Research Paper

The Safety of Chemotherapy for Breast Cancer Patients with Hepatitis C Virus Infection

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Abstract

Background: Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease, and more than 880,000 people are estimated to be infected with HCV in Japan. Little information is available on the outcomes of HCV during chemotherapy for solid tumors, and the impact of HCV infection on toxicity of chemotherapy is unknown.

Materials and methods: We performed a retrospective survey of 1,110 patients diagnosed with breast cancer between January 2006 and March 2011 at our institution. All patients had been screened for hepatitis C serology at diagnosis of breast cancer. We retrospectively investigated the change in HCV load and the toxicities of chemotherapy, based on review of their medical records.

Results: 23 patients were identified as having a positive test for anti-HCV antibodies. Ten of these patients received chemotherapy. Their median age was 66 years. No patient had decompensated liver disease at baseline. Eight patients received cytotoxic agents with or without trastuzumab, and two patients received trastuzumab alone. Four of eight patients who received cytotoxic chemotherapy developed febrile neutropenia and one developed transaminases elevation. Serum HCV-ribonucleic acid (RNA) level before and after chemotherapy was evaluated in six patients. Median serum HCV-RNA level at baseline and after chemotherapy was 6.5 and 6.7 logIU/ml, respectively.

Conclusion: Chemotherapy for breast cancer patients with HCV infection is feasible, and viral load doesn't change during the chemotherapy.

Key words: HCV, HCV-RNA, febrile neutropenia, Child-Pugh criteria, liver cirrhosis, chemotherapy.

Introduction

Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease, and more than 880,000 people are estimated to be infected with HCV in Japan (1). The estimated number of HCV carriers increases with age, therefore, carriers aged from 40 to 69 years account for more than 80% of cases (1). Breast cancer is the most common cancer among Japanese women (2). Furthermore, the age-adjusted breast cancer incidence rate has been increasing since 1975, and the incidence rate of breast cancer is highest in the

age group of 40-49 years in Japan (2).

Little information is available on the status of HCV during chemotherapy for solid tumors and the influence of HCV infection on toxicity of chemotherapy is also unknown. Although there are guidelines for management of patients with Hepatitis B virus during chemotherapy, there are no data to support the use of chemotherapy to treat HCV-positive patients with solid tumors (3, 4). Some reports have noted the reactivation of HCV in patients with lymphoma who have received rituximab and combination chemotherapy (5, 6). However, there are substantial differences in immunosuppressive mechanisms between rituximab-based chemotherapy for hematologic malignancies and conventional chemotherapy for solid tumor, because rituximab, an anti-CD20 antigen, mainly inhibits B-cell function. Therefore, it may not be appropriate to use the same management during chemotherapy for HCV carrier patients with solid tumors.

The purpose of this study was to evaluate the safety profile and the change in HCV viral load during chemotherapy for HCV-carrier patients with breast cancer.

Materials and methods

Following data collection and analysis was approved by the Institutional Review Board of Toranomon hospital.

Patients

We performed a retrospective survey of 1,110 patients diagnosed with breast cancer between January 2006 and March 2011 at our institution. All patients had been screened for hepatitis C serology determined by anti-HCV antibody at diagnosis of breast cancer. Our survey identified 23 patients who were positive for anti-HCV antibodies. The incidence of HCV-positive in breast cancer patients in our institution (23/1,100 [2.1%]) is comparable to that in same age range of general women population (3,221/151,501 [2.1%]) (1). Ten of these 23 patients received cytotoxic agents and/or trastuzumab. We retrospectively investigated the baseline patient and tumor characteristics, the changes in HCV load, and the toxicities of chemotherapy for these ten patients, based on review of their medical records.

Assessment of breast cancer characteristics

We collected American Joint Commission on Cancer stage, hormone receptor (HR) status and human epidermal growth factor-2 (HER2)/neu status using immunohistochemistry (IHC) and/or fluorescent *in situ* hybridization (FISH) at breast cancer di-

agnosis. We classified HR-positive as estrogen receptor (ER) positive and/or progesterone receptor (PgR) positive using IHC. The cut point for ER and PgR positivity was an Allred score of 3 (7). HER2 status was defined as positive if an IHC assay demonstrated 3+ or an IHC score of 2+ with FISH demonstrated a gene copy ratio of HER2: CEP17 more than 2.2 (8).

Assessment of HCV infection status

The presence of anti-HCV antibodies was detected using chemiluminescence enzyme immunoassay (Lumipulse Ortho HCV antigen, Ortho-Clinical Diagnostics, Tokyo, Japan) at breast cancer diagnosis. HCV ribonucleic acid (RNA) in serum was detected by a TaqMan Real-Time polymerase chain reaction (PCR) assay (SRL, Tokyo, Japan). In 6 patients, serum HCV-RNA was evaluated before the initiation of chemotherapy and within two months after completing chemotherapy.

