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Ciências da Saúde

Serological profile of hepatitis B infection in patients receiving chemotherapy for solid tumors at a cancer referral center in Manaus, northern Brazil

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Abstract

The Amazon Basin has one of the highest prevalences of HBV infection in the world. Reactivation of HBV infection in cancer patients receiving cytotoxic chemotherapy negatively affects the response to the immunosuppressive therapy. A cross-sectional study evaluated patients receiving chemotherapy for solid tumors from March 2013-July 2015. 131 patients were analyzed. Fifty-six (42.7%) patients were positive for at least one HBV marker. Approximately a third of patients in our sample were at an increased risk for viral reactivation during cytotoxic chemotherapy. Thus, we recommend routine screening for HBV infection in all cancer patients from the Amazon region.

Key-words: Viral reactivation, screening, cytotoxic chemotherapy.

Perfil sorológico da infecção pelo vírus da hepatite B em pacientes em tratamento quimioterápico para tumores sólidos em um centro de referência em câncer em Manaus, norte do Brasil. Perfil sorológico da infecção por hepatite B em pacientes recebendo quimioterapia para tumores sólidos em um centro de referência em câncer em Manaus, norte do Brasil. A Bacia Amazônica tem uma das mais altas taxas de prevalência de infecção pelo vírus HBV no mundo. A reativação da infecção pelo HBV em pacientes com câncer recebendo quimioterapia citotóxica afeta negativamente a resposta à terapia imunossupressiva. Um estudo transversal avaliou pacientes recebendo quimioterapia para tumores sólidos de março de 2013 à Julho de 2015. 131 pacientes foram analisados. Cinquenta e seis (42.7%) pacientes foram positivos para, ao menos,

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um marcador de HBV. Aproximadamente um terço dos pacientes da amostra encontrava-se em risco aumentado para reativação viral durante a quimioterapia citotóxica. Portanto, recomendamos triagem de rotina para infecção pelo HBV em todos os pacientes com câncer da região da Amazônia.

Palavras-Chave: Reativação viral, triagem, quimioterapia citotóxica

1. Introduction

Hepatitis B is one of the most common infectious diseases and a major global health problem (CASTILHO *et al.*, 2012; TAUIL *et al.*, 2012, WORLD HEALTH ORGANIZATION, 2017). Infection with hepatitis B virus (HBV) is one of the leading causes of acute and chronic liver disease and may lead to liver cirrhosis and hepatocellular carcinoma (PALMORE *et al.*, 2009; LUDWIG *et al.*, 2015). In 2015, the global prevalence of HBV infection in the general population was 3.5%. Overall, about 257 million persons were living with HBV infection (WORLD HEALTH ORGANIZATION, 2017). The prevalence of HBV infection varies markedly across the world: HBV is highly endemic in Central and Southeast Asia, sub-Saharan Africa, and the Amazon Basin, where at least 8% of the population are chronic HBV carriers, whereas most developed regions such as the United States, Northern Europe, Australia, and parts of South America are low endemicity areas where the prevalence of hepatitis B surface antigen (HBsAg) is less than 2% (LUDWIG *et al.*, 2015; SOUTO, 2015).

According to the Epidemiological Bulletin of Viral Hepatitis of 2017, in Brazil, there were 15,033 deaths from hepatitis B between 2000 and 2017. There are still regions with high prevalence, particularly in the Amazon Basin, where there is also co-infection with the hepatitis D virus, as well as specific groups, such as the homeless in large cities and isolated communities of Afro-descendants in the center of the country (SOUTO, 2015). In 2017, the standardized mortality rate of hepatitis B was highest in the North Region: 0.4 per 100,000. This high mortality rate may be related to the high prevalence of HBV in the Amazon Basin and coinfection with hepatitis D virus (SOUTO, 2015; CASTILHO *et al.*, 2012; TAUIL *et al.*, 2012; BRAGA *et al.*, 2004).

