

Incidence of Hepatitis in Patients with Evidence of Past or Current Hepatitis B or C During Chemotherapy for Early Breast Cancer

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Abstract. *Aim/Background:* Few data are available about the prevalence of hepatitis B and C infections in early breast cancer patients and its impact on systemic treatments. The objectives of this study were to determine the incidence of positive serology for hepatitis B and C in women with early breast cancer and to assess the clinical course and its impact on liver function during adjuvant treatments. *Patients and Methods:* we retrospectively reviewed hepatitis B and C serology [HBs antigen (HBsAg), HBc antibodies (HBcAb), HBs antibodies (HBsAb) and HC (HCV) antibodies] in 746 consecutive patients with early breast cancer treated at our Institution between 2009 and 2011. *Results:* Among 375 evaluable patients, we identified 312 controls (83.2%) and 63 patients (16.8%) with positive serology (cases): 15 patients (4%) with HCV, 8 (2.1%) with resolved HBV without anti-HBs (HBsAg-negative, HBsAgAb-negative, HBcAgAb-positive), 36 (9.6%) with resolved HBV with anti-HBs (HBsAg-negative, HBsAgAb-positive, HBcAgAb-positive) and 4 (1%) with chronic HBV (HBsAg-positive, HBsAgAb-negative, HBcAgAb-positive). During systemic treatments, hepatitis (defined as at least a three-fold increase in serum alanine aminotransferase level) occurred in nine (20.4%) out of 44 evaluable cases and in 14 (5.9%) out of 234 evaluable controls. *Conclusion:* Approximately 20% of patients with

early breast cancer with positive serology for viral hepatitis may develop hepatitis during systemic treatment. Pre-treatment serum detection of viral hepatitis B and C antigens and antibodies may be useful in the adjuvant therapy decision-making process and for adequate monitoring of liver function during antineoplastic therapy.

It is estimated that 2 billion people worldwide have been infected with the hepatitis B virus (HBV) and over 350 million are chronic carriers. The regional prevalence of chronic HBV varies widely. In areas of high endemicity in the Asia-Pacific region, it approaches 20%, while in the United States it is estimated at 0.5% and in Italy as 1.5% (1). Approximately 3% (170 million) of the world's population is infected with hepatitis C virus (HCV). For most countries, including the United States and Italy, the prevalence of HCV infection is <3%. The prevalence is higher (up to 15%) in some countries of Africa and Asia; Egypt has the highest (>15%) prevalence (2).

Patients who have been infected with HBV are vulnerable to disease re-activation during immunosuppressive therapy. This syndrome has been reported following treatment of hematological malignancies and solid tumours (3). The clinical consequences vary from asymptomatic elevation of hepatic enzymes to severe hepatitis and death from fulminant hepatic failure. The risk for HBV reactivation is influenced by both the type of malignancy and chemotherapeutic agent employed (4). Most patients with HBV reactivation are positive for hepatitis B surface antigen (HBsAg) but a small proportion of those who have apparently recovered from HBV infection, as reflected by HBsAg negativity and HBV core antigen-antibody (HBcAg Ab) positivity, may also experience reactivation when host immunity is severely compromised by cancer chemotherapy (5).

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Key Words: Breast cancer, chemotherapy, hepatitis B virus, hepatitis C virus.

Little is known about the changes in HCV replication and associated hepatic flares during immunosuppressive therapy. Re-activation of HCV replication (6) and fulminant hepatitis (7) were reported among patients with chronic HCV infection receiving chemotherapy for oncohaematological disease.

In addition to direct liver damage, re-activation of HBV and HCV in patients with cancer can lead to schedule modifications (dose reductions or delays) of cancer therapies (8); few data exist about the adherence to systemic treatments in patients with breast cancer with HBV or HCV infection.

The objectives of this study were to determine the incidence of positive serology for HBV and HCV in women with early breast cancer and to assess the clinical course and the impact on liver function of hepatitis during systemic adjuvant treatments.