Assessment of liver function

Liver cirrhosis was assessed by clinical criteria (Child-Pugh criteria) at baseline. Data of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin 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.

Assessment of other toxicities

White blood cell count, neutrophil count, platelet count at baseline and during chemotherapy were collected and assessed by CTCAE version 4.0. Events of febrile neutropenia and the use of growth factor support during chemotherapy were collected.

Results

Patients' characteristics

Ten of 23 HCV-positive patients with breast cancer received cytotoxic agents and/or trastuzumab. Among the remaining 13 patients, ten received only endocrine therapy, two had ductal carcinoma in situ and one was lost to follow-up. The reasons for receiving only hormone therapy among the ten patients included the following; five were low risk of recurrence, three were elderly, age over 75, and two had decompensated liver function.

Patients and tumor characteristics are shown in Table 1. The median age at receiving chemotherapy was 66 (range 55-77). Most patients (80%) had stage II or III disease. Tumor histology of all patients was invasive ductal carcinoma. Tumors were classified on the bases of estrogen/progesterone receptor and

HER2 status. Three tumors were HR-positive/ HER2-positive, one was HR-positive/HER2-negative, three were HR-negative/HER2-positive, and three tumors were HR-negative/ HER2-negative, respectively. Three patients had a diagnosis of liver cirrhosis. One patient was classified Child B, the remaining two patients were Child A. No patient had decompensated liver disease at baseline.

Treatment course and safety

Table 2 shows the chemotherapy regimens and their associated documented toxicities. Among the 10 patients who received chemotherapy, three patients received an anthracycline-based regimen, two received anthracycline followed by taxane, two received trastuzumab, two received combination therapy with docetaxel, cyclophosphamide and trastuzumab, and one received gemcitabine.

All patients other than the two who received trastuzumab used dexamethasone as antiemetic prophylaxis. The dose of dexamethasone followed American Society of Clinical Oncology Clinical Practice Guidelines (9, 10).

Six (75%) of eight patients who received cytotoxic chemotherapy developed grade 4 neutropenia and four (50%) developed febrile neutropenia. Transaminases elevated in one (13%) of eight patients who received cytotoxic chemotherapy. This patient had Child A liver cirrhosis and transaminase elevation at baseline. Four patients received granulocyte colony-stimulating factor (G-CSF). All received the non-pegylated formulation G-CSF. Three patients received G-CSF as a therapeutic use for neutropenia without fever. Two of these patients developed febrile neutropenia. One patient who received G-CSF as a secondary prophylaxis did not develop febrile neutropenia during G-CSF support. No patients received prophylactic antibiotics.

HCV-RNA status

Table 3 showed the change in HCV-RNA in six patients. The median HCV-RNA before the initiation of chemotherapy was 6.5 log IU/ml and after completing chemotherapy was 6.7 log IU/ml.

Table 1. Patients' characteristics.

Case	Age	Stage	Histology	Hormone receptor	HER2 status	LC	Prior HCV therapy
1	63	IIA	IDC	negative	negative	negative	positive
2	50	IIA	IDC	positive	negative	negative	negative
3	50	IIIA	IDC	positive	negative	negative	negative
4	61	IIB	IDC	negative	positive	negative	negative
5	71	IIA	IDC	negative	positive	negative	positive
6	64	IIA	IDC	positive	positive	positive	negative
7	67	IV	IDC	negative	negative	positive	positive
8	69	IIA	IDC	negative	positive	negative	negative
9	60	IIA	IDC	negative	negative	negative	negative
10	74	IV	IDC	positive	negative	positive	negative

LC: liver cirrhosis, HCV: hepatitis C virus, IDC: invasive ductal carcinoma.

Table 2. Toxicities

Case	Chemotherapy regimen	Transaminase baseline	Transaminase increase (grade)	WBC/Plt baseline	Neutropenia (grade)	Thrombocytopenia (grade)	G-CSF	FN	dose reduction (%)
1	EC	increase	0	normal	4	3	positive	positive	0
2	EC	normal	0	normal	0	0	negative	negative	0
3	EC	normal	0	normal	4	1	positive	negative	0
	DTX	normal	0	normal	4	0	positive	positive	75
4	TCH	normal	0	normal	4	1	positive	negative	0
5	H	normal	0	normal	0	0	negative	negative	0
6	H	normal	0	decrease	0	0	negative	negative	0
7	EC	increase	1	decrease	4	3	negative	positive	75
8	TCH	normal	0	normal	3	0	negative	negative	0
9	EC	normal	0	normal	4	3	positive	positive	0
	wPTX	normal	0	decrease	4	2	positive	negative	0
10	G	increase	0	decrease	4	3	negative	negative	75

WBC: white blood cell count, Plt: platelets count, G-CSF: granulocyte colony stimulating factor, FN: febrile neutropenia, EC: epirubicine + cyclophosphamide, DTX: docetaxel, TCH: docetaxel + cyclophosphamide + trastuzumab, H: trastuzumab, wPTX: weekly paclitaxel, G: gemcitabine.

