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# Hepatitis B and cancer: A practical guide for the oncologist

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ABSTRACT

Hepatitis B virus (HBV) infection is a worldwide disease associated with significant morbidity and mortality and after acute infection, HBV infection can persist in about 1-2% of immunocompetent hosts. Chemotherapy-induced immunosuppression can lead to HBV reactivation and may cause discontinuation of anticancer treatment, fulminant hepatitis with liver failure and death. During immunosuppressive treatments such as chemotherapy, reactivation of HBV infection is a life-threatening complication that can occur in HBV active or inactive carriers but also in patients with OBI. Occult HBV infection (OBI) is defined as the presence of detectable very low levels of HBV DNA in HBsAg-negative patients. Many literature data showed a benefit from prophylactic antiviral treatment in cancer patients at risk for HBV reactivation, however there is no evidence in determining the benefit of routine screening for chronic HBV infection in all patients undergoing cytotoxic and immunosuppressive chemotherapy. Major guidelines recommend HBV screening in HBV-infection high risk patients or if the immunosuppression caused by the treatment is expected to be high.



## 1. Hepatitis B and cancer: numbers and burden of disease

Hepatitis B virus (HBV) infection is a worldwide problem associated with significant morbidity and mortality. It has been estimated that two billion people have had hepatitis B virus exposure and near 400 million have experienced chronic infection (Sagnelli et al., 2012). After acute hepatitis, HBV infection persists in about 1–2% of immunocompetent hosts and in higher percentage of immunosuppressed patients (Lavanchy, 2005).

The chronic infection increases the risk of developing cirrhosis and hepatocellular carcinoma up to 40% (McQuillan et al., 1999; De Jongh et al., 1992). Moreover, HBV-carrier patients could present, during their course of life, other malignancies unrelated to hepatitis viruses for which chemotherapy treatment is indicated. Furthermore, chemotherapy-induced immunosuppression can lead to HBV reactivation and may cause hepatitis and liver failure, discontinuation of anticancer treatment and death.

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Malignant cancer is a worldwide disease and in developed countries one in three people will develop cancer during their lifetimes (Torre et al., 2015).

In cancer patients, over the last decades, chemotherapy has demonstrated a significant role in achieving cancer recovery and prolonging survival. The HBV reactivation during anticancer treatment can results in life-threatening events and in poor outcome due to early discontinuation of chemotherapy.

In clinical practice, the oncologists deal with a large number of patients undergoing anticancer treatments and with the uncertainties about screening and prophylaxis against HBV.

The aim of this review is to provide a practical and concise guide for the medical oncologist about diagnosis, definitions, screening and management of HBV infection in cancer patients.

## 2. Hepatitis B infection: several ways to wear a mask

The pathogenesis and clinical manifestations of hepatitis B infection are due to the interaction between the virus replication and the host's immune system response, especially lymphocyte lineage. The immunologic reaction causes liver injury and, if impaired or tolerant, can result in chronic hepatitis (Jung et al., 1994; Chisari, 1997). Five stages can be identified in the viral life cycle of HBV (Torres and Davila, 2012; Hoofnagle, 2009).

- The immune tolerance stage represents the incubation period. The virus replicates without a deep activation of immune system, often with normal levels of serum alanine aminotransferase (ALT).
- The immune active stage is an inflammatory reaction with hepatocyte necrosis. In patients with acute infection the duration of this stage is approximately one month and is accompanied by a variety of symptoms. In chronic infections this phase can last over ten years before onset of cirrhosis, immune clearance phase taking place or hepatocellular carcinoma development.
- The inactive chronic infection consists in low or non-measurable viral replication and serum ALT levels within the normal range. During this phase the integration of viral genome into hepatocyte genetic code could take place.
- Chronic disease can result from the inactive chronic infection phase or from immune active stage.
- Recovery is the disease stage in which virus can not be detected in the blood and antibodies to viral antigens are produced.

HBV infection is associated with characteristic changes in the serum levels of hepatitis B antigens and antibodies and these markers are useful to define different clinical stages of disease (Figs. 1 and 2).

Hepatitis B surface antigen (HBsAg) is the serologic hallmark of HBV infection; it appears in serum during the incubation period, after 1–10 weeks the acute exposure to HBV and prior to the onset of hepatitic symptoms or elevation of serum ALT. In patients who recovered from the infection, HBsAg is undetectable after a period of four to six months. On the other hand, the persistence of the marker for more than six months reveals a chronic infection.

The disappearance of HBsAg is followed by the appearance of hepatitis B surface antibodies (anti-HBs). In most patients, anti-HBs confer long-term immunity and often a lifelong one. In some cases, there is a window period of several weeks during which neither HBsAg nor anti-HBs can be detected in the serum. On the other hand, in 24% of HBsAg positive patients, HBsAg and anti-HBs can coexist but these antibodies are unable to neutralize the circulating viruses (Tsang et al., 1986).

Hepatitis B core antigen (HBcAg) is not detectable in the serum because is an intracellular antigen of infected hepatocytes.

Hepatitis B core antibodies (anti-HBc) appear at the onset of symptoms in acute infection and may persist lifelong. The presence of anti-HBc suggests previous or ongoing HBV infection: during the acute phase anti-HBc are predominantly of IgM class and, notably, IgM anti-HBc are the markers of HBV infection during the window period cited above. IgM anti-HBc may be detectable after the recovery from acute infection for a period up to two years and they increase during exacerbations of chronic hepatitis B (Maruyama et al., 1994). IgG anti-HBc persist in association with anti-HBs in patients who recovered from acute hepatitis B and they also persist along with HBsAg in those who develop chronic HBV infection.

