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ORIGINAL ARTICLE

Chemotherapy and targeted therapy for breast cancer patients with hepatitis C virus infection

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Abstract

Background Hepatitis C virus infection (HCV) is a major health problem in Egypt. Breast cancer is the most common cancer among Egyptian women. Considering that both diseases are frequent in the Egyptian population, it is likely that many women are affected by both.

Purpose To evaluate patient safety and applicability of chemotherapy in chronic hepatitis C virus-infected patients with breast cancer.

Subjects and methods We performed retrospective survey of 58 Egyptian patients diagnosed with both diseases. We retrospectively investigated the baseline patient and tumor characteristics, the toxicities of chemotherapy, and the changes in HCV viral load before and after chemotherapy, in addition to treatment received for HCV infection.

Results Forty-four (75.9%) out of the 58 patients received chemotherapy with or without trastuzumab and one patient received lapatinib. We reported 2 patients who had HCV viral reactivation. Treatment with trastuzumab or Lapatinib was not associated with elevation in liver enzymes or change in HCV RNA viral load. Treatment discontinuation occurred in 31.8% (14/44) of patients due to complications. Dose reductions and/or dose delays were common (27.2%). Elevated liver enzymes were developed in 20 out of 44 (45.5%) patients who received chemotherapy. Three patients received antiviral treatment concomitant with chemotherapy with no significant complications.

Conclusions Greater attention should be paid to the possibility of complications including HCV reactivation, fulminant hepatitis, and interrupted chemotherapy treatments in breast cancer patients with chronic HCV infection receiving immunosuppressive drugs. Close monitoring of patients with breast cancer and HCV infection should be done

Keywords Hepatitis C virus infection · Breast cancer · Chemotherapy · Targeted therapy · HCV viral load

Introduction

Hepatitis C virus infection (HCV) is a major health problem in Egypt. Infection claims the lives of 170,000 Egyptians yearly with the incidence rate ranging from 2 to 6 per 1000 each year [1]. Seventy-five percent of the individuals are always asymptomatic, and remain undiagnosed. Chronic HCV infection may result in the development of Liver cirrhosis or hepatocellular carcinoma [2]. Breast cancer is the most common form of cancer among Egyptian women. It accounts for 18.9% of total cancer cases (35% in females and 2.2% in males). It appears the youths and young adults are more affected, together with advanced tumor stage compared to cases in North American countries and the Europe [3, 4]. Considering that both diseases are frequent in the Egyptian population, it is likely that heavy casualties are recorded among the female gender. Adjuvant chemotherapy is crucial in the treatment of patients with breast cancer. Chemotherapeutic agents used to treat breast cancer mostly are metabolized in the liver [5]. So, in patients with liver cirrhosis, abnormal clearance and metabolism of anticancer agents may occur [6]. Additionally, liver disease progression, including decompensated cirrhosis may occur as a consequence of chemotherapy [6]. Discontinuation or dose

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reduction of chemotherapy may be needed due to liver disease, which may affect prognosis. The effect of HCV infection on chemotherapy and vice versa are more investigated in hematological malignancies. However, there is little information available on the HCV-infected patients with solid tumors receiving chemotherapy [7]. Therefore, the purpose of this study is to evaluate patient safety and applicability of chemotherapy in chronic hepatitis C virus-infected patients with breast cancer.

Patients and methods

Patients

A retrospective survey was performed on patients diagnosed with both diseases; breast cancer and HCV infection between January 2016 and January 2017. The patients were treated at Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine. Retrospective review of the following data was done; the baseline patient and tumor characteristics, the toxicities of chemotherapy, and the changes in HCV viral load before and after chemotherapy, in addition to treatment received for HCV infection based on review of the patient's medical records. Approval by the institutional review board (IRB) was obtained. All provisions of the Helsinki Declaration were followed.

Patients who had positive HCV antibodies, but not confirmed by HCV-RNA test were excluded from the study. Additionally, patients with metastasis to the liver or with hepatocellular carcinoma were excluded from our analysis to avoid the resultant affection of liver chemistry tests caused by infiltration of the liver.

Tumor characteristics and treatment

The following data were reported from tumor assessment: stage of the disease according to American Joint Commission on Cancer (AJCC) [8], tumor histology, hormone receptor status [estrogen receptor (ER) and progesterone receptor (PR)]. Breast cancers that had at least 1% of cells staining positive for ER were considered ER-positive [9], Also human epidermal growth factor receptor 2 (HER-2)/neu status was assessed. HER2 status was considered positive if an immunohistochemistry (IHC) assay demonstrated 3+ [10].

