₀ increase should determine the transition to a combined treatment regimen with adefovir or tenofovir or lamivudine discontinuation and start of a prophylactic treatment with emtricitabine-tenofovir [24, 25].

Regarding the extension of prophylactic treatment more than six months after the end of immunosuppressive treatment, prospective studies showed an increased incidence of re-emergence for this "window", especially in patients with HBV DNA levels higher than 10⁵ copies/ml at baseline.

The prospective study published by Hui et al in 2005 showed an increased incidence of HBV re-emergence: 23.9% for an average duration of 26 months after chemotherapy and 23 months after the end of lamivudine treatment [28].

The objective of prophylactic antiviral treatment is the coverage of the time period characterized by disturbances in the virus-host interaction, and treatment discontinuation when the imbalance induced by immunosuppression ends.

There are controversies in the literature on the antiviral treatment benefits in HBsAg negative patients with detectable antiHBc antibodies, with or without detectable antiHBs antibodies.

Patients developing de novo hepatitis, due to apparently cured infection re-emergence during a cytotoxic-immunosuppressive treatment, usually have a 100-fold increase in HBV DNA levels before the HBsAg seroconversion [29]. The mean duration of time before hepatic cytolysis is 18.5 weeks from the increase in viral replication. This delay can be explained by a late recovery of the immune system caused by the prolonged immunosuppressive effect of some chemotherapy agents [13, 29].

Current recommendations are that negative HBsAg, positive antiHBc antibodies patients should be frequently monitored (HBV DNA levels every other 4 weeks) to detect the increase in viral replication as soon as possible. Since the risk of de novo hepatitis is the same as in patients without antiviral treatment if prophylaxis starts after the HBsAg seroconversion, the antiviral treatment must be started right after the increase of the viral load [29]. The monitoring period should be 6-8 months after the completion of chemotherapy, especially for treatment regimens including rituximab [29].

De novo hepatitis often leads to severe liver dysfunction and it is associated with the risk of fulminant hepatic failure [29]. The liver decompensation and death rate caused by HBV infection re-emergence varies between 5 and 40% in HBsAg carriers undergoing chemotherapy [30]. Preventing the HBV re-emergence can improve the outcome of chemotherapy in patients with cancer and chronic HBV infection [30].

Conclusion

The issue of chronic HBV hepatitis in patients receiving immunosuppressive treatment is insufficiently known and

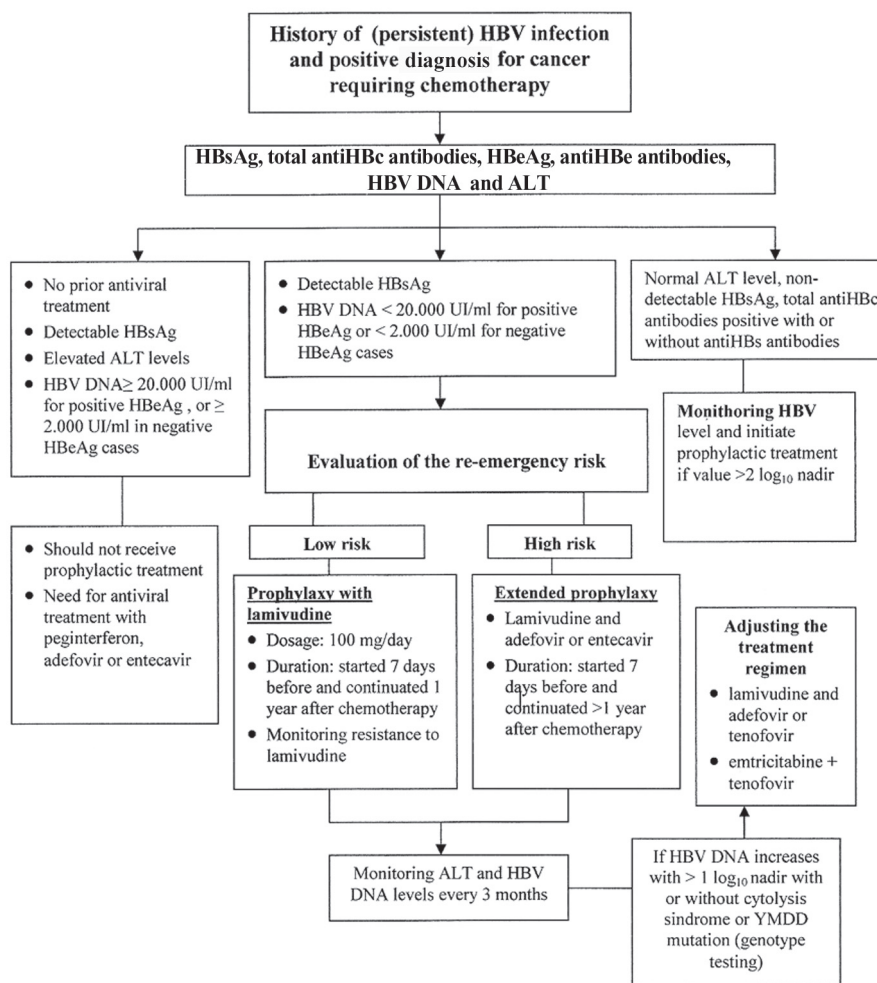


Fig 1. Management of HBsAg carriers to receive immunosuppressive or cytotoxic treatment [3].

applied in current clinical practice. Any (especially blood) cancer patient undergoing chemotherapy should be tested for hepatic serological viral markers (HBsAg and total antiHBc antibodies). If HBsAg is detectable, further tests should be performed for HBeAg, antiHBe antibodies and viral load and, depending on the every patient's risk profile, prophylactic antiviral treatment should be initiated.

An inappropriate approach seems to be the waiting for the patient to develop hepatitis due to the HBV infection re-emergence: despite of antiviral treatment after the occurrence of hepatitis, with or without symptoms, patients are still at risk to develop hepatic failure or die.

Since HBV hepatitis re-emergence was also noticed in other immunosuppressive treatments (glucocorticoids with immunosuppressive dosage for autoimmune diseases; infliximab in Crohn's disease) it is recommended to extend HBsAg and antiHBc antibodies screening to other categories of patients.

Conflicts of interest

Nothing to declare.

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