Hepatitis B e antigen (HBeAg) is a secretory protein generally considered a marker of HBV replication and infectivity. The presence of HBeAg is usually associated with high levels of HBV DNA in the serum and higher rates of HBV transmission. In patients with acute infection the seroconversion from HBeAg to hepatitis B e antibodies (anti-HBe) occurs early, prior to HBsAg to anti-HBs seroconversion; however, HBeAg seroconversion may be postponed for many years in patients with chronic HBV infection, often revealing active liver disease and high serum levels of HBV DNA. The seroconversion from HBeAg to anti-HBe is usually related with a decrease in serum HBV DNA and often with a remission of liver disease (Hoofnagle et al., 1981; Realdi et al., 1980).

When patients recover from acute hepatitis, serum levels of HBV DNA disappear when determined by hybridization or bDNA assays, but they could remain detectable if tested by PCR assays (Carman et al., 1989). This fact suggests that HBV, even if a patient recovers from infection, may persist in the host controlled by the immune system. HBV DNA is a major instrument for the assessment of viral replication that is in turn the principle criteria influencing the clinical decision about the timing of antiviral therapy and response evaluation to treatment.

## 3. How many types of hepatitis are there? Navigating a sea of definitions

*Chronic hepatitis B*: Chronic necroinflammatory disease of the liver caused by HBV persistent infection. Serological marker of chronic infection is HBsAg persisting more than six months; moreover, it can be divided in HBeAg-positive and negative forms.

*Active HBsAg carrier*: A patient presenting HBsAg in serum is considered HBV active carrier in the presence of HBeAg or anti-HBe and HBV DNA >20000 UI/mL.

*Inactive HBsAg carrier*: A patient presenting HBsAg in serum is considered HBV inactive carriers if HBeAg is absent, anti-HBe present and HBV DNA <20000 UI/mL.

*Occult HBV carrier*: HBsAg-negative patient presenting HBV DNA in the liver, with undetectable or very low (<200 UI/mL) HBV DNA in the serum.

*Resolved hepatitis B*: Previous HBV infection without virological, biochemical, or histological evidence of virus infection.

*Window period*: Time between the disappearance of HBsAg and the appearance of anti-HBs. It takes place in several weeks or months and the serological diagnosis can be made by the detection of anti-HBc IgM.

*Acute exacerbation or flare of hepatitis B*: An abrupt increase in serum aminotransferase levels with or without symptoms of hepatitis in a patient with underlying chronic liver disease.

*Reactivation of hepatitis B*: Reappearance of necroinflammatory disease of the liver in an inactive HBsAg carrier or in a patient with a resolved hepatitis B. In occult infection, the conversion of serum HBV DNA test from negative to positive or the reappearance of HBsAg are signs of reactivation.

*HBeAg clearance*: Disappearance of HBeAg serum levels in a previously HBeAg-positive patient.