Laboratory tests

Levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin (T.BIL) and prothrombin time (PT) were assessed at baseline and prior to every chemotherapy cycle. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to measure the severity of liver toxicity [11]. Child-Pugh criteria were used to assess liver cirrhosis [12]. In addition; hematological toxicity was assessed by measuring baseline white blood cell count, hemoglobin, and platelet count and during chemotherapy. Grading of toxicity was assessed by CTCAE version 4.0 [11].

Assessment of HCV infection status

Qualitative assessment of Hepatitis C virus Antibodies

For qualitative detection of antibodies of hepatitis C virus (anti-HCV), serum samples were tested using the ABBOTT Architect i1000 SR system (Singapore, US) which is a chemiluminescent micro-particle immunoassay (CMIA). Cut off value according to manufacturer's protocol, samples which did not react were considered as non-reactive for HCV antibodies. Reactive samples were considered as positive for HCV antibodies. The overall specificity of Architect Anti-HCV kit was 99.60% with a 95% confidence interval at a range of 99.45–99.71%. The sensitivity was 99.10% with a 95% confidence interval at a range of 96.77–99.89%. Some cases were seropositive. PCR negative cases were excluded from the study.

Quantitative assessment of Hepatitis C virus by qRT-PCR

EDTA peripheral blood samples from the patients were separated into plasma and cellular components by centrifugation at 800–1600×*g* for 20 min within 6 h. The isolated plasma was transferred into a sterile tube and stored at a temperature of − 80 °C. RNA was extracted from 140µL of plasma using QIAamp Viral RNA Kit (Qiagen, Germany) according to the manufacturer's protocol. The extracted RNA was eluted in elution buffer and used for the quantitative RNA PCR. TaqmanqRT-PCR was done using quantitative HCV kit with a lower limit of sensitivity of 50 IU/mL (AgPath-IDTM One-step RT-PCR Kit, Applied biosystems, USA). Procedures were performed according to the manufacturer's protocol using Step One real-time PCR machine (Applied Biosystems, USA). The threshold cycle (CTs) values from the samples were plotted on the standard curve, and the numbers of copies were calculated.

Definitions

HCV reactivation was defined as tenfold or more increase in the HCV RNA level following chemotherapy compared with the baseline level [13]. This study reported changes in HCV viral load prior to and after chemotherapy. Acute exacerbation of chronic HCV infection was defined as a threefold or greater increase in serum ALT level in the absence of

(1) infiltration of the liver by tumor [14] (2) use of hepatotoxic drugs [15] (other than chemotherapeutics), (3) recent blood transfusion (within 1 month of ALT level elevation), or (4) other systemic infections (including hepatitis A, HBV, cytomegalovirus, adenovirus, herpes simplex virus, varicella zoster virus, and human immunodeficiency virus infections).

Data analysis

Results are expressed as mean, standard deviation, standard error, minimum and maximum or number (%). Comparison between categorical data [number (%)] was carried out using Chi square test or Fisher exact test instead if the cell count is less 5. Test of normality, Kolmogorov–Smirnov test, were used to measure the distribution of data. Accordingly, comparison between variables in the two groups was performed using either unpaired *t* test or Mann–Whitney test whenever it was appropriate. Comparison between HCV viral load measured before and after treatment was performed using Wilcoxon signed ranks test. Statistical Package for Social Sciences (SPSS) computer program (version 19 windows) was used for data analysis. P value ≤ 0.05 was considered significant.

Results

Patients' characteristics

Our survey identified 58 patients who had positive HCV by HCV-RNA quantitative polymerase chain reaction (qRT-PCR). Forty-four patients (75.9%) out of the 58 patients received chemotherapy with or without trastuzumab and one patient received lapatinib. Demographic factors and tumor characteristics are shown in Table 1 for patients who received chemotherapy and patients who did not receive chemotherapy.

Most patients (96.5%) were females. The average age at breast cancer diagnosis in the chemotherapy group and non-chemotherapy group was 53.11 ± 8.76 and 56 ± 8 years, respectively. ALT, AST and total bilirubin levels were higher in patients in the non-chemotherapy group (53.79 ± 46.77 vs. 84.43 ± 62.44, $P = 0.049$, 54.40 ± 43.82 vs. 91.07 ± 64.94, $P = 0.024$ and 0.76 ± 0.51 vs1.47 ± 0.69, $P = 0.001$). Three patients had grade 1 ALT elevations at baseline while grade 2 ALT elevations was present in two patients. The elevations of AST at baseline was grade 1 in 3 patients, grade 2 in 4 patients and grade 3 in 2 patients. Total bilirubin grade 2 toxicity was present in 8 patients at baseline. No patient in both groups demonstrated evidence of decompensated liver disease before the start of systemic chemotherapy. Liver cirrhosis was detected by abdominal ultrasonography in 28 (48.2%) of patients at the time of diagnosis. Eleven (20%) of patients were scored B by child pug score.

