The Breast 35 (2017) 191–195

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Liver toxicity of chemotherapy and targeted therapy for breast cancer patients with hepatitis virus infection

Yu Liu [a, 1], Zhan-Yi Li [b, 1], Xi Li [a], Jia-Ni Wang [a], Qun-Ai Huang [a], Yong Huang [a, *]

[a] Department of Thyroid and Breast Surgery, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510000, China
[b] Department of Infectious Diseases, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510000, China

ARTICLE INFO

Article history:
Received 2 August 2017
Accepted 5 August 2017

Keywords:
Hepatitis B virus (HBV)
Hepatitis C virus (HCV)
Breast cancer
Chemotherapy
HBV/HCV reactivation
Toxicity

ABSTRACT

Background: Chemotherapy has greatly improved the prognosis of breast cancer patients. However, it may also result in undesirable side effects such as hepatitis virus reactivation. Little information is available on the liver toxicity of chemotherapy and targeted therapy for breast cancer patients with hepatitis virus (HBV/HCV) infection.

Methods: We performed a retrospective survey of 835 patients diagnosed with breast cancer between January 2010 and December 2015 at our institution. All patients had been screened for HBV/HCV infection at the time of breast cancer diagnosis. We retrospectively investigated the toxicity of chemotherapy and the changes in HBV/HCV load based on a medical record review.

Results: 52 patients with positive anti-HBV antibody test and 21 patients with positive anti-HCV antibody tests received chemotherapy. 762 patients without HBV and HCV infection served as the control group. The morbidity of liver toxicity and disruptions in chemotherapy attributable to liver toxicity were not significantly different among control group, HBV group and HCV groups (27.7% vs 34.6% vs 42.9%, P = 0.189 and 5.0% vs 9.6% vs 9.5%, P = 0.173, respectively). No patients presented with HBV/HCV reactivation.

Conclusion: Breast cancer patients with HCV can be treated with chemotherapy and targeted therapy with trastuzumab. Breast cancer patients with HBV who accept antiviral therapy can be treated with chemotherapy and targeted therapy with trastuzumab and patients can benefit from prophylactic antiviral therapy before chemotherapy. However, a multidisciplinary cooperation and closely monitoring liver function during the course of chemotherapy may benefit patients.

1. Introduction

Chronic hepatitis virus (CHV) infection including chronic hepatitis B (CHB) and chronic hepatitis C (CHC) have become a global health problem and pose a serious health burden. More than 185 million people are infected with the hepatitis C virus (HCV), and 350,000 of these individuals died each year. One third of people who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma [1]. Worldwide, there are an estimated 240 million persons chronically infected with the hepatitis B virus (HBV) and between 20% and 30% of them will develop liver cirrhosis or hepatocellular carcinoma. An estimated 650,000 people will die annually due to chronic hepatitis B (CHB) [2]. In China, there are approximately 20 million patients with CHB and 5.6 million patients with chronic hepatitis C (CHC) [3,4].

Breast cancer is one of the most common and deadly diseases among Chinese women [5], accounting for 248,620 new cases and 60,473 cancer-related deaths in 2011 [6]. Although the death rate has declined with medical advances, the incidence and mortality of breast cancer remain high [7].

It has been reported that reactivation of hepatitis B virus (HBV) occurs in 24%–88% of HBV-infected persons who receive chemotherapy, which may result in hepatitis, liver failure, or even death [8]. Hepatitis and liver failure may reduce the effectiveness of

Abbreviations: HCV, hepatitis C virus; CHC, chronic hepatitis C; HBV, hepatitis B virus; CHB, chronic hepatitis B; DAAs, direct-acting antiviral agents; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; HBsAg, hepatitis B surface antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; PT, prothrombin time; CTCAE, Common Terminology Criteria For Adverse Events; ADL, activities of daily living.

* Corresponding author.
E-mail address: dryonghuang@189.cn (Y. Huang).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.breast.2017.08.001
0960-9776/

chemotherapy or lead to treatment failure [8–10]. Similarly, reactivation of HCV during chemotherapy has been reported among HCV-infected patients with hematologic malignancies who have received rituximab, an anti-CD20 antigen that mainly inhibits B-cell function, therapy or combination chemotherapy [9,10]. It was reported that acute exacerbation of chronic HCV infection occurred in 6 of 9 (67%) episodes of HCV reactivation [10]. However, the immunosuppressive mechanisms of rituximab-based therapy for hematologic malignancies and conventional chemotherapy for solid tumors are essentially different.

Despite guidelines for the management of HBV-infected patients during chemotherapy [2], limited data exist to support the use of chemotherapy to treat solid tumors in HCV-infected patients. Although direct-acting antiviral agents (DAAs) have drastically improved the prognosis of HCV infection [1], the course of treatment is at least 12 weeks, and the interaction of DAAs with chemotherapy drugs has not been defined.