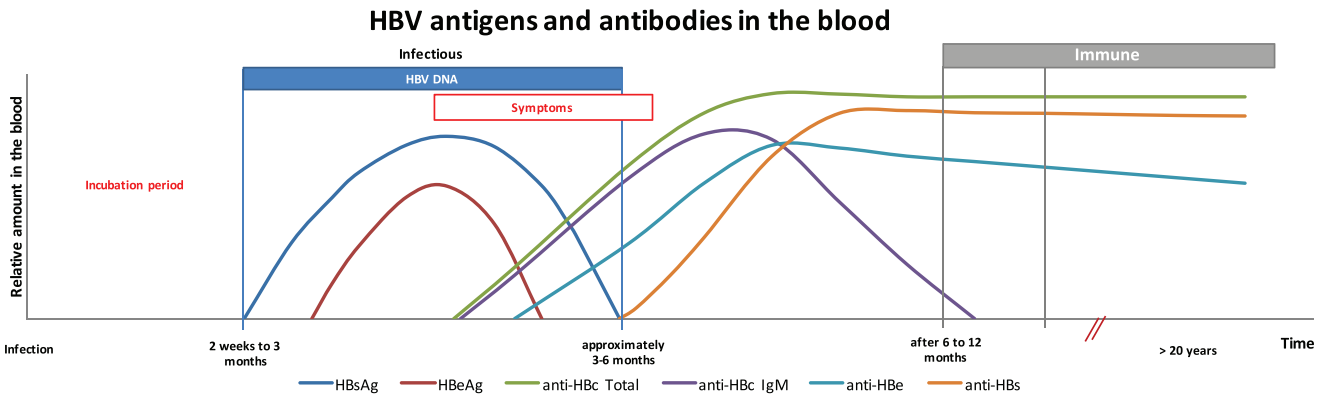


**Fig. 1.** Antigens and antibodies profile in acute HBV infection.

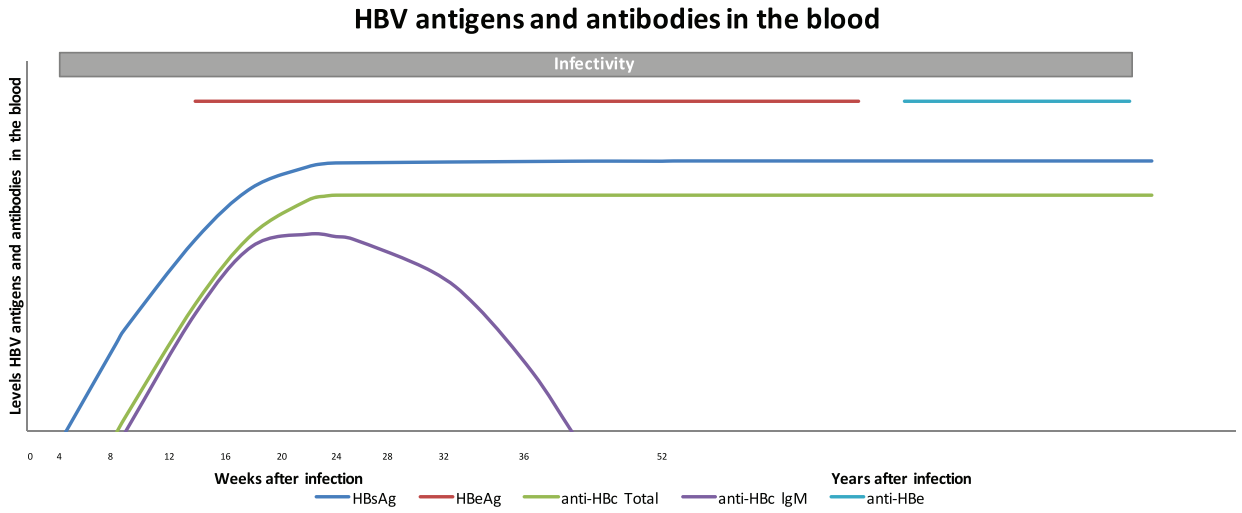


**Fig. 2.** Antigens and antibodies profile in chronic HBV infection.

*HBeAg seroconversion*: Disappearance of HBeAg serum levels and appearance of anti-HBe.

## 4. HBV serology: unravelling the puzzle

Serologic tests for HBV antigens and antibodies are useful in confirming the diagnosis of HBV infection, in selecting patients for antiviral treatment and in the evaluation of the response to treatment. The following table shows the interpretation of serological tests for HBV (Table 1).

The diagnosis of acute hepatitis is characterized by the serum detection of HBsAg and anti-HBc IgM; in the initial phase of infection, HBeAg and HBV DNA are also present. Recovery phase is accompanied by the disappearance of HBV DNA, the seroconversion from HBeAg to anti-HBe and subsequently from HBsAg to anti-HBs.

When HBsAg-positive acute hepatitis is suspected clinicians have to consider potential differential diagnosis such as acute hepatitis B, exacerbations of chronic hepatitis B, reactivation of occult hepatitis B, superinfection of a HBV carrier with other hepatitis viruses (Chu et al., 1989) and acute exotoxic hepatitis in a HBV carrier.

Previous HBV infection is characterized by the presence of anti-HBs and antiHBc IgG. Acquired immunity due to vaccination is indicated by the presence of the only anti-HBs.

The diagnosis of chronic HBV infection is based upon the persistence of HBsAg for more than six months. The inactive carrier state is characterized by normal ALT levels, absence of HBeAg, presence of anti-HBe, and HBV DNA levels <2000 UI/mL. Active carrier state is determined by high viral load (>20000 UI/mL), whereas HBeAg could be present or absent with anti-HBe positivity (Marcellin et al., 1990).

Occult HBV infection (OBI) is defined as the presence of detectable very low levels of HBV DNA in HBsAg-negative patients. OBI may be observed in the window period during acute HBV infection, in the absence of HBsAg and anti-HBs (isolated anti-HBc), or in others conditions linked to immunodepression, such as HIV and HCV infection or pharmacological immunosuppression (Sagnelli et al., 2014).

The isolated serological presence of anti-HBc in the absence of HBsAg and anti-HBs has been reported in less than 2% of healthy volunteers in low HBV prevalence areas and up to 20% of endemic areas population (Lok et al., 1988). This serological condition can occur in three different situations:

- during the window period of acute hepatitis B
- after recovery from acute hepatitis B when anti-HBs has fallen to undetectable levels
- after many years of chronic HBV infection when HBsAg may be undetectable because the loss of HBsAg. This finding occurs in 0.5% of chronic hepatitis B patients per year.

The clinical significance of isolated anti-HBc is unclear, therefore clinicians should repeat serologic testing for HBsAg, anti-HBs, anti-HBc, anti-HBe. If these tests are negative, anti-HBc IgM should be

**Table 1**
Interpretation of HBV serology.

| | HBsAg | Anti-HBc | Anti-HBs | IgM anti-HBc |
|---|---|---|---|---|
| Susceptible patient | Negative | Negative | Negative | – |
| Previously infected patient | Negative | Positive | Positive | – |
| Vaccinated patient | Negative | Negative | Positive | – |
| Acute hepatitis | Positive | Positive | Negative | Positive |
| Chronic patient | Positive | Positive | Negative | Negative |
| Unclear interpretation | Negative | Positive | Negative | – |

tested to rule out window period of acute infection. The detection of anti-HBc could be also a false positive finding. In this case HBV DNA determination could be considered in order to find chronic infection with low viral load.

## 5. HBV reactivation during chemotherapy: clouds on the horizon

During immunosuppressive treatments such as chemotherapy, reactivation of HBV infection is a life-threatening complication that can occur in HBV active or inactive carriers and in patients with OBI.

In fact, after exposition to HBV the virus can persist in the body even after serological recovery from acute hepatitis. HBsAg-positive patients receiving chemotherapy have a higher risk of reactivation that range approximately from 20 to 50% (Yeo et al., 2004a; Hsu et al., 2014).