Reactivation of HBV infection in patients receiving cytotoxic chemotherapy has been a subject of debate in the oncology community for some time. HBV reactivation can lead to exacerbation of chronic liver disease with accelerated loss of liver function and increased risk of liver failure (HWANG *et al.*, 2012; HUANG; LIN; LEE, 2012; BOZZA *et al.*, 2016; SANAGAWA *et al.*, 2015).

It is well accepted that HBV reactivation induced by chemotherapy is caused by a disruption in the ability of

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the host immune system to control viral replication (PALMORE *et al.*, 2009; BOZZA *et al.*, 2016).

The use of cytotoxic therapies may suppress normal immune function, resulting in a sudden increase in HBV DNA level, an indicator of virus that remained latent in the nucleus of infected hepatocytes (PALMORE *et al.*, 2009; HWANG *et al.*, 2012; BOZZA *et al.*, 2016).

The main identified risk factors for HBV reactivation include lymphoma development, breast cancer development, male gender, young age, previous HBV infection, certain cytotoxic drugs, and elevated HBV DNA titers (HUANG; LIN; LEE, 2012; SANAGAWA *et al.*, 2015). HBV reactivation may also occur in HBsAg carriers, negative HBsAg patients with resolved infection, and in patients positive for hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti-HBc) (HWANG *et al.*, 2012; HUANG; LIN; LEE, 2012).

Considering the high endemicity of HBV infection in the state of Amazonas, northern Brazil (CASTILHO *et al.*, 2012; SOUTO, 2015) and that cancer patients in the region are at an increased risk of HBV exposure, in this study we aimed to describe the serological profile of HBV infection in patients receiving chemotherapy for solid tumors at a public cancer referral center in the state capital, Manaus.

2. Materials and methods

This is a cross-sectional study that evaluated patients receiving chemotherapy for solid tumors from March 2013 to July 2015. The study was approved by the Ethics Committee for Research at Fundação Centro e Controle de Oncologia do Estado do Amazonas (FCECON), Manaus, Brazil (CAAE: 09741012.2.0000.0004).

Patients receiving cytotoxic chemotherapy for malignant solid tumors between March 2013 and July 2015 were included in the study. Patients who were under 18 years were included only under permission from a legal guardian and a signed informed consent form (ICF). Patients with hematologic malignancies were excluded from the study.

The epidemiological variables investigated were age, place of birth, origin, type of tumor, and information on HBV infection. The following serological markers and liver enzymes were measured either before or during chemotherapy: HBsAg, total anti-HBc, anti-HBs, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP). Data on demographic variables and pathology diagnosis were obtained from the patients' medical records. The data were analyzed using descriptive statistics and presented in frequency tables.

3. Results and discussion

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One hundred thirty-one patients were analyzed from March 2013 to July 2015 (Table 1), of whom 40 (30.5%) were men and 91 (69.5%) were women. Mean age was 53.2 years (standard deviation: 16,08). Sixty-one patients (46.6%) were from inland Amazonas, 44 (33.6%) were from Manaus, and 26 (19.8%) patients were from other states. The most common cancer was breast (25.2%), followed by cervical (13.0%).

Table 1. Sample characteristics

Gender (M/F)	M	F
	40 (30.5%)	91 (69.5%)
Mean age (years/standard deviation)	54,8 (19,87)	52,5 (14,09)
Origin		
Manaus		44 (33.6%)
inland Amazonas		61 (46.6%)
other states		26 (19.8%)
Frequent cancer diagnosis		
Breast		33 (25.2%)
Cervical		17 (13.0%)
Colon		15 (11.4%)
Prostate		13 (9.9%)
Rectal		9 (6.9%)
On chemotherapy		131
Serological profile		
HBsAg+/ total anti-HBc +		2 (1.5%)
anti-HBs +/ total anti-HBc +		41 (31.3%)
isolated anti-HBs +		10 (7.6%)
isolated total anti-HBc +		3 (2.3%)
non-reactive		75 (57.3%)

Fifty-six (42.7%) patients were positive for at least one HBV marker, of whom 10 patients (7.6%) were anti-HBs positive, three (2.3%) were isolated total anti-HBc positive, 41 (31,3%) were anti-HBc/anti-HBs positive, and two (1.5%) were HBsAg/anti-HBc positive (Table 1). In addition, 18 reactive patients (32.2%) were men and 38 (67.8%) were women and the most common cancer type in men was prostate cancer (38.9%), whereas breast cancer was the most prevalent cancer in women (39.5%) (Table 2). The mean age of these patients was 57.4 years (standard deviation: 15,78) and 31 patients (55.4%) were from inland Amazonas, 13 (23.2%) were from Manaus, and 12 (21.4%) were from other states in Brazil.

