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CLINICAL TRIAL

A single-center, prospective and randomized controlled study: Can the prophylactic use of lamivudine prevent hepatitis B virus reactivation in hepatitis B s-antigen seropositive breast cancer patients during chemotherapy?

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Abstract Over the past four decades, chemotherapy has played an important role in prolonging survival in breast cancer patients. However, it may also result in undesirable side effects such as hepatitis B virus (HBV) reactivation seen in this study. With the increasing use of chemotherapy paralleling the rise in breast cancer incidence, the occurrence of HBV reactivation is likely to further increase. Several strategies use lamivudine to deal with this problem. Initially, lamivudine had been used to treat patients who developed alanine transaminase elevation attributable to HBV reactivation during chemotherapy. However, using this strategy, fatal reactivation has also been reported. Later studies have suggested that prophylactic lamivudine significantly reduces HBV reactivation and its associated morbidity. However, these studies were based mainly on patients with lymphoma, whereas studies on breast cancer patients were few. Moreover, these studies were retrospective. Recently, a prospective study has recommended that deferred preemptive lamivudine could be a comparable alternative to the prophylactic strategy. However, it was not a randomized controlled study. In this study, it was examined the efficacy of the prophylactic strategy in hepatitis B s-antigen seropositive breast cancer patients during chemotherapy using a prospective, randomized controlled study. Two groups were studied. One group consisted of 21 patients who were treated with prophylactic lamivudine, the other group consisted of 21 patients who were not treated with prophylactic lamivudine. The results showed that the prophylactic lamivudine strategy significantly decreased the incidence of HBV reactivation (0 vs. 28.6%, $P = 0.021$). It was conclude that the prophylactic lamivudine strategy significantly reduces the incidence of HBV reactivation for hepatitis B s-antigen seropositive breast cancer undergoing chemotherapy.

Keywords Breast cancer · Chemotherapy · Hepatitis B virus reactivation · Lamivudine

Introduction

Recently, many patients with breast cancer have received chemotherapy after (adjuvant) or before (neoadjuvant) locoregional treatment. Chemotherapy is also used for the treatment of metastatic breast cancer (salvage). An increasing number of clinical trials have shown that chemotherapy can prolong survival in breast cancer patients. However, chemotherapy is a toxic therapy. For this reason, it is important to evaluate not only which breast cancer patients can benefit from chemotherapy but also what consequences they suffer from receiving it.

China is an area with a high prevalence of hepatitis B virus (HBV) infection. For hepatitis B s-antigen seropositive (HBsAg+) cancer patients who are undergoing chemotherapy, HBV reactivation has become a well-known complication [1].The condition is characterized by elevated levels of serum HBV-DNA, abnormal liver function tests, and clinical hepatitis of varying degrees of severity that ranges from anicteric hepatitis to severe, progressive hepatic failure, which may result in death. Early reports

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of HBV reactivation mainly involved patients with hematologic malignancies [1–7], but more recently, reports have described reactivation in patients with solid tumors [8–10]. In patients receiving chemotherapy for solid tumors, the highest rates of HBV reactivation have been reported in breast cancer patients, in whom the incidence ranges between 41% and 56% [11, 12]. With the increasing use of chemotherapy paralleling the rise in breast cancer incidence, the occurrence of HBV reactivation is likely to further increase, and it is becoming a critical clinical problem.

Since 1998, the administration of the antiviral agent lamivudine after alanine transaminase (ALT) elevation attributable to HBV reactivation in HBsAg+ cancer patients has been reported to have a role in controlling HBV reactivation during chemotherapy [13–16]. However, using this approach, fatal reactivation has also been reported [10, 15, 17]. Even for those who do recover from this complication, their cancer prognosis may be impaired because of the disruption in the chemotherapy treatments. If HBV reactivation could be prevented during chemotherapy, it would do more good than harm for cancer patients.

Over the past decade, it has been recognized that HBV reactivation and its associated fatality during chemotherapy can be prevented effectively by the use of prophylactic lamivudine. However, the relevant studies have been based mainly on patients with lymphoma [18–21], whereas information on breast cancer patients has been lacking [12, 22–24]. Studies addressing breast cancer patients have been retrospective.

Recently, a prospective study suggested that deferred preemptive lamivudine based on HBV DNA surveillance was able to control HBV replication and prevent its reactivation in breast cancer patients undergoing chemotherapy [25]. However, it was not a randomized controlled study. Therefore, to reduce spurious causality and bias and to obtain the highest-quality scientific conclusion, a prospective, randomized controlled clinical study should be initiated.

The purpose of this study was to examine the efficacy of the prophylactic lamivudine strategy using a prospective, randomized controlled study in HBsAg+ breast cancer patients.