Reactivation of HBV infection was first described referring to treatments of hematological disease, such as anti-CD20 monoclonal antibodies (Seto et al., 2014), CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) (Hsu et al., 2014) or fludarabine (Dominguez et al., 2015).

Nevertheless, an increasing number of cases have been described among patients treated with chemotherapy for solid tumors giving evidence of HBV reactivation in these cases.

In particular, patients undergoing chemotherapy for breast cancer have higher rate of HBV reactivation (41–56%) than other cancer patients (14–21%) (Liu et al., 2015; Yeo et al., 2003). In addition, more patients with reactivation undergo permanent discontinuation or delay of treatment (76%) compared with those without evidence of reactivation (33%) (Yeo et al., 2003).

HBV reactivation is characterized by an important early enhancement of viral replication after the start of chemotherapy with spread of HBV to hepatocytes and rising serum HBV DNA levels. These modifications can occur up to three weeks earlier than laboratory alterations and can be accompanied by serological reappearance of HBeAg and HBsAg (seroreversion). In a subsequent phase, after chemotherapy withdrawal, the immunological function is restored leading to cytotoxic-T-cells mediated destruction of HBV infected hepatocytes. This results in increasing ALT levels (hepatic flare) and may cause several clinical manifestations that can range from asymptomatic self-limiting hepatitis to fulminant hepatic failure or even death. During this phase, HBV DNA levels may decrease.

There is not a defined consensus about the definition of HBV flare. Frequently, it is described an increase in serum ALT higher than 5 times the upper limit of normal or more than 3 times the baseline value, whichever was higher (Perrillo et al., 2015; Lok et al., 1987).

Because of severe hepatic flares may be characterized by increased anti-HBc IgM, the risk of misdiagnosis of acute hepatitis B in unknown HBsAg positive-patient is relevant. Clinical history, higher titers of anti-HBc IgM and a lower viral load can help the clinician in differential diagnosis between acute hepatitis B and a flare of chronic infection.

Moreover, also other factors such as drugs, superinfections with other hepatitis viruses, tumor infiltration and systemic infections can cause an increase of ALT levels and should be considered in the clinical decision-making.

In the third stage of reactivation, liver injury is recovered and virus markers normalize.

The risk of HBV reactivation in cancer patients receiving chemotherapy is influenced by predisposing factors related to the virus, the host and specific immunosuppressive treatment, although the complete magnitude of risk is unknown.

Viral factors are represented by HBsAg and HBeAg seropositivity, the presence of B genotype of the virus and above all by a high HBV DNA level (>$10^5$ copies/mL); host predisposing factors are male sex, young age, high ALT serum levels at baseline and absence or decrease of anti-HBs levels during the anticancer treatment (Yeo et al., 2003; Lau et al., 2002; Yeo et al., 2004b).

The type of chemotherapy and the concomitant use of glucocorticoids are other risk factors; notably, the use of anthracyclines, cyclophosphamide and vinca alkaloids is associated with an increased risk of reactivation (Yeo et al., 2004b). In particular, epirubicin seems to upregulate the in vitro HBV replication levels and the pathological effects of HBV (Xu et al., 2014). It follows that the chemotherapy combination AC (doxorubicin-cyclophosphamide) in the adjuvant setting of breast cancer is one of the most predisposing therapeutic regimen for HBV reactivation.

The association with HBV reactivation is reported also for gemcitabine (Cheong et al., 2003) and everolimus, one of the targeted therapies approved for breast cancer treatment (Sezgin et al., 2013).

## 6. Prophylaxis and treatment of HBV reactivation: the state of the art

For managing a possible HBV reactivation during chemotherapy, the clinician could adopt two different strategies: to employ a prophylactic treatment for high risk patients or to prescribe an antiviral therapy when reactivation is detected. However, the second strategy could lead to an early discontinuation of chemotherapy and it does not usually stop liver damage caused by viral reactivation (Yun et al., 2011; Yeo et al., 2004c).

Lamivudine, an oral nucleoside reverse transcriptase inhibitor, is indicated in treatment of chronic hepatitis B associated with evidence of viral replication and active liver inflammation.

Many literature data showed a benefit from prophylactic antiviral treatment in cancer patients at risk for HBV reactivation (Hsu et al., 2014; Leaw et al., 2004; Martyak et al., 2008; Loomba et al., 2008). Most of the studies were limited on preventive use of lamivudine and based on hematologic patients, however few studies were conducted on patients with solid tumors, especially with breast cancer.

A meta-analysis of 14 studies involving 275 patients undergoing chemotherapy for hematological or solid malignancies found that prophylactic lamivudine reduced the risk of HBV reactivation and the incidence and severity of HBV-related hepatitis by 80–100% (Loomba et al., 2008).

Referring to breast cancer, Sohn et al. (2011) analyzed the efficacy of pre-emptive use of lamivudine in 169 HbsAg positive-patients receiving anthracycline-based adjuvant chemotherapy. They found that prophylactic lamivudine seems to reduce the

severity of hepatic dysfunction and the incidence of hepatitis flare-up during chemotherapy compared with patients receiving therapeutic antiviral treatment at the onset of increasing liver enzymes.