Patients and Methods

Medical records of women with stage I-III breast cancer surgically-treated at the National Institute for Cancer Research of Genoa from January 2009 to March 2011 were reviewed in order to evaluate serology for HBV and HCV retrospectively. Patients with a diagnosis of breast carcinoma *in situ* and metastatic breast cancer were excluded from analysis. We identified six serological categories: uninfected patients (HCV-, HBsAg-, HBsAg Ab- and HBcAg Ab-negative); patients with resolved HBV without anti-HBs (HBsAg-negative, HBsAg Ab-negative, HBcAg Ab-positive); patients with resolved HBV with anti-HBs (HBsAg-negative, HBsAg Ab-positive, HBcAg Ab-positive); patients with chronic HBV (HBsAg-positive, HBsAg Ab-negative, HBcAg Ab-positive); patients vaccinated for HBV (HBsAg-negative, HBsAg Ab-positive, HBcAg Ab-negative); patients with HCV (HCV-Ab-positive).

Other variables considered were age, tumour stage, histology, lymph node involvement, grading, receptor status, human epidermal receptor 2 (HER2) status, type of surgery and type of systemic treatment received. For all patients in the study undergoing chemotherapy, we recorded the values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) before, during and after completion of this treatment. The changes in these values during and at the end of systemic treatment compared with baseline were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (grade 1 when $ALT \leq 2.5 \times$ upper limit of normal (ULN), grade 2 when ALT between $2.5 \times$ ULN and $5 \times$ ULN, grade 3 \times ULN if ALT between 5 and $20 \times$ ULN, and grade 4 when $ALT > 20 \times$ ULN) (9). We also analysed adherence (delays, interruptions, dose reductions) to systemic therapies (chemotherapy, trastuzumab, hormone therapy). The collected data were compared between the group of patients with positive serology for hepatitis (cases) and the control group comprising patients with negative serology for HBV and HCV and vaccinated patients. Cases included patients with resolved HBV without anti-HBs, patients with resolved HBV with anti-HBs, patients with chronic HBV and patients with HCV infection. Controls included uninfected patients and patients vaccinated for HBV.

Results

We evaluated retrospectively serology for HBV and HCV of 746 women. Out of these, 371 (49.7%) patients were excluded due to lack or incompleteness of this serological evaluation. The remaining 375 (50.2%) patients were evaluated before surgery for HBsAg, HBcAb, HBsAg Ab and HCV antibodies. Among the 375 patients, 312 (83.2%) were classified as controls and 63 (16.8%) as cases.

The 63 patients (16.8%) defined as cases were divided as follows: 36 patients (57%) with resolved HBV with anti-HBs, 8 patients (12.5%) with resolved HBV without anti-HBs, 4 patients (6.3%) with chronic hepatitis B and 15 patients (23.8%) with a diagnosis of hepatitis C. Among the 312 controls 291 patients had negative serology for hepatitis B or C (77.6%) and 21 patients were vaccinated for hepatitis B (5.6%).

The characteristics of cases and controls are shown in Table I. Patients' characteristics were described by median and range values as appropriate. The median age of patients at diagnosis of breast cancer was 66 (range=41-85) and 59 (range=23-90) years for cases and controls, respectively. Within the two groups (cases *vs.* controls), the majority of patients had disease stage I/II (79.2% *vs.* 73.7%), infiltrating ductal histology (74.1% *vs.* 75.0%) and endocrine-responsive disease (85.2% *vs.* 82.5%); 15.4% of cases and 14.5% of controls had HER2-positive disease.

Among the 63 cases 26 (41.2%) patients received chemotherapy: 16 (25.3%) a regimen containing anthracyclines and taxanes, six (9.5%) taxanes alone, and four (6.3%) other regimens of chemotherapy. Among the cases who did not receive chemotherapy, 37 (58.7%) patients received endocrine therapy. Among the 312 controls 149 (47.7%) patients received chemotherapy: 128 (41%) received a regimen containing anthracyclines and taxanes, 10 (3.2%) a regimen of taxanes-alone, and 11 (3.5%) other chemotherapy regimens; 143 (45.8%) patients received endocrine therapy alone; 12.6% of cases and 13.4% of controls received systemic treatment containing trastuzumab.

At baseline, before initiating chemotherapy, 3.2% of patients in the control group (10 patients) and 14.2% of cases (9 patients) had transaminases elevated to more than grade 1. The analysis of transaminases during chemotherapy was possible in 278/375 patients (74%): 234/312 controls (75%) and 44/63 cases (69.8%). The 44 evaluable cases are divided as follows: 25 patients with resolved HBV with anti HBs, five patients with resolved HBV without anti HBs, three patients with chronic hepatitis B and 11 patients with hepatitis C. This analysis was not possible for 78/312 patients in the control group (25%) and 19/63 (30.1%) patients in the group of cases.