Overall, there is little information available on the effect of HCV during chemotherapy for solid tumors and the influence of HCV infection on the toxicity of chemotherapy [11] and the effect of preventive antiviral therapy on HBV-infected breast cancer patients during chemotherapy. Therefore, the purpose of this study was to evaluate patient safety during chemotherapy in chronic hepatitis B or C virus infected patients with breast cancer.

2. Patients and methods

We performed a retrospective survey of 835 patients diagnosed with breast cancer at the Third Affiliated Hospital of Sun Yat-sen University between January 2010 and December 2015. All patients had been screened for HBV and HCV serology based on the presence of HBsAg and anti-HCV antibodies. We identified 52 patients who were positive for HBsAg and 21 patients who were positive for anti-HCV antibodies; all of these patients received chemotherapy, including cytotoxic agents with or without trastuzumab. We assigned 762 patients without HBV and HCV infection to be the control group. The exclusion criteria included patients who had decompensated liver disease; those who had not been treated with prophylactic antiviral therapy against HBV according to the guideline [2,3]. We retrospectively investigated patients' characteristics including age, tumor histology, hormone receptor status (estrogen receptor (ER) and/or progesterone receptor (PR)), human epidermal growth factor receptor 2 (HER-2)/neu status (according to immunohistochemistry and/or fluorescent in situ hybridization), baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, total bilirubin (TBIL), prothrombin time (PT), changes in HBV load (in the HBV infected patients), changes in HCV load (in the HCV infected patients), type of chemotherapy and the toxicities of chemotherapy based on a review of patients' medical records.

This research was approved by ethics committee of the third affiliated hospital of Sun Yat-sen University.

2.1. Screening tests for hepatitis B surface antigen (HBsAg)

Abbott Architect i2000 chemiluminescence immunoassay systems (Abbott Laboratories, Abbott Park, IL, USA) were used to screen for HBsAg in accordance with the manufacturer's instructions. The cutoff values used to determine positive reactivity were established based on the manufacturer's recommendations. Samples with a signal/cutoff index (s/co) < 1.0 were regarded as negative, whereas samples with a signal/cutoff index (s/co) ≥ 1.0 were considered to be positive.

2.2. Qualitative tests for HBV DNA

HBV DNA in serum was quantified using a commercially available polymerase chain reaction approach (COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, v1; Roche Diagnostics, Basel, Switzerland) with a quantification range of 20–69,000,000 IU/ml (1.30–7.84 log10 IU/ml). This test's limit of sensitivity is 20 IU/ml.

2.3. Screening tests for antibodies to HCV

Abbott Architect i2000 chemiluminescence immunoassay systems (Abbott Laboratories, Abbott Park, IL, USA) were used to screen for antibodies against HCV in accordance with the manufacturer's instructions. The cutoff values used to determine positive reactivity were established based on the manufacturer's recommendations. Samples with a signal/cutoff index (s/co) < 1.0 were regarded as negative, whereas samples with a signal/cutoff index (s/co) ≥ 1.0 were considered to be positive.

2.4. Qualitative tests for HCV RNA

HCV RNA in serum was quantified using a commercially available polymerase chain reaction approach (COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, v1; Roche Diagnostics, Basel, Switzerland) with a quantification range of 15–69,000,000 IU/ml (1.18–7.84 log10 IU/ml). This test's limit of sensitivity is 15 IU/ml.

2.5. Assessment of ER, PR and HER2 status

ER and PR status were assessed by immunohistochemistry (IHC). HER-2 status was evaluated by IHC and/or fluorescence in situ hybridization (FISH).

A semi-quantitative histochemical score was used to evaluate the results of ER and PR staining according to the system established by Allred et al. [12]. This system considers both the proportion and intensity of stained cells. Tumor cells with a total score of 3–8 were considered positive, whereas those with a total score less than 3 were considered negative.

HER-2 membranous staining was evaluated as 0 if no cells showed staining; as 1 if incomplete, faint staining was present in >10% of cells; as 2 if complete, moderate staining was present in >10% of cells; and as 3 if complete, strong staining was present in >10% of cells [13].

For the FISH assay, we used a PathVysion HER-2 DNA Probe Kit (Vysis Inc., Downers Grove, IL, USA). According to the ASCO/CAP guidelines for HER2 testing in breast cancer [14], the number of HER2 gene signals and the number of chromosome 17 centromere (CEP17) signals per nucleus were counted for 20 tumor cells. The her-2 gene status was scored as the ratio between HER-2 red signals and CEP17 green signals. A HER-2/CEP17 ratio >2.2 was interpreted as positive for gene amplification, whereas a HER-2/CEP17 ratio <1.8 was defined as negative for gene amplification.

Overall, samples were considered positive for HER-2 in cases in which the IHC was 3 + or the IHC was 2 + and the FISH signal was amplified.

2.6. Assessment of liver function

Data of AST, ALT, TBIL and PT at baseline, during chemotherapy and three months after completion chemotherapy were collected and assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The severity of liver toxicity s was measured using a grade of 1 through 5. Grade 1 means mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 means moderate; minimal, local or