A more recent metanalysis (Liu et al., 2015) regarding HBsAg-positive breast cancer patients demonstrated that lamivudine prophylaxis had a significant reduction in the risk of HBV reactivation (RR = 0.23, 95% CI: 0.13–0.39, $p < 0.00001$) and the rates of moderate and severe hepatitis were significantly lower than the patients group with no prophylaxis (RR = 0.25, 95% CI: 0.1–0.62, $p < 0.003$; RR = 0.25, 95% CI: 0.1–0.59, $p < 0.0002$). Furthermore, patients in lamivudine-prophylaxis group presented fewer chemotherapy disruptions and delays (RR = 0.36, 95% CI: 0.21–0.64, $p = 0.0004$; RR = 0.42, 95% CI: 0.21–0.82, $p = 0.01$).

There is clinical evidence that reserving the use of lamivudine in patients who develop ALT elevation due to HBV reactivation is not effective compared to prophylactic strategy. This finding can be explained by the biology of viral reactivation: studies suggested that viral replication occurs 1–2 weeks before hepatitis flare (Liaw, 2003; Yeo and Johnson, 2006; Yeo et al., 2001; Lau et al., 2003; Kohrt et al., 2006), so the prophylactic use of lamivudine have a clinical stronger rational than therapeutic strategy. In these patients, despite use of lamivudine, the reported mortality is in the range of 20–30% (De la Revilla et al., 2013).

During chemotherapy, when hepatitis B flare is detected, antiviral treatment should be started as soon as possible because the effects of antiviral therapy are not immediate on the liver damage.

An important concern related to the use of lamivudine is the potential development of lamivudine-resistance mutation (YMDD-mutations), related to high HBV DNA levels (Torres and Davila, 2012) at baseline and associated with clinical and biochemical flare (Tan et al., 2015). Because of this resistance, lamivudine could be ineffective to prevent HBV reactivation and hepatitis, so that it is appropriate to avoid this drug and use other ones in patients who need extended periods of chemotherapy. Indeed, newer antiviral drugs such as entecavir, tenofovir, adefovir and telbivudine are now available. Experts recommended the use of lamivudine or telbivudine if the duration of treatment is no longer than 12 months and HBV DNA levels at baseline are low. On the other hand, entecavir (Watanabe et al., 2010) or tenofovir should replace lamivudine for patients who require longer duration of prophylaxis (more than 12 months) or have higher HBV DNA titers (De la Revilla et al., 2013).

On the basis of recent guidelines (European Association For The Study Of The Liver, 2012), the prophylactic treatment of HBsAg-positive patients depends on HBV- DNA load: if <2000 UI/mL and the patient is going to receive a conventional chemotherapy lamivudine could be prescribed. The prophylactic employment of entecavir or tenofovir should be reserved to hematological patients undergoing stem-cell transplantion or monoclonal antibody therapy and in case of HBV-DNA load >2000 UI/mL.

## 7. Occult HBV infection: the hidden enemy

The prevalence of occult HBV infection (OBI) varies from 1% to 95% worldwide, according to endemicity, cohort factors and sensitivity of diagnostic techniques (Raimondo et al., 2008).

OBI is characterized by the presence of HBV DNA in liver tissue with undetectable or very low (<200 UI/ml) serum levels in HBsAg-negative patients (Kwak and Kim, 2014). We can classify OBI into seropositive (anti-HBc and/or anti-HBs positive) and seronegative (absence of anti-HBc and anti-HBs) group (Squadrito et al., 2014; Coppola et al., 2013; Hu, 2002; Bréchot et al., 1998; Dos et al., 2014; Torbenson and Thomas, 2002; Raimondo et al., 2013).

The extraction of HBV DNA from the liver tissue would be the gold standard for diagnosis of occult HBV infection. However, serum HBV DNA assay is the most commonly used method for diagnosis, because of the better feasibility in routine clinical practice despite serum DNA is sometimes undetectable (Raimondo et al., 2008).

In OBI carriers patients, HBV reactivation represents a relevant clinical implication, particularly in immunosuppressed patients such as cancer ones; OBI reactivation could cause liver failure, leading to chemotherapy discontinuation with consequent progression of the disease, fulminant hepatitis and life-threatening conditions too (Schmeltzer and Sherman, 2010; Coppola et al., 2011). The highest risk of OBI reactivation occurs in hematologic patients, in liver and hematopoietic stem cell transplantation or in anti-CD20-treated patients (Squadrito et al., 2014; Raimondo et al., 2007; Pei et al., 2010). Regarding solid tumors, there are not conclusive studies about HBV reactivation in occult hepatitis, but systemic chemotherapy has been reported as possible cause of OBI reactivation (Raimondo et al., 2007; Saitta et al., 2013). The use of prophylactic treatment in OBI patients is still debated and based on viral serological status, type of cancer and chemoterapic drugs (Sagnelli et al., 2014); actually, the use of antiviral therapy is recommended only for previously-mentioned patients at high risk of reactivation, while it is indicated only ALT and HBV DNA monitoring in the other clinical conditions (Squadrito et al., 2014; European Association For The Study Of The Liver, 2009; Barclay et al., 2008).

Moreover, OBI may be involved in the transmission of infection through blood donations or organ transplantation; this situation may occurs when the donor is an OBI-carrier or when the blood comes from a donor in the window period of acute HBV infection. Moreover, the blood could be infected with variant viruses (so-called S-escape mutants) not detectable by the available diagnostic HBsAg assays (Candotti and Allain, 2009).

Other clinical implication is the possibility of HBV reactivation in OBI-carriers. Finally, occult HBV infection plays a role in the progression of chronic liver diseases and HCC, expecially in HCV patients.

Clinicians should pay attention to the presence of OBI, particularly in immunosuppressed clinical conditions such as cancer patients undergoing chemotherapy. Further studies are needed to clarify clinical implications, preventive measures and the management of occult infections in this category of patients.