During the systemic treatment, 57/234 patients in the control group (24.3%) and 11/44 patients in the group of

Table I. Tumour and patient characteristics.

	Cases N (%)	Controls N (%)
N 63 (16.8%)	312 (83.2%)	
Age, years		
Median (range)	66 (41-85)	59 (23-90)
Stage		
I	28 (44.4%)	140 (44.8%)
II	17 (26.9%)	105 (33.6%)
III	16 (25.3%)	64 (20.5%)
Unknown	2 (3.17%)	3 (0.9%)
Histology		
IDC	46 (73%)	234 (75%)
ILC	6 (9.5%)	45 (14.4%)
Other	11 (16.8%)	33 (10.5%)
Oestrogen receptor		
Negative	11 (17.4%)	46 (14.7%)
Positive	52 (82.5%)	266 (85.2%)
HER2		
Negative	53 (84.1%)	263 (84.2%)
Positive	9 (14.2%)	48 (15.3%)
Unknown	1 (1.5%)	1 (0.3%)
Surgery		
Conservative	45 (71.4%)	230 (73.7%)
Radical	13 (20.6%)	65 (20.8%)
Programmed	4 (6.3%)	16 (5.1%)
Unknown	1 (1.5%)	1 (0.3%)
Systemic therapy		
CT with/without HT	18 (28.5%)	106 (33.9%)
CT with T with/without HT	8 (12.6%)	43 (13.7%)
HT	37 (58.7%)	143 (45.8%)
AST/ALT at baseline		
Normal	55 (87.3%)	302 (96.7%)
Increased	8 (12.6%)	10 (3.2%)

AST/ALT: Aspartate aminotransferase/alanine aminotransferase; HER2: human epidermal receptor 2; IDC: infiltrating ductal carcinoma; ILC: infiltrating lobular carcinoma; CT: chemotherapy; T: trastuzumab; HT: hormone therapy.

cases (25%) had an increase of transaminases. Among patients with positive serology for HBV and HCV (cases) who developed a deterioration of liver function, two patients (18.1%) had resolved HBV with anti-HBs, two patients (18.1%) HBV resolved without anti-HBs, two patients (18.1%) chronic hepatitis B, and five patients (45.5%) hepatitis C. In both groups of patients, the rise in transaminases occurred mainly during chemotherapy (93% vs. 73%, cases vs. controls, respectively); in the remaining patients, the increase in transaminases occurred at the end of chemotherapy, and in particular, in 5.1% and 9.0% of patients (cases vs. controls) this increase occurred during therapy with trastuzumab. A total of 57 controls and 11 cases developed an increase of transaminases (Table II). No patient showed elevation of total bilirubin or severe liver dysfunction (grade 4 transaminase elevation or fulminant hepatitis).

Table II. Grade of transaminase elevation among cases and controls.

	Transaminase elevation (grade)			
	G1	G2	G3	G4
Cases (N=44)	2 (4.5%)	7 (15.9%)	2 (4.5%)	0
Controls (N=234)	42 (17.9%)	13 (5.5%)	1 (0.4%)	0

The increase in transaminases resulted in discontinuation of systemic treatment in two patients (0.85%) in the control group (both patients discontinued chemotherapy) and in three patients (6.8%) among cases: 2 patients HCV positive and 1 patient with resolved HBV without anti HBs (1 patient discontinued hormonal therapy and 2 patients discontinued trastuzumab) (Table III). Increase in transaminases did not lead to dose reductions or delays of chemotherapy in the remaining patients. Twenty-five patients (10.6%) in the control group and three patients (4.7%) among cases had to discontinue chemotherapy for reasons other than liver toxicity (Table IV); the most common causes that led to discontinuation were: neurotoxicity (7 patients), severe fatigue (4 patients) and diarrhea (4 patients). Twenty-three cases (9.8%) and one control (2.2%) delayed or reduced doses of chemotherapy for reasons other than hepatotoxicity.

In the group of patients with positive serology for hepatitis B or C, 13 patients (20.6%) were referred to an infectious disease specialist for evaluation of treatment options during chemotherapy with increased transaminase levels. None of the patients received antiviral prophylaxis during systemic therapy.