One hundred twenty-four patients (94.6%) had abnormal levels in at least one liver marker. The incidence among HBV positive patients was 96,4% (54 patients). The most common isolated finding was elevated ALP levels in 68 (54.8%) patients, followed by

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combined elevated ALP and GGT levels in 15 (12.0%) patients.

Table 2. Comparison of patients with reactive and non-reactive serologic tests for HBV.

Variable	Reactive		Non-reactive	
Gender	M	F	M	F
	18 (32.2%)	38 (67.8%)	22 (29.3%)	53 (70.7%)
Mean age (years/standard deviation)	63,5 (16,35)	54,5 (14,63)	47,4 (19,61)	51,2 (13,47)
Cancer diagnosis	M	F	M	F
	prostate 7 (38.9%)	breast 15 (39.5%)	prostate 6 (27.3%)	breast 18 (34.0%)
	lung 3 (16.7%)	cervical 9 (23.7%)	colon 3 (13.6%)	cervical 8 (15.0%)
	kidney 2 (11.1%)	colon 4 (10.5%)	larynx 3 (13.6%)	colon 6 (11.3%)
	colon 2 (11.1%)	rectum 3 (7.9%)	stomach 2 (9.1%) lung 2 (9.1%) rectal 2 (9.1%)	rectal 4 (7.5%)
	bladder 1 (5.5%) esophagus 1 (5.5%) larynx 1 (5.5%) stomach 1 (5.5%)	ovary 3 (7.9%)	bladder 1 (4.5%) kidney 1 (4.5%) pancreas 1 (4.5%) esophagus 1 (4.5%)	ovary 4 (7.5%)

Most patients analyzed in this study were women, which is consistent with the frequent use of cytotoxic chemotherapy in breast cancer patients (VUGTS *et al.*, 2016) and the fact that breast cancer was the most common type of cancer (25.0%) in our sample.

The abnormal liver enzyme levels observed in almost all patients analyzed, especially the isolated elevated ALP levels, may be due to bone involvement in the course of the cancer progression (LI *et al.*, 2015). Moreover, viral infection can increase the levels of AST, ALT, and GGT, whereas chemotherapy drugs can cause liver damage (BOZZA *et al.*, 2016), (CHEUNG *et al.*, 2016).

Isolated anti-HBs positive samples were detected in only 10 (7.6%) patients, indicating that few had been

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vaccinated for HBV. The low vaccination rate in our sample may be related to the low immunization coverage for HBV in the region, because an HBV vaccine was only introduced in Brazil in the late 1980s (BRAGA *et al.*, 2004, 2012).

Thus, considering the advanced average age of the patients included in this study, it is likely that most of them did not have access to immunization. Moreover, most patients with reactive serologic tests for HBV were from municipalities in inland Amazonas, an expected finding considering the local epidemiology of HBV infection in the region (SOUTO, 2015; BRAGA *et al.*, 2004).

The sero-prevalence rates of HBV found in our study are similar to those described for the general population (SILVA *et al.*, 2006).

An interesting finding was the high rate of patients at risk for viral reactivation or exacerbation (35.0%), especially that of HBsAg-carrier patients (1.5%). This group of patients is at an increased risk for viral exacerbation during cytotoxic therapy, which may result in loss of liver function and liver failure (BOZZA *et al.*, 2016; CHEUNG *et al.*, 2016). In these cases, patients should be immediately started on prophylactic and/or therapeutic antiviral therapy, depending on viral load and liver damage detected on subsequent screenings.

