HEPATITIS B VIRUS REACTIVATION DURING CHEMOTHERAPY FOR BREAST CANCER

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Abstract

There are two different matters with worldwide interest but with even a greater impact when associated hepatitis B virus infection and breast cancer. Hepatitis B Virus (HBV) represents o global health matter due to its considerable high morbidity and mortality. Regarding neoplasia, in developed countries, one in three persons will develop at least one malignancy during their lives, with no correlation to HBV infection. Breast cancer represents the malignant pathology most frequently diagnosed, with over one million new cases each year. Today, immunosuppressive therapy such as chemotherapeutic medication represents an essential mean of treatment when fighting against breast malignant tumors. Hepatitis B virus reactivation in active or inactive carriers undergoing chemotherapy for breast cancer is a serious concern when facing its potential complications that vary widely from asymptomatic liver enzymes elevation to hepatic failure and even death. This medical situation is nowadays debated by many specialists. Although many literature data support the administration of prophylactic antiviral treatment to cancer patients at risk for HBV reactivation, the extensive screening in order to detect occult HBV infection patients is questionable. Thus, experts debate nowadays the benefits of routine screening for chronic HBV infection in all women who will undergo immunosuppressive medication for breast cancer. We aim through this article to present the current data concerning the HBV reactivation in patients with breast cancer who undergo chemotherapeutic treatment, to report the advantages of administrating prophylactic antiviral treatment to patients at risk of HBV reactivation, to bring to your attention weather the cost-benefits balance inclines to routine screening in order to detect patients with different phases of HBV infection for a more careful approach as well and further perspective.

This topic is the theme of a doctoral study conducted in Filantropia Clinical Hospital and Matei Balş National Institute of Infectious Diseases.

Rezumat: Reactivarea virusului hepatitic B în timpul chimioterapiei pentru cancer mamar

Există două probleme medicale distincte, de interes global, cu un impact major atunci când se asociază infecţia cu virus hepatitic B şi cancerul de sân. Virusul hepatitic B (VHB) reprezintă o problemă de sănătate publica la nivel mondial din cauza riscurilor crescute de morbiditate şi mortalitate. În ceea ce priveşte patologiile maligne, în ţările dezvoltate, una din trei persoane va dezvolta cel puţin un cancer pe parcursul vieţii, fără nici o corelaţie cu infecţia VHB. Cancerul de sân reprezintă patologia malignă cea mai frecvent diagnosticată, cu mai mult de un milion de cazuri noi diagnosticate în fiecare an. Astăzi, terapia imunosupresivă precum medicaţia chimioterapeutică reprezintă un mijloc de tratament esenţial în lupta împotriva tumorilor de sân maligne. Reactivarea virusului hepatitic B la purtătorii activi sau inactivi care urmează tratament cu citostatice împotriva tumorilor maligne de sân reprezintă o problemă reală şi serioasă atunci când luăm în calcul potenţialele complicaţii care pot varia de la creşterea enzimelor hepatice, neînsoţită de simptomatologie clinică, până la insuficienţă hepatică şi chiar deces. Acest subiect este dezbătut de mulţi specialişti. Deşi datele din literatura de specialitate susţin administrarea tratamentului profilactic cu antivirale la pacienţii cu cancer de sân aflaţi la risc pentru reactivarea VHB, screening-ul extensiv pentru detectarea pacienţilor cu infecţie VHB ocultă este pus sub semnul întrebării. Astfel, experţii dispută în zilele noastre beneficiile screeningului de rutină pentru infecţia cronică cu VHB la toate femeile care vor urma tratament cu medicaiţe imunosupresivă împotriva cancerului de sân. Obiectivele urmărite în acest articol sunt de a prezenta atât noutăţile privind reactivarea VHB la pacienţii cu cancer de sân cărora li se administrează

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chimioterapie, cât şi avantajele administrării tratamentului profilactic cu antivirale la pacienţii cu risc crescut de reactivare a VHB, de a aduce în atenţia dumneavoastră dacă balanţa cost-beneficiu înclină către screeningul de rutină pentru a detecta pacienţii cu infecţie VHB în diferite faze pentru o abordare mai atentă a conduitei, cât şi perspective de viitor.