All enrolled patients were intermediate and high risk breast cancer and recommended to receive chemotherapy including cytotoxic agents with or without trastuzumab. Chemotherapy regimens included anthracycline-based chemotherapy in the form of: cyclophosphamide, Doxorubicin and 5-fluorouracil (CAF regimen); or Doxorubicin and Cyclophosphamide (AC) followed with weekly Taxanes; or 5-flurouracil, Epirubicin and Cyclophosphamide (FEC) followed by Taxanes.

Treatment with trastuzumab or Lapatinib wasn't associated with elevation in liver enzymes or change in HCV-RNA viral load. The reasons for not receiving chemotherapy ($n = 14$, 24.1%) were as follow; 2 patients had luminal A disease and received only hormonal therapy, one patient was over 70 years and had luminal B disease and received hormonal treatment, three patients had baseline persistent neutropenia (absolute neutrophilic count $< 1.5 \times 10^3/cm^3$), four patients had baseline persistent thrombocytopenia (platelet count $< 50 \times 10^3/cm^3$), and two patients presented with grade 2 hepatic toxicity and preferred not to receive chemotherapy and two patients lost follow up.

Treatment course

Among patients planned to receive chemotherapy ($n = 44$, 75.9%), thirty patients (30/44, 68.2%) completed their treatment. The remaining patients (14/44, 31.8%) didn't complete their intended number of chemotherapy cycles. The reasons for this were as follows: 8 patients developed persistent neutropenia and/or thrombocytopenia, 3 patients had grade 3 liver toxicity and 3 patients developed both neutropenia and grade 2 liver toxicity.

Twenty-five patients (56.8%) out of the 44 patients who received chemotherapy, experienced chemotherapy complications based upon the CTCAE. The most common complications were neutropenic fever (eight patients), non-neutropenic infection (four patients), grade 2 nausea and vomiting (five patients), diarrhea (three patients), thrombocytopenia (two patients), and peripheral neuropathy (three patients) as shown in Tables 2.

Elevated liver enzymes were developed in 20 out of 44 (45.5%) patients who received chemotherapy. Among the twenty patients who experienced transaminitis, fifteen (75%) patients developed grade 2 increase in AST or ALT while grade 3 elevations in ALT or AST occurred in five (25%) patients. Twelve (12/20, 60%) of the patients who developed transaminitis with chemotherapy had baseline elevated one or more of the liver functions before chemotherapy. Dose reductions and/or dose delays were common ($n = 12/44$, 27.2%) due to neutropenia in 5 patients, elevated

Table 1 Patient's characteristics

Patient's characteristics	Patients who received chemotherapy (chemotherapy group) ($N=44$)	Patients who did not received chemotherapy (non-chemotherapy group) ($N=14$)	P value	Total ($N=58$)
Age				
Mean ± SD	53.11 ± 8.76	56 ± 8	0.278	53.81 ± 8.61
Median	54	55		54
Range	35–67	46–74		35–74
Sex				
Female	42 (95.4%)	14 (100%)		56 (96.5%)
Male	2 (4.5%)	0 (0%)		2 (3.4%)
Comorbidities				
DM	6 (13.6%)	7 (50%)		13 (22.4%)
HTN	2 (4.5%)	1 (7.1%)	0.782	3 (5.2%)
Both	8 (18.1%)	2 (14.2%)		10 (17.2%)
No	28 (63.6%)	4 (50%)		32 (55.2%)
Stage				
I	2 (4.5%)	1 (7.1%)		3 (5.2%)
II	21 (47.7%)	4 (28.5%)	0.189	25 (43.1%)
III	21 (47.7%)	8 (57.1%)		29 (50%)
IV	0 (0%)	1 (7.1%)		1 (1.7%)
Histology				
IDC	36 (84%)	14 (100%)		50 (86.2%)
ILC	7 (16%)	0 (0%)	0.234	7 (12.1%)
Other (medullary)	1 (2.2%)	0 (0%)		1 (1.7%)
Immunohistochemistry ER status				
Positive	26 (59.1%)	12 (85.7%)	0.468	38 (65.5%)
Negative	18 (40.9%)	2 (14.3%)		20 (34.5%)
PR status				
Positive	30 (68.2%)	9 (64.3%)	0.518	39 (67.3%)
Negative	14 (31.8%)	5 (35.7%)		19 (32.7%)
HER2 NEU				
Positive	7 (16%)	4 (28.6%)		11 (18.9%)
Negative	37 (84%)	10 (71.4%)	0.485	47 (81.1%)
KI 67				
High	29 (65.9%)	10 (71.4%)		39 (67.3%)
Low	13 (29.5%)	4 (28.6%)	0.300	17 (29.3%)
Unknown	2 (4.5%)	0 (0%)		2 (3.4%)
Molecular subtype				
Luminal A	8 (18.1%)	4 (28.6%)		12 (20.7%)
Luminal B	24 (54.5%)	4 (28.6%)	0.097	28 (48.3%)
Luminal (undefined)	2 (4.5%)	0 (0%)		2 (3.4%)
Her2 positive disease	4 (9%)	1 (7.1%)		5 (8.6%)
Triple negative disease	6 (13.6%)	5 (35.7%)		11 (19%)
Liver cirrhosis				
No	27 (61.4%)	3 (21.4%)	0.090	30 (51.8%)
Yes	17 (38.6%)	11 (78.6%)		28 (48.2%)
Child-Pugh score (55 patients)				44 (80%)
A	34	10	0.084	11 (20%)
B	7	4		
ALT (reference range = 0–65 U/L)			0.049*	
Mean ± SD	53.79 ± 46.77	84.43 ± 62.44		
AST (reference range = 0–37 U/L)			0.024*	