4. Conclusion

Considering the high rate of patients with reactive serologic tests for HBV found in our study and the risk for reactivation associated with cytotoxic therapy, we recommend routine screening for chronic HBV infection in cancer patients from the Amazon region. Reactivation of HBV infection during chemotherapy is a potentially life-threatening complication that may lead to loss of liver function and liver failure (LUDWIG *et al.*, 2015; HWANG *et al.*, 2012).

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Divulgation

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References

BOZZA, C. *et al.* Hepatitis B and cancer: A practical guide for the oncologist**. Crit Rev Oncol Hematol.** 2016;98:137-46.

BRAGA, W. S. M. *et al.* Prevalência da infecção pelos vírus da hepatite B (VHB) e da hepatite Delta (VHD) em Lábrea, Rio Purus, Estado do Amazonas. **Epidemiol Serv Saude**. Brasília: 2004;13(1):35-46.

BRAGA, W. S. M. *et al.* Prevalence of hepatitis B virus infection and carriage after nineteen years of vaccination program in the Western Brazilian Amazon. **Rev Soc Bras Med Trop**. Uberaba: 2012;45(1):13-17.

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Revista on-line http://www.scientia-amazonia.org
ISSN:2238.1910

BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. **Boletim Epidemiológico – Hepatites Virais.** Brasília: Ministério da Saúde; 2017.

CASTILHO, M. C. *et al.* Epidemiology and Molecular Characterization of Hepatitis B Virus Infection in Isolated Villages in the Western Brazilian Amazon. **AM J Trop Med Hyg**. 2012;87(4):768-74.

CHEUNG, K. S. *et al.* Prevention and management of hepatitis B virus reactivation in cancer patients. **Hepatol Int.** 2016;10(3):407-14.

HUANG, Y. H.; LIN, H. C.; LEE, S. D. Management of chemotherapy-induced hepatitis B virus reactivation. **J Chin Med Assoc**. 2012 ;75(8):359-62.

HWANG, J. P. *et al*. Hepatitis B virus management to prevent reactivation after chemotherapy: a review. **Support Care Cancer.** 2012;20(11): 2999–3008.

LI, X. *et al.* Clinical analysis of 64 patients with lung-cancer-associated hypercalcemia. **J Cancer Res Ther.** 2015;11Suppl:C275-9.

LUDWIG, E. *et al*. Screening and Prevention of Hepatitis B Virus Reactivation During Chemotherapy. **Oncology (Williston Park)**. 2015;29(12):937-940,943.

PALMORE, T.N. *et al.* Reactivation of Hepatitis B with Reappearance of Hepatitis B Surface Antigen After Chemotherapy and Immune Suppression. **Clin Gastroenterol Hepatol**. 2009;7(10):1130-37.

SANAGAWA, A. *et al*. Outcomes of the implementation of the computer-assisted HBView system for the prevention of hepatitis B virus reactivation in chemotherapy patients: a retrospective analysis. **J Pharm Health Care Sci**. 2015;1:29.

SILVA, R. S. U. *et al.* Evaluation of the sorologic pre-selection for the hepatitis B virus marker (total anti-HBc) in candidates to blood donation in the State of Acre, 2002. **Rev Soc Bras Med Trop.** Uberaba: 2006;39(2):179-182.

SOUTO, F. J. D. Distribution of hepatitis B infection in Brazil: the epidemiological situation at the beginning of the 21st century. **Rev Soc Bras Med Trop.** 2015;49(1):11-23.

TAUIL, M. C. *et al*. Mortalidade por hepatite viral B no Brasil, 2000-2009. **Cad Saúde Pública**. 2012;28(3):472-78.

VUGTS, G. *et al.* Patterns of Care in the Administration of Neo-adjuvant Chemotherapy for Breast Cancer. A Population-Based Study. **Breast J**. 2016; 22(3):316-21.

WORLD HEALTH ORGANIZATION. **Global Hepatitis Report 2017**. Geneva: World Health Organization; 2017.