Acest subiect este tema unui studiu doctoral desfăşurat în Spitalul Clinic Filantropia şi Institutul Naţional de boli infecţioase Matei Balş.

Cuvinte cheie: Cancer de sân, Chimioterapie, Infecţie cu VHB, Reactivare

Hepatitis B infection and breast cancer

Despite being not only preventable but also treatable nowadays, hepatitis B infection is still representing a worldwide concern when taking into consideration the significant complications (including cirrhosis and hepatocellular carcinoma) that raise considerably both morbidity and mortality through society.

The lowest prevalence of VHB infection has been reported to be in developed countries such as North America, Northern and Western Europe and Australia. In these areas, HBV infects a percentage of 5–7% of the population, and only 0.5–2% of the citizens is reported to be chronic carriers [1]. The population at risk is well defined and is represented by young adults exposed to drug injections, homosexual males, people that work in the health care system, patients who require regular blood transfusion or hemodialysis [2].

However, in undeveloped counties, the percentage of population reported to have had serological evidence of VHB infection during lifetime is 70-95%. Moreover, at least 8% of the population is HBV chronic carrier in regions such as South East Asia, China, sub-Saharan Africa and the Amazon Basin [2].

Romania is a highly endemic country when taking about hepatitis B infection; studies report a prevalence of 74.6% regarding chronic VHB infection and 70.5% having a history of previous VHB infection [3].

Serological tests of HBV antigens and antibodies are mandatory for an accurate diagnose, to properly select patients that require treatment and to evaluate the response to the chosen management.

The following table presents the interpretation of serological tests in order to evaluate the clinical phase of HBV infection (Table 1 [4]):

Another major health problem is breast cancer, the most frequent occurring cancer in women.

World Health Organization reported that the incidence rates of breast cancer vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. Moreover, specialists predict that by 2050 the incidence of breast cancer in women will reach almost 3.2 million new cases per year [5].

In Romania, the incidence rate of breast cancer is reported to be 66.2 per 100,000 women [6].

Thus, when talking about Romanian women, it is not uncommon the association between breast cancer and hepatitis B infection.

There are various features regarding breast cancer, some cases are aggressive and some tumors have excellent prognosis. However, when dealing with breast cancer, the management includes most of the times chemotherapy, which although greatly increases the odds of the outcome, it also has side effects. One of the unwanted consequences is the reactivation of the HBV virus in patients with active and inactive carriers and in patients with occult HBV infection. Occult HBV infection refers to HBsAg negative patients with very low or undetectable levels of HBV DNA.

Tabel 1. The interpretation of serological tests to evaluate the clinical phase of HVB infection [4].

	HBs Ag	Anti-HBc	Anti-HBs	IgM anti-HBc
Previously infected patient	-	+	+	
Vaccinated patient	-	-	+	
Active hepatitis	+	+	-	+
Chronic infection	+	+	-	-

Modified after: Bozza C, Cinausero M, Iacono D, Puglisi F. Hepatitis B and cancer: A practical guide for the oncologist. Crit Rev Oncol Hematol. 2016 Feb; 98:137-46 [4].

Table 2. Serological and virological profiles in chronic HVB reactivation [9]

	HBV status at baseline	HBV status at reactivation
HBsAg	+	+
Anti HBe	+	+
HBV DNA	-	+
HBsAg	-	+
Ig G Anti HBc	-	
Anti HBs	+	
HBV DNA	-	+
HBsAg	+	+
HBeAg	-	+
Anti HBe	+	+
HBsAg	-	+
Ig G Anti HBc	+	+
HBV DNA	-	+
HBsAg	-	+
Ig G Anti HBc	+	+
HBV DNA	-	-
HBsAg	-	-
HBV DNA	-	-

Modified after: Philips CA, Sarin SK. Potent antiviral therapy improves survival in acute on chronic liver failure due to hepatitis B virus reactivation. World J Gastroenterol. 2014 Nov 21;20(43):16037-52 [9].