Table 1 (continued)

Patient's characteristics	Patients who received chemotherapy (chemotherapy group) ($N=44$)	Patients who did not received chemotherapy (non-chemotherapy group) ($N=14$)	P value	Total ($N=58$)
Mean ± SD	54.40 ± 43.82	91.07 ± 64.94		
T BIL (reference range = 0–1 mg/dl)				
Mean ± SD	0.76 ± 0.51	1.47 ± 0.69	0.001*	
ALT increase				
Grade 1	1 (2.2%)	2 (14.2%)		3 (5.1%)
Grade 2	2 (4.5%)	0 (0%)		2 (3.4%)
Grade 3	0 (0%)	0 (0%)		0 (0%)
AST increase				
Grade 1	3 (6.8%)	0 (0%)		3 (5.1%)
Grade 2	2 (4.5%)	2 (14.2%)		4 (6.8%)
Grade 3	0 (0%)	2 (14.2%)		2 (3.4%)
T bil				
Grade 1	2 (4.5%)	2 (14.2%)		4 (6.8%)
Grade 2	2 (4.5%)	6 (42.8%)		8 (13.7%)
Grade 3	0 (0%)	0 (0%)		0 (0%)
Baseline HCV RNA (IU/ml log10)				
Mean ± SD	5.66 ± 0.84	6.04 ± 0.79	0.137	
Chemotherapy regimens				
Anthracycline + taxanes based	32 (55.2%)			
Anthracycline based	9 (15.5%)			
Other	3 (5.2%)			
Trastuzumab therapy	8 (18.1%)			
Lapatinib	1 (2.2%)			
Antiviral treatment (7 patients)				7 (12%)
With chemotherapy	3	0		3 (5.2%)
Without chemotherapy	2	2		4 (6.8%)

*Statistically significant P value < 0.005

liver enzymes in 4 patients, and due to both neutropenia and elevated liver enzymes in 3 patients. Twelve (12/44, 27.3%) patients received growth factor support during chemotherapy cycles.

HCV-RNA status

Data about the alterations in HCV-RNA viral load before and after chemotherapy were available for 34 patients. The timing of the HCV-RNA test after the end of chemotherapy ranged from 1 to 3 months. The median HCV-RNA before the initiation of chemotherapy was 5.7 log IU/ml (range 3–7.3) and after completing chemotherapy was 5.9 log IU/ml (range 0-7.1). No significant change in the HCV-RNA level before and after chemotherapy ($p=0.884$), Fig. 1.

We reported 2 patients who had HCV viral reactivation after chemotherapy. The 2 patients didn't receive antiviral treatment. *Patient 1*: A 46 years, diabetic and hypertensive female with a 4-year history of post-transfusion, chronic HCV infection (associated with cirrhosis), developed locally advanced triple negative breast cancer. She was planned to receive neoadjuvant combination chemotherapy of Anthracycline and cyclophosphamide (AC) every 3 weeks alternating with Taxol weekly regimen. Her HCV-RNA at baseline was 6 log (1,034,000 IU/ML). Baseline liver function tests revealed elevated AST [G1, 2.5 × under normal limit (UNL)] and elevated ALT (G1, 1.9 × UNL). The patient received 5 cycles of chemotherapy with progressive increase in her liver function tests, Figs. 2, 3, 4. The sixth cycle was postponed due to development of neutropenia (Neutrophilic count $< 1.5 \times 10^3$/cm^3). 35 days after stopping chemotherapy, the patient developed fulminant hepatitis; ALT 821 Units/L (G3, 12 × UNL), AST 355 Units/L (G3, 12 × UNL) and total bilirubin 4 mg/dl (G3, 4 × UNL). HCV-RNA level was found to be elevated 1 log as compared to pretreatment level (12,500,000 IU/ML, 7 log IU/ML) at the time of hepatic flare. Other potential causes of hepatic flare were excluded serological markers of HBV, Hepatitis A Virus (HAV), Epstein Barr Virus, Cytomegalovirus, Herpes Simplex Virus. No history of alcohol abuse, intake of drugs or herbal remedies nor blood transfusion. The