Table 3. HCV viral load.

Case	HCV-RNA baseline	HCV-RNA after chemotherapy
1	NA	NA
2	6.3	6.9
3	6.7	6.7
4	NA	NA
5	6.2	6.5
6	6.5	6
7	6.7	6.7
8	6.5	6.9
9	NA	NA
10	NA	NA

NA: not assessed.

Discussion

The present study demonstrates that chemotherapy for breast cancer patients with HCV infection is feasible, and viral load does not vary during the chemotherapy.

A previous study reported that chemotherapy induced elevation of transaminases in patients with HCV infection (5, 11); however the relationship between increase in HCV-RNA and transaminase elevation is poorly investigated. Morrow et al. showed that nine of 36 (25%) HCV positive patients who received chemotherapy for breast cancer developed elevated liver enzymes, but their study did not evaluate HCV load (12). Our study demonstrated no clinically meaningful changes in HCV-RNA viral load in breast cancer patients who received cytotoxic chemotherapy and/or trastuzumab. It also showed that only one patient (13%) had transaminase elevation during chemotherapy. This patient's HCV-RNA was the same before and after chemotherapy. These findings suggest that the elevation of transaminase in our study might not be related to viral reactivation but direct liver toxicity from cytotoxic agents.

Some studies have suggested that B-cell mediated immunosuppression induced by rituximab results in the elevation of transaminase (5, 6, 13). Coppola et al. showed that rituximab-based chemotherapy resulted in an increase in HCV-RNA at least 1.5 log IU/ml (median 2.2 [range 1.5-2.6]) followed by hepatic flare (defined as ALT elevation of more than five times of upper limit of normal or more than 3.6 time of baseline ALT) among patients with lymphoma (6). However, the mechanism of liver injury in HCV infection is still unclear. Further investigations in the relationship between HCV load and liver injury are warranted.

Previous studies showed a negative impact of corticosteroids on HCV viral load (14). These studies also demonstrated that cumulative exposure to corticosteroids is associated with higher levels of HCV viremia (14). Meanwhile, our study showed that the exposure to dexamethasone use as an antiemetic might not affect HCV viral load.

Our study showed that 87.5% patients who received cytotoxic agents developed grade 3-4 neutropenia. Although the incidence of neutropenia depends on the timing and the frequency of blood tests, it is important to note that febrile neutropenia occurred in 50% of patients who received cytotoxic chemotherapy in our study. A previous study from MD Anderson Cancer Center showed that eight of 36 (22%) developed febrile neutropenia (12). Some hypotheses can be raised concerning the causes of the high incidence of febrile neutropenia in our study. The median age of 66 years in the current study was higher than that of the previous report from MD Anderson Cancer Center (48 years) and the highest incidence age of breast cancer in Japan (40-49 years) (2, 12). These findings suggest that older age might contribute to developing the greater incidence of febrile neutropenia as seen in our study. Previous studies of adjuvant chemotherapy for older patients with breast cancer showed that older patients had greater hematologic toxicity, especially neutropenia and febrile neutropenia compared to younger individuals (15, 16). Other potential causes of the high incidence of febrile neutropenia could be considered. Chronic HCV infection may lead to an immunocompromised status such as neutrophil or T-cell dysfunction. Neutropenia can be seen in patients with chronic hepatitis C infection due to cirrhosis and hypersplenism. Although four of ten patients had white blood cell counts decrease (grade 1-2) at baseline in the current study, only one of them developed febrile neutropenia (table 2). Although the relationship between HCV infection and the high incidence of febrile neutropenia is uncertain, clinicians should be concerned with the risk of high-grade neutropenia and febrile neutropenia in HCV-positive patients who receive cytotoxic agents.

Conclusion

Chemotherapy for breast cancer patients with HCV infection is feasible and clinically indicated therapy should not be withheld due to positive HCV serology. Caution regarding neutropenia/ febrile neutropenia is warranted. Use of growth factors may be considered. However, the present study is too small to draw a definite conclusion on the safety of chemotherapy for solid tumors. Further large-scaled investigations are warranted.

Abbreviations

HCV: Hepatitis C virus; RNA: ribonucleic acid; HR: hormone receptor; IHC: immunohistochemistry; HER2: human epidermal growth factor-2; FISH: fluorescent *in situ* hybridization; PCR: polymerase chain reaction; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; G-CSF: granulocyte colony-stimulating factor.

Acknowledgement

Ethics Committee Approval

The data collection and analysis of the current study was approved by the Institutional Review Board of Toranomon hospital.

Competing interests

Dr. Kumada received grant from MSD K.K., Bristol-Myers Squibb K.K., Dainippon Sumitomo Pharma, and Daiichi Sankyo. All other authors state that they have no conflicts of interest.

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