HBV reactivation in breast cancer patients who undergo chemotherapy

Although the first time when immunosuppressive medication such as chemotherapy was observed to have the ability to reactivate HBV infection was when dealing with hematologic diseases, same thing was observed when managing solid tumors. When comparing the rate of HBV reactivation, breast cancer has a higher rate (41-56%) than other cancer patients (14-21%) [7, 8]. Thus, patients will face permanent discontinuation or delay of treatment (76%) leading to inefficient management of the breast pathology [8].

Although the reactivation mechanism of HBV infection starts early in the hepatocytes after the first administration of chemotherapy by raising serum HBV DNA levels, it can take up to three weeks until laboratory tests will come up modified (serological reappearance of HBeAg and HBsAg) (Table 2 [9]), thus leading to abandoning the chemotherapy treatment. Though HBV DNA levels might decrease at this point, the cytotoxic-T-cells mediated destruction of HBV infected hepatic cells will lead to increasing ALT levels (hepatic flare). Hepatic flare it is frequently described as 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 [10, 11] and it can lead to death in severe cases [4].

There are a few predisposing factors incriminated for raising the risk of HBV reactivations when women diagnosed with breast cancer receive chemotherapy. These factors concern not only the virus but also the host and specific immunosuppressive medications. Regarding the virus, the HBsAg and HBeAg seropositive, B genotype of the virus and a high level of HBV DNA level (>105 copies/mL) raise the risk of reactivation. Concerning the host, male patients, young age, high ALT serum levels at baseline and absence or decrease of anti-HBs levels during the anticancer treatment are incriminated to be the predisposing factors [8, 12, 13].

Adding glucocorticoids also raises the risk of HBV reactivation. The following chemotherapeutics are reported to increase the risk of reactivation: anthracyclines, cyclophosphamide and vinca alkaloids [13]. Moreover, chemotherapy combination AC (doxorubicin-cyclophosphamide) in the adjuvant management of breast cancer is reported to be one of the most predisposing therapeutic combinations for HBV reactivation [4]. Also, gemcitabine [14] and everolimus, two of the highest targeted therapies approved for breast cancer treatment are reported to raise the risk of reactivation [15].

Should we administer prophylactic treatment?

When these two global matters face each other, a fine question nurtures between clinicians: should they prevent the reactivation of HBV infection by administrating prophylactic medication such as Lamivudine, or withdraw the chemotherapeutics and try to treat the reactivation if only occurs? Several studies support that the use of Lamivudine as a prophylactic strategy in breast neoplasia has a significant role in reducing the risk of reactivating the VBH infection [7, 16].

However, due to the risk of potential development of lamivudine-resistance-mutation [17], and thankfully to the new antiviral drugs, experts recommend nowadays to use lamivudine or telbivudine as prophylactic strategy if the chemotherapeutic treatment is needed no longer than 12 months and HBV DNA levels are low and administer entecavir and tenofovir if the patient needs longer treatment or has a high HBV DNA titers [18, 19].

Are there real benefits for routine screening for chronic VHB infection?

Another controversy debated by specialists involves the patients with occult VHB infection. Not only affects up to 95% of the global population [20] but the reactivation of VHB infection in these women can sometimes lead to serious clinical consequences including hepatic failure and even death. Specialists question if there are enough benefits in order to support the effort of costs for routine screening for chronic HBV infection in all the patients undergoing

chemotherapeutic treatment for breast cancer in order to see whether to receive prophylactic treatment for reactivation or not. If we were to overcome the costs, how the outcomes would for these women modify and how would their mortality and morbidity improve remains the subject for further research.

Conclusions

The association between HBV infection and breast cancer patients is frequent. The reactivation of HBV infection in active and inactive carriers and also in occult HBV infection patients can lead to serious consequences including death. There is solid evidence that confirm the benefits of administrating antiviral treatment for preventing reactivation of HBV infection in women at risk, with breast neoplasia who will undergo chemotherapy. If there is a real benefit in routine screening for chronic HBV infection is still debatable nowadays. Until then the lamivudine strategy remains the antiviral of choice for patients at risk for reactivation if the chemotherapeutic treatment is needed no longer than 12 months and HBV DNA levels are low. Nevertheless, further research is required concerning how often reactivation truly occurs, if there are benefits of routine screening for occult HBV infection and which regimens involves a high risk of reactivation.

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