Table 2 Treatment course

	Total No. (44)
Occurrence of elevated liver enzymes during chemotherapy	20 (45.5%)
Baseline elevated liver enzymes	12/20 (60%)
Newly elevated liver enzymes with chemotherapy	8/20 (40%)
Occurrence of hepatitis viral reactivation	2 (4.5%)
Interruption of chemotherapy	
Incomplete course of chemotherapy	14 (31.8%)
Neutropenia ± thrombocytopenia	8/14
Elevated LFT[a] (grade 3)	3/14
Neutropenia + Elevated LFT (grade 3)	3/14
Dose reduction and/or dose delay	12 (27.2%)
Neutropenia	5/12
Elevated LFT	4/12
Neutropenia + elevated LFT	3/12
Toxicity of chemotherapy other than hepatitis	
Neutropenic fever	8 (18.2%)
Sever nausea and vomiting	5 (11.4%)
Non-neutropenic infections	4 (9%)
Diarrhea	3 (6.8%)
Peripheral neuropathy	3 (6.8%)
Thrombocytopenia	2 (4.6%)

[a]LFT liver function test

patient developed decompensated liver failure in the form of an increase in bilirubin levels, liver enzymes and died.

Patient 2 A 52-year-old female, with a 2-year history of community-acquired, chronic HCV infection (with cirrhosis). Pretreatment HCV RNA level was 5.8 log IU/ml. Baseline liver functions were G1 CTCAE with (ALT 1.5 X UNL, AST 2.4 X UNL). The patient received 6 cycles of chemotherapy (anthracycline-based treatment). Two weeks after completion of the six cycle, she developed elevated ALT, AST and bilirubin levels (G3 toxicity), Figs. 2, 3, 4. Post-treatment HCV-RNA level rose to 6.8 log IU/ml performed 1 month after the end of chemotherapy. The ALT levels declined but remained high till the end of follow up (2 months after last cycle of chemotherapy). All possible aetiological factors of hepatic flare were investigated.

Hepatitis C treatment

Seven patients in our cohort (12%) received antiviral treatment in the form of sofosbuvir (SOVALDI). Antiviral treatments were initiated before start of chemotherapy in three patients before being diagnosed with breast cancer, during the course of chemotherapy in three of patients and after the course of chemotherapy in one patient. Anthracycline-taxanes-based chemotherapy was given to these three patients with concomitant treatment. The most common adverse events (AEs) occurred during concomitant treatment were constitutional in the form of fever, fatigue, flu-like symptoms and myalgias (3; 100%), and gastrointestinal in the form of anorexia, nausea, vomiting, abdominal pain (2, 66.6%). All AEs graded as 2 and 3 grades. One patient (33.3%) who received concomitant treatment required dose modification of chemotherapy owing to AEs (Fatigue and peripheral neuropathy). No discontinuation of chemotherapy was done. Of all patients, four (4/7, 57.1%) achieved sustained viral response (SVR) (HCV-RNA level measured at 3 months after completion of treatments). Only one out of the 3 patients, who received concomitant antiviral treatment with chemotherapy, didn't achieve SVR. Two more patients did not achieve SVR, one patients received antiviral treatment before chemotherapy and the other patient received it after chemotherapy (Table 3).

Discussion

Chronic Hepatitis C Virus infection and Breast cancer are two frequent diseases in Egypt. Chemotherapy greatly improves the prognosis of breast cancer patients. However,

Table 3 HCV treatments for the 7 patients in our cohort

Age (years)	Comorbidities	BMI[a]	Fibrosis grade	Pre-antiviral viral load (IU/ml log10)	Timing of antiviral treatment	Post-antiviral viral load (IU/ml log10)	SVR after 3 mon
67	DM&HTN	40.6	3	6.4	With chemo	5.1	No
35	No	27.7	2	5.5	With chemo	Undetected	Yes
49	No	22.8	2	4.7	With chemo	Undetected	Yes
46	DM&HTN	25.1	3	5.3	Before chemo	Undetected	Yes
59	DM	35	2	5.8	Before chemo	5.6	No
60	No	29.4	3	5.2	Before chemo	Undetected	Yes
56	HTN	27.8	2	6.5	After chemo	5.7	No