Discussion

Accurate data on the prevalence of HBV and HCV infections and on the potential clinical sequelae of reactivation during treatment of patients with cancer are limited. The prevalence of chronic HBV in patients with diagnosis of tumors may be different from that of the general population and may vary among different tumor types. In patients with solid tumours, HBV prevalence ranged from 5.3% among 1,008 patients in Greece (8) to 12.5% among 626 patients in China (10). Ludwig *et al.* screened 3,343 patients with cancer who started an immunosuppressive therapy in a period of six months and reported a prevalence of 1.3% for chronic HBV and 9% for occult HBV (11). Very few data are available about the prevalence of chronic HCV in oncohaematological diseases. In our study, among 375 patients with newly-diagnosed breast cancer, the prevalence of chronic HBV and HCV was 1% and 4%, respectively, similar to the prevalence in the Italian population (1.5% and 3%) (1, 2).

Table III. Discontinuation of systemic treatment for transaminases elevation among patients treated with chemotherapy.

	CT with/without HT	CT with T with/without HT	HT	Total
Cases (N=44)				
HCV (N=11)	0	1 (2.2%)	1 (2.2%)	2 (4.6%)
Resolved HBV without anti-HBs (N=5)	0	1 (2.2%)	0	1 (2.2%)
Resolved HBV with anti-HBs (N=25)	0	0	0	0
Chronic HBV (N=3)	0	0	0	0
Controls (N=234)	2 (0.85%)	0	0	2 (0.85%)

CT: Chemotherapy; HBV: hepatitis B virus; anti-HBs: hepatitis B surface antibody; T: trastuzumab; HT: hormone therapy.

Table IV. Discontinuation of systemic treatment for reasons other than transaminases elevation among patients treated with chemotherapy.

	CT with/without HT	CT with T with/without HT	HT	Total
Cases (N=44)				
HCV (N=11)	0	1 (2.2%)	1 (2.2%)	2 (4.6%)
Resolved HBV without anti-HBs (N=5)	0	1 (2.2%)	0	1 (2.2%)
Resolved HBV with anti-HBs (N=25)	3 (6.8%)	0	0	3 (6.8%)
Chronic HBV (N=3)	0	0	0	0
Controls (N=234)	27 (11.5%)	0	0	27 (11.5%)

CT: Chemotherapy; HCV: hepatitis C virus; HBV: hepatitis B virus; anti-HBs: hepatitis B surface antibody; T: trastuzumab; HT: hormone therapy.

Patients who have been infected with HBV are vulnerable to disease re-activation during immunosuppressive treatment or cancer chemotherapy. Although the relationship between chemotherapy and HCV re-activation is less clear, severe hepatitis from re-activation of HCV infection has been documented. The reported clinical spectrum of virus reactivation ranges from asymptomatic hepatitis to fatal hepatic failure, however, available data regarding the spectrum and proportions of potential clinical sequelae in patients with HBV or HCV undergoing chemotherapy for breast cancer are limited.

Recently Shoji *et al.* retrospectively reviewed the presence of hepatotoxicities among patients with breast cancer with HBV or HCV infection who received chemotherapy: among 32 patients with HBV infection, three experienced grade 3/4 hepatotoxicities, requiring two treatment delays and one treatment revision (12). Among 52 HCV patients treated with chemotherapy, five experienced grade 3/4 hepatotoxicities and required treatment delays. Morrow *et al.* described the follow-up of 45 HCV patients treated with chemotherapy for breast cancer; comparison with historical controls showed similar rates of hepatic toxicity (13). In this study, 25% of patients experienced elevations of aminotransferases and 44% of patients required dose reductions or a delayed chemotherapy. However, 92% of patients were able to complete the planned chemotherapy.

In the present retrospective study, the percentage of patients experiencing an increase of transaminases was similar between cases and controls (25% vs. 24.3%) but the incidence of grade 3 transaminase elevation was higher in cases than in controls (4.5% vs. 0.4%). No patients showed elevation of total bilirubin or severe liver dysfunction (grade 4 transaminase elevation or fulminant hepatitis). Moreover, the increase in transaminases resulted in discontinuation of systemic treatment in two patients (0.85%) in the control group and in three patients (6.8%) among cases (two patients with HCV Ab and one with resolved HBV without anti-HBs).