## 8. HBV: to screen or not screen

There is no evidence in determining the benefit of routine screening for chronic HBV infection in patient undergoing cytotoxic and immunosuppressive chemotherapy. Major guidelines (Hoofnagle, 2009; De la Revilla et al., 2013; European Association For The Study Of The Liver, 2012; Lok and McMahon, 2009; Artz et al., 2010; Weinbaum et al., 2008) (Table 2) recommend HBV screening in HBV-infection high risk patients or if the immunosuppression caused by the treatment is expected to be high (Table 3). Apart from this general recommendation, the guidelines, given the inaccuracies in ascertaining risks for HBV infection, do not demonstrate unanimous consent in offering HBV screening for all patients undergoing chemotherapy. In fact, if patients receiving chemotherapy are considered at high risk for reactivation of HBV *per se*, the screening strategy should be universal. Furthermore, there is no unanimous consent regarding serological tests: the majority of guidelines recommend screening with HBsAg and anti-HBc, even though the United States Centers of Disease Control and Prevention (CDCP) consider a screening marker also anti-HBs.

In North America and Western Europe the universal screening for HBV infection with HBsAg and anti-HBc in patients with solid tumours is probably not a cost-effective strategy (Day et al., 2011), because of the low prevalence of HBV infection in general pop-

**Table 2**
Principle guidelines recommendations for HBV in cancer patients.

| | Screening | | Prophylaxis | | Other recommendations |
|---|---|---|---|---|---|
| | For whom? | How? | For whom? | How long? | |
| Lok and McMahon (2009) | HBV-High risk patients before chemotherapy or immunosuppressive therapy | HBsAg and antiHBc | HBV carriers ant the onset of cancer chemotherapy or immunosuppressive therapy | For six months after the completion of chemotherapy or immunosuppressive therapy if baseline HBV DNA <2000 UI/mL<br>Patients with HBV DNA baseline value >2000 UI/mL should continue treatment as immunocompetent patients. | If the treatment is expected to be short (<1 year) and basal HBV DNA is low lamivudine and telbivudine can be used<br>If the treatment is expected to be longer than 1 year tenofovir or entecavir are preferred.<br>Avoid Interferon alpha because of the bone marrow suppressive effect. |
| Artz et al. (2010) | Insufficient evidence to determine the benefits and the harms of routine screening in patients undergoing a chemotherapic or immunosuppressive treatment<br>HBV screening requires clinical judgment<br>May be considered in HBV high risk patients or if highly immunosuppressive therapy is planned | HBsAg<br>In some populations, testing for antiHBc should also be considered<br>No evidence to support serologic testing for antiHBs | In HBV chronic patients, an antiviral treatment should be considered to reduce the risk of HBV reactivation, although evidence is limited | – | Screening and/or treating should not delay the initiation of chemotherapy |
| European Association For The Study Of The Liver (2012) | All candidates for chemotherapy and immunosoppressive treatment | HBsAg<br>antiHBc | HBsAg-positive patients should receive pre-emptive antiviral treatment regardless of HBV DNA level<br>HBsAg-negative, antiHBc positive patients with detectable HBV DNA should be treated as HBsAg positive patients<br>HBsAg-negative, antiHBc positive patients with undetectable HBV DNA should be closely monitored | – | If the treatment is expected to be short and basal HBV DNA is low lamivudine and telbivudine can be used<br>If the treatment is expected to be longer and basal HBV DNA tenofovir or entecavir are preferred |
| Hoofnagle (2009) | All patients undergoing cancer chemotherapy and marked immunosuppressive treatments. | HBsAg<br>antiHBc | HBsAg-positive patients should be evaluated for indications for HBV treatment and started on appropriate therapy<br>Inactive HBsAg carrier should receive antiviral prophylaxis<br>HBsAg-negative, antiHBc positive patients with undetectable HBV DNA should be considered for antiviral treatment if aggressive or long term chemotherapy/immunosuppression are expected | In HBsAg-positive patients therapy should continue for as long as required for management of underlying chronic disease<br>In other patients, prophylaxis should continue for at least six months after stopping chemotherapy | – |
| Weinbaum et al. (2008) | All patients needing immunosoppressive treatment should undergo serologic testing | HBsAg<br>antiHBc<br>antiHBs | All patients HBsAg-positive should receive antiviral prophylaxis<br>Patients antiHBc-positive should be closely monitored | – | – |
| De la Revilla et al. (2013) | All candidates for chemotherapy should be screened for before initiation of therapy<br>For people living in areas of low prevalence, it may be sufficient to screen only those patients who belong to high-risk groups for HBV infection | HBsAg<br>antiHBc | All patients HBsAg-positive should receive antiviral prophylaxis<br>HBV DNA positive patients should receive antiviral prophylaxis according to HBV DNA levels, as for HBsAg-positive patients<br>HBsAg-negative, antiHBc-positive with HBV DNA test negative should be closely monitored, but they should be considered for antiviral treatment if aggressive or long term chemotherapy/immunosuppression are expected | Patients with HBV DNA levels > 2000 UI/mL should be treated from one week before initiating chemotherapy until the same endpoints used for immunocompetent patients<br>Patients with undectectable levels or HBV DNA <2000 UI/mL should continue treatment for 12 months after cessation of chemotherapy | If the treatment is expected to be short (<1 year) and basal HBV DNA is low (<2000 UI/mL) lamivudine can be used<br>If the treatment is expected to be longer than 1 year or HBV DNA load is >2000 UI/mL tenofovir or entecavir are preferred. |