SVR sustained viral response

[a]BMI (body mass index): ≥ 30: obese; < 30: non-obese

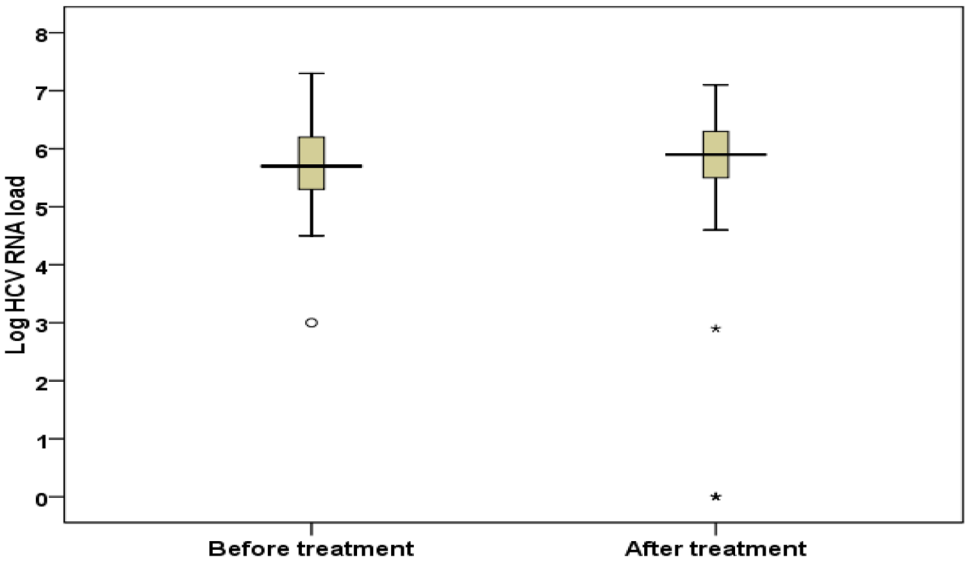

Fig. 1 HCV-RNA level before and after chemotherapy were available in 34 patients ($p = 0.884$)

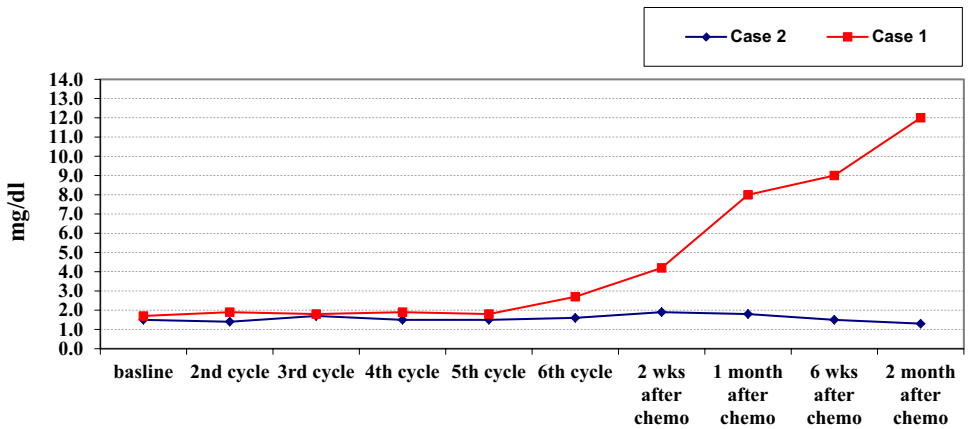

Fig. 2 Graphical evolution of total bilirubin levels in the two cases with HCV reactivation measured during the cycles of chemotherapy and at the time of fulminant hepatitis