Rates of HBV reactivation in HBV carriers who undergo chemotherapy is variable across studies, with reported values ranging from 14-72%; little is known about the changes in HCV replication and associated hepatic flares during chemotherapy (14-16). Variability in associated factors underlying different rates of re-activation include: patient populations, types of malignancy, chemotherapy regimens, and definitions of reactivation. HBV or HCV reactivation is usually defined as a hepatitis associated with either a reappearance of or a 1-log increase in the level of viremia. In our study, because of the lack of routine clinical use of serum HBV DNA and HCV RNA evaluation, in patients experiencing elevation of transaminases, viral reactivation or replication could not be confirmed. If we adopt only a clinical definition, *i.e.* at least three-fold increase in serum

ALT level, hepatitis during systemic treatments was observed in nine (20.4%) out of 44 evaluable patients with positive serology for HBV or HCV. In control patients, hepatitis was observed in 14 out of the 234 evaluable patients (5.9%). The lack of HCV RNA or HBV DNA assessment, in accordance with local policy, represents the main limitation of our study.

Hepatitis due to HBV re-activation can occur during immune restoration on withdrawal of chemotherapy caused by a much enhanced immune response against HBV-infected hepatocytes; in our study 7% of cases experienced transaminase elevation after the end of chemotherapy.

Guidelines from the Centers for Disease Control and Prevention and the European Association for the Study of the Liver recommend screening all patients prior to starting chemotherapy (17). American Society of Clinical Oncology (ASCO) in 2010 stated that insufficient evidence exists to determine the net benefits and harm (costs) of routine screening for chronic HBV infection in patients with cancer who are candidates to receive immunosuppressive therapy. ASCO recommends screening in selected high-risk patients (such as those born in countries of high endemicity), or if highly immunosuppressive therapy is planned (*i.e.* treatment with rituximab) (18, 19). Despite our country having low-level endemicity for HBV and HCV, our data suggest that the rate of transaminase elevation during chemotherapy is similar to that of countries with high endemicity. Based on the present evaluation, screening limited to high-risk individuals, as recommended by ASCO, does not apply to patients with breast cancer in our area, as it would require recognition of the high-risk population and would miss patients who are at true risk for reactivation.

Although the majority of patients with HBV reactivation are positive for HBsAg, a small proportion of those who have apparently recovered from HBV infection, as reflected by HBsAg negativity and HBcAg Ab positivity may also experience reactivation when host immunity is severely compromised by cancer chemotherapy. The true incidence of chemotherapy-induced reactivation of hepatitis B in these patients is uncertain (15,16). Therefore the role of anti-HBc testing is less clear and recommendations from various societies differ: ASCO does not recommend its use during screening.

Notably in our study, transaminase elevation occurred in almost half the patients diagnosed with HCV (45%) and resolved HBV without anti-HBs (40%), and in 66% of patient with chronic HBV. These data indicate that almost half of the patients who had apparently cleared HBV experienced a rise in transaminases during systemic therapy, supporting the utility of anti-HBc testing during screening.

In addition to the direct harm caused by HBV and HCV re-activation, patient care may be compromised because of the need to delay or prematurely cease cancer therapies. In this study, an interruption in systemic treatment was

necessary in 18% of HCV-positive patients and in 20% of patients with resolved HBV without anti-HBs.

In conclusion, although it is not possible to demonstrate specific correlation between viral infection and hepatitis, our results show that a substantial proportion of patients with breast cancer and HBV or HCV infection may develop liver dysfunction when undergoing chemotherapy. Understanding the risk of hepatotoxicity in patients with early breast cancer and evidence of past or current HBV and HCV infection may be useful in the adjuvant therapy decision-making process. Moreover, in patients undergoing chemotherapy, close monitoring of transaminases and viral load may be helpful to detect liver dysfunction early, to differentiate between viral re-activation and drug toxicity, and to appropriately manage the patients. Since there is no anti-viral therapy available for patients with HCV, and deferred antiviral therapy has lower efficacy in patients with resolved HBV without anti-HBs and evidence of HBV re-activation during chemotherapy, appropriate management may be early an interruption of chemotherapy in order to avoid severe liver dysfunction.

Conflicts of Interest

All Authors declare no conflicts of interest.

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Received February 25, 2014

Revised May 5, 2014

Accepted May 7, 2014