**Table 3**
Individuals at high risk for HBV infection.

| People born in these countries at high or intermediate prevalence rates of infection: | | |
|---|---|---|
| Asia | Africa | Eastern Europe |
| South and Central America | The Arctic | European Mediterranean |
| South Pacific Island | Middle East | |
| Other people recommended for screening | | |
| People born in low HBV prevalence countries not vaccinated and whose parents were born in high prevalence region | | |
| Sexual contacts with HBsAg-positive person | | |
| Inmates of prison | | |
| People who have multiple sexual partners | | |
| Patients infected with HCV and HIV | | |
| People that have injected drugs | | |
| Persons needing immunosuppressive treatment | | |

ulation and the expected risk of immunosuppression lower than haematological patients.

Screening strategy may be economically favourable in selected patients and with a more simple serological marker, such as the use of only HBsAg in adjuvant patients but further studies are needed in order to consider this screening approach in clinical practice.

## 9. What about HCV?

Hepatitis C virus (HCV) is one of the most important and frequent cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Prevalence of HCV infections is reported to be higher in haematological malignancies, in particular in patients with a diagnosis of Non-Hodgkin's lymphoma.

In patients with solid cancer, the incidence of HCV-related liver dysfunction is not well established because of limited data from few and retrospective studies (Morrow et al., 2010).

While the knowledge from previous research supports the management of hepatitis B during the treatment of breast cancer, little information are available about treatment of patients with solid cancer and chronic hepatitis C.

We know that there is a close relation about HCV replication and immunosuppressive therapy, such as chemotherapy treatment. Previous studies have shown a high rate of chemotherapy discontinuation and hepatotoxicity in patients with cancer and HCV-related hepatitis because of HCV reactivation due to an increased HCV replication (Mahale et al., 2012).

HCV reactivation seems to be less common than HBV reactivation and is generally associated with a good outcome and less severe medical consequences. Only a few deaths related to HCV reactivation during a chemotherapy treatment have been reported. Despite this report, mortality rates of HCV-infected patients was similar to those of HBV-infected patients when a severe hepatitis due to a viral reactivation developed (Torres and Davila, 2012).

Currently, no direct methods to predict patient's risk of HCV reactivation was point out.

Recommendations from CDCP suggest screening with a baseline anti-HCV test, detecting specific antibodies against HCV (anti-HCV) before starting a chemotherapy treatment (Hwang et al., 2014).

HCV reactivation can be defined as at least a threefold increase in serum ALT level in a patient without liver involvement (liver metastasis or primary tumor), who does not receive hepatotoxicity drugs and have no systemic infections with the exception of HCV (De la Revilla et al., 2013).

The timing of HCV reactivation caused to a chemotherapy drug administration could vary. Acute exacerbation of HCV infection can occur during the cytotoxic treatment but usually it was observed weeks or months after the last drug administration. No clinically symptomatic acute ALT or HCV RNA levels elevation was seen in the most patients with HCV reactivation and usually liver enzymes elevation was mild and transient.

Patients with evidence of HCV infection (anti-HCV positive and/or HCV RNA positive) should be closely monitored for liver enzymes during and after chemotherapy. Monitoring ALT every 1–2 weeks and HCV RNA every 4 weeks during chemotherapy and for at least 3 months after treatment end is recommended. If ALT level increase more than 3 fold from baseline it's necessary to establish a close supervision in HCV RNA levels. If there is at least 1 log IU/mL increase in HCV RNA compared to baseline viral load, it is reasonable to consider discontinuation of chemotherapy if increasing of liver enzymes precludes the use of cytotoxic drugs (De la Revilla et al., 2013) (Fig. 3).

Increasing of liver enzymes should be associated with the increase in HCV RNA levels, but this issue was poorly investigated. Moreover, few studies demonstrated none direct correlation between transaminase elevation and increase HCV-RNA levels during chemotherapy in patients with breast cancer and HCV-related hepatitis. These findings suggest that elevation of liver enzymes could be related to liver toxicity caused to cytotoxic drugs (Miura et al., 2013).

Currently no specific drugs for the prevention of HCV reactivation are available in patients with solid tumors during a chemotherapy treatment and only supportive therapy is considered. The risk of HCV reactivation could be reduced using lower doses of cytotoxic and immunosuppressive drug, close monitoring of liver enzymes and measuring HCV RNA levels early if a potential viral reactivation was supposed.

Anti-HCV therapy is avoided during chemotherapy because it can worsen toxicity caused by cytotoxic drugs, in particular haematological adverse effects.

In a retrospective cohort of patients with an early breast cancer and HCV-related hepatitis, the treatment with anthracyclines with or without taxane and trastuzumab was feasible even through in approximately one-half of patients it was required dose reductions and delays during the therapy. The reason was related to complications or side effects due to treatment and rather due to elevations of transaminases (Morrow et al., 2010).

Data from literature revealed that in patients with solid cancer and HCV infection, the administration of targeted therapy such as anti-HER therapy (trastuzumab, pertuzumab and lapatinib), mTOR inhibitors (everolimus), anti-epidermal growth factor receptor therapies (cetuximab, panitumumab) seemed safe (Yazici et al., 2014).

Despite of poor data, chemotherapy and targeted therapy for patients with a diagnosis of breast cancer and HCV infection appear feasible and safety. Caution regarding neutropenia with or without fever is recommended and the use of growth factors may be considered. Close monitoring of liver function during the treatment is the critical step in the management of these patients.