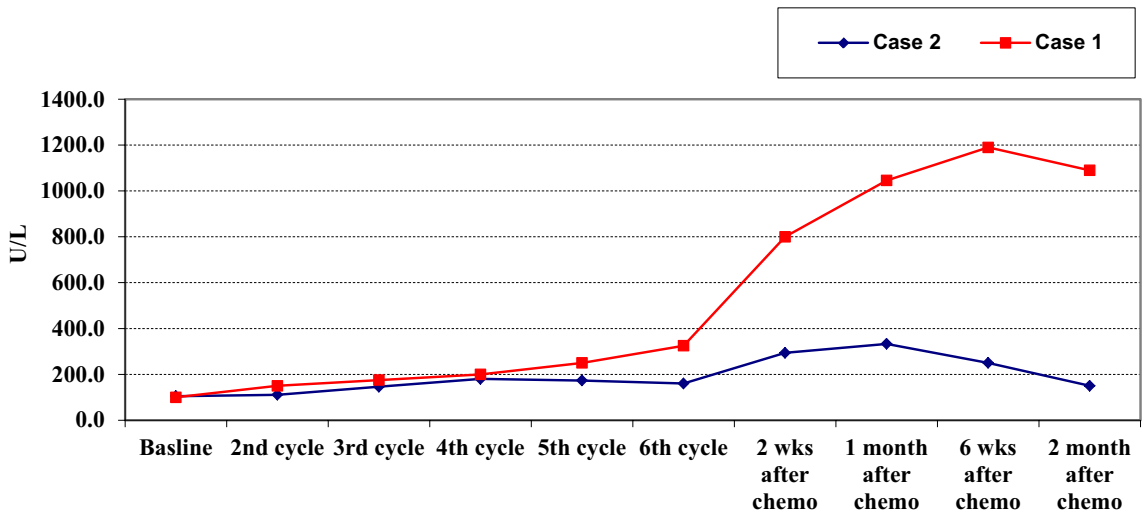

Fig. 3 Time course of ALT measured during the cycles of chemotherapy and at the time of fulminant hepatitis, in the two cases with HCV reactivation

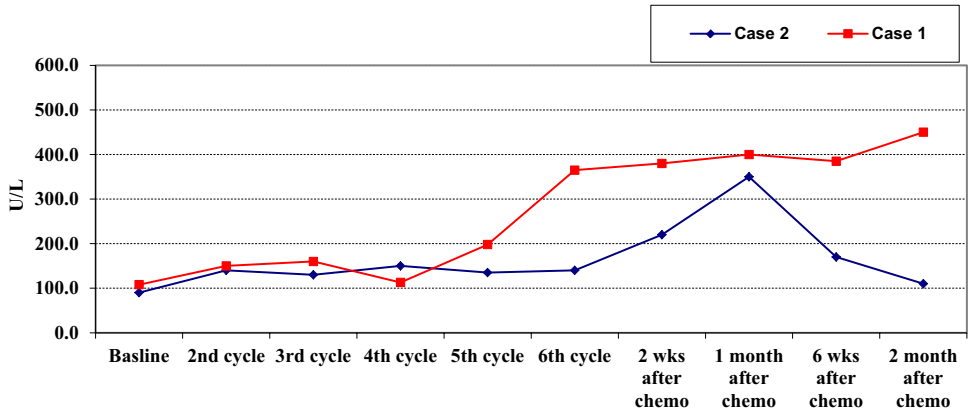

Fig. 4 Time course of AST measured during the cycles of chemotherapy and at the time of fulminant hepatitis, in the two cases with HCV reactivation

it may result in undesirable side effects such as HCV reactivation. The clinical spectrum of viral reactivation ranges from asymptomatic hepatitis to fatal hepatic failure [16]. Little is known with respect to changes in HCV status and viral reactivation during chemotherapy for breast cancer and the influence of HCV infection on chemotherapy remains unclear.

To the best of our knowledge, our data is the largest in the research field of HCV infection associated with breast cancer. Among our group of patients, 2 (3.4%) of patients had HCV viral reactivation. The two patients developed accompanied hepatitis flare. One of them died due to fulminant hepatitis, 2 months after the end of chemotherapy. Currently, no reliable methods exist to predict an individual's risk of HCV reactivation. However, greater attention should be paid to the possibility of HCV reactivation in any patient with a history of HCV infection undergoing immunosuppressive therapy.

Both patients had viral reactivation and liver dysfunction after the end of chemotherapy. The timing of HCV reactivation caused by chemotherapy drug administration could vary. However, several studies observed that HCV reactivation and liver dysfunction generally occurs 2–4 weeks after the cessation of chemotherapy [17–19].

This may be explained by rebound phenomena. During period of immunosuppression by chemotherapy, viral replication occurs leading to infection of hepatocytes. Withdrawal of immunosuppressive therapy and subsequent restoration of the immune function, results in destruction of infected hepatocytes with hepatic injury and necrosis [20].

Anthracycline chemotherapy is known to be associated with increased risk of HBV reactivation. In particular, epirubicin was found to be associated with in vitro upregulation of HBV replication level [21]. There is need for further research to verify whether similar mechanisms of reactivation of HCV virus occur with anthracyclines.

The presence of liver cirrhosis (LC) was found to be a risk factor for enhanced HCV replication. In a retrospective study by Lee, et al., in patients who underwent systemic chemotherapy, corticosteroid therapy, or other immunosuppressive therapies, four of five patients with LC had enhanced HCV replication [22]. Altered immunity or the profound abnormalities in B-cell phenotype and function which are commonly found in patients with cirrhotic liver may contribute in HCV reactivation [23]. LC was present in both of our patients with HCV reactivation.