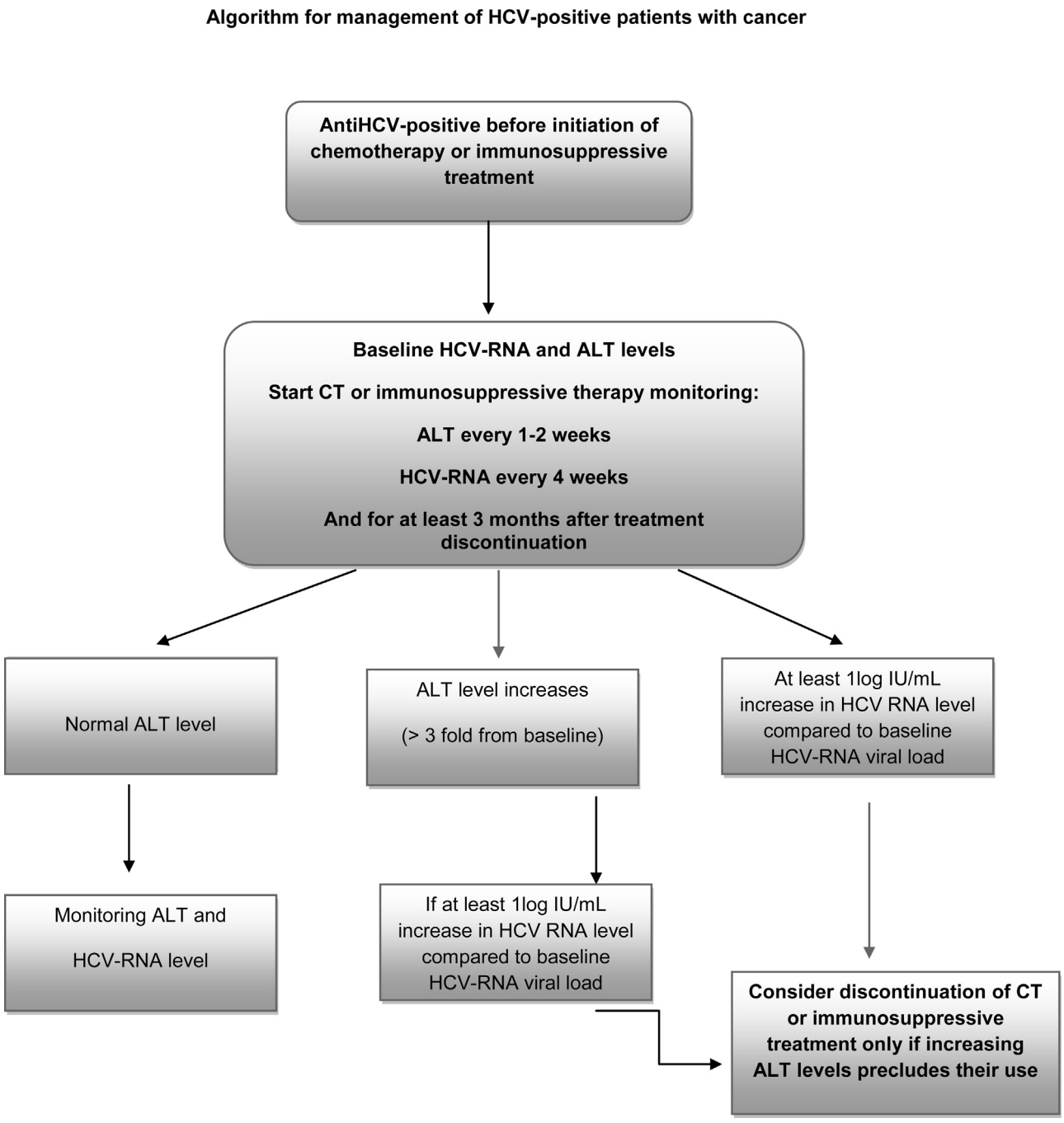


**Fig. 3.** Algorithm for management of HCV-positive patients with cancer.

## 10. Conclusions: take stock of the situation!

During immunosuppressive treatments such as chemotherapy, reactivation of HBV infection is a life-threatening complication that can occur in HBV active or inactive carriers and in patients with OBI. There is a clinical benefit deriving from prophylactic antiviral treatment in cancer patients at risk for HBV reactivation: lamivudine is the drug of choice if DNA viral load is <2000 UI/mL, in other cases tenofovir or entecavir are indicated. On then other side, there is no evidence in determining the benefit of routine screening for chronic HBV infection in patient undergoing cytotoxic and immunosuppressive chemotherapy: the universal screening for HBV infection with HBsAg and anti-HBc in patients with solid tumours is probably not a cost-effective strategy. Underutilization of screening for hepatitis B virus and of prophylaxis for reactivation is frequent in clinical practice, but it can be lead to high rates of hospitalization, discontinuation of chemotherapy, liver failure and death (Hwang et al., 2015). HCV reactivation seems to be less common than HBV reactivation and is generally associated with a good outcome and less severe medical consequences and currently, no direct methods to predict patient's risk of HCV reactivation was point out. No specific drugs for the prevention of HCV reactivation are available.

## Conflict of interest

All authors take full responsibility for the content of the present publication; they confirm that the article reflect their viewpoint and medical experience. The content of the manuscript is not

influenced by any pharma company. Authors did not receive any compensation for authoring the manuscript. No writing assistance was provided.

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