Moreover, both of our patients with HCV reactivation had elevated baseline ALT. Alanine transferase levels are generally known as sensitive indicators of liver injury [24]. Patients with higher incidence to develop HCV reactivation were found to have elevated baseline ALT [25].

Steroid medications were reported to be a risk factor for HCV reactivation. In a study by Magy et al., steroids were found to stimulate HCV replication in vitro [26]. Moreover, Fong, et al. found that patients with chronic hepatitis C had an increase in their HCV-RNA levels upon administration of a 7-week course of a tapering dose of prednisone [27]. However, if used for only a short time as an antiemetic per each cycle, was not found to be a significant factor for HCV reactivation [22].

Elevated liver enzymes were developed in 20 (45.5%) out of 44 patients who received chemotherapy. These elevations weren't accompanied with clinically meaningful changes (< 1 log) in HCV-RNA viral load. Welaya et al. reported that, throughout the whole six cycles of chemotherapy, 21 (42%) patients of HCV seropositive patients developed elevated SGOT compared to 28% in HCV seronegative. As regards SGPT level, 34% of patients in HCV seropositive had elevated SGPT level compared to 18% in HCV seronegative [28]. However, Morrow et al. reported that 25% of their patients experienced elevations in aminotransferases and HCV viral load wasn't evaluated in their study [29]. In the study of Liu Y et al., HCV-infected patients with breast cancer, five (23.8%) patients who received chemotherapy developed hepatitis. No patients presented with HCV reactivation [29]. Among our patients who planned to receive chemotherapy, only thirty patients (30/44, 68.2%) completed their treatment. The remaining patients (14/44, 31.8%) didn't

complete their intended number of chemotherapy cycles due to either chemotherapy sequelae and/or abnormal liver functions. Dose reductions or dose delays were common ($n = 12/44$, 27.2%). A retrospective study conducted by Morrow et al. in HCV-positive breast cancer patients treated in MD Anderson Cancer Center (MDACC) reported that 36 out of 44 (81%) of patients received chemotherapy. Thirty-three (92%) of them were able to complete the initial planned number of cycles [29]. More patients were able to complete treatment in their study as compared to our and this is may be due to the antiviral treatment received by about 20% of their cases compared to 7 out of 58 (12%) patients in our cohort. Antiviral therapy was given to our patients with no major complications observed.

Antiviral therapy and viral eradication may improve liver function allowing for better tolerance of multiple cancer chemotherapies and reduce the risk of developing HCV reactivation which can lead to hepatic flare and death [25]. In our study 7 patients received antiviral treatment. Antiviral therapy was initiated concomitantly with chemotherapy in 3 of the patients with minimal side effects. concomitant antiviral treatment with selected antineoplastic agents could achieve viral clearance, normalization of ALT levels and prevent delays in the administration of chemotherapy in HCV-infected patients with cancer [30]. SVR rates seem to be similar to those observed in HCV-infected patients without cancer. In our study, 3 patients didn't achieve SVR. The causes of not achieving SVR are unclear but may be due to old age, comorbidities or high pretreatment viral load.

In the current study, 8 (13.8%) patients with HER-2-positive breast cancer received trastuzumab therapy and one patient received lapatinib. No clinically meaningful HCV-RNA viral load or increased liver enzymes were observed in breast cancer patients receiving trastuzumab therapy. This data may confirm the safe administration of trastuzumab in breast cancer patients with HCV infection. Coinciding with our results, Yu Liu et al. confirmed the safety of trastuzumab administration in her2 positive patients with breast cancer and HCV infection [31].

Conclusion and future directions

Our findings indicate that greater attention should be paid to the possibility of complications including HCV reactivation, fulminant hepatitis and interrupted chemotherapy treatments in breast cancer patients with chronic HCV infection receiving immunosuppressive drugs. Data about risk factors to predict complications and viral replication are still lacking. Further prospective studies on the incidence, risk factors and clinical outcome of enhanced HCV replication during chemotherapy are warranted.

Recommendations

Close monitoring of patients with breast cancer and HCV infection should be done. Measurement of ALT every 1–2 weeks and HCV-RNA every 4 weeks during and after chemotherapy is recommended. If ALT level increased > threefold and HCV-RNA level increased at least 1 log IU/Ml compared to baseline level, it is reasonable to consider discontinuation of chemotherapy if increasing of liver enzymes precludes the use of cytotoxic drugs.

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Compliance with ethical standards

Conflict of interest Authors declared no conflicts of interest.

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