Patients and methods

The authors studied two groups of patients. One group consisted of 21 patients who were treated with prophylactic lamivudine. The other group consisted of 21 patients who were not treated with prophylactic lamivudine. HBsAg+ breast cancer patients who required chemotherapy were enrolled into these two groups randomly, and all of the patients in this study signed informed consent agreements. The protocol was approved by the Clinical Research Ethics Committee of the Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University.

Entry and exclusion criteria

Based on criteria initially described by Yeo et al. [23] and subsequently modified by us, breast cancer patients who were HBsAg+ were eligible if they were otherwise fit for intravenous chemotherapy and if they were able to visit the clinic at least every 21 days during the study.

For both groups, the exclusion criteria included patients who had decompensated liver disease at screening (as indicated by any of the following: ALT $> 10\times$ upper limit of normal (ULN) (i.e., >580 U/l), total bilirubin (TBIL) >50 μmol/l, albumin (ALB) <20 g/l, prothrombin time (PT) >4 s prolonged, history of ascites, variceal hemorrhage, or hepatic encephalopathy); those who had been treated with chronic antiviral therapy known to have activity against HBV (e.g., α-IFN, adefovir, entecavir, telbivudine, or tenofovir) within the previous 6 months; those who had acute fulminant hepatitis; those who were recipients of any investigational new drug (new chemical entity) within 30 days of the first dose of the study drug; and those who were pregnant, lactating, or had pancreatitis.

Investigations

Before beginning the study, both groups of patients underwent the following tests: viral marker status (VMS, which included hepatitis B s-antigen/antibody (HBsAg/HBsAb), hepatitis B e-antigen/antibody (HBeAg/HBeAb), hepatitis B c-antigen/antibody (HBcAg/HBcAb), hepatitis B PreS1-antigen (HB-PreS1-Ag) and HBV DNA quantitation), liver function test (LFT, which included ALT, TBIL, ALB, and PT), complete blood picture (CBP, which included white cell count, red cell count and hemoglobin, and platelet count), renal function test (RFT, which included sodium, potassium, urea, creatinine, and creatinine clearance) and liver ultrasonography.

During the course of chemotherapy, on day 1 of each cycle, CBP, RFT, LFT, and HBV DNA quantitation were monitored along with clinical signs and symptoms in all patients. Monitoring of these parameters was continued for 8 weeks after the completion of chemotherapy.

When a patient was found to have hepatitis attributable to HBV reactivation (as defined in the Definitions section) during the course of chemotherapy, tests for hepatitis A, C, D, E, and G were performed; and other parameters as clinically indicated.

HBV DNA assay

The HBV DNA quantitation was measured with real-time fluorescent PCR, which has a detection limit of 1×10^3 copies/ml.

Definitions

Based on a definition initially described by Lok et al. [4] and subsequently modified by Yeo et al. [10], hepatitis has been defined as a threefold or more increase in ALT that exceeds the ULN (<58 U/l) or an absolute increase of ALT to more than 100 U/l when compared with the baseline prechemotherapy value. Hepatitis attributable to HBV reactivation was defined as an increase in the HBV DNA level of tenfold or more when compared with the baseline level or an absolute increase of the HBV DNA level that exceeds 1×10^9 copies/ml in the absence of any other systemic infection.

Use of lamivudine

The prophylactic lamivudine group

Patients received oral lamivudine (100 mg) daily for 7 days prior to the commencement of their chemotherapy. Treatment was then continued throughout the course of chemotherapy and until 8 weeks after its discontinuation.

Patients were withdrawn from the study if there was undue toxicity from lamivudine, if a female patient was found to be pregnant at any point during the study or upon a patient's request.

The control group

Prophylactic lamivudine was not administered. Patients received lamivudine 100 mg orally daily only after proven HBV reactivation during chemotherapy. Treatment was continued for at least 8 weeks after the discontinuation of chemotherapy.

Statistical methods

The baseline characteristics between the two groups of patients were compared. These included age; stage; type of surgery; pathology of tumor; VMS; LFT; liver ultrasonography; and whether the chemotherapy was given as neoadjuvant, adjuvant, or salvage. In addition, the chemotherapeutic regimens given to the two groups of patients were compared.

The primary outcomes of this study were the proportion of patients with HBV reactivation and HBV-associated morbidity, as defined in the previous section.

Statistical significance was evaluated by use of the χ^2 test (Fisher's exact test) for categorical variables and the Mann–Whitney U test for numerical variables; differences were deemed significant when $P < 0.05$.

Results

Baseline characteristics of the two groups of patients (Table 1)

A total of 42 patients were studied; all were female. Twenty-one patients were included in the control group, and 21 were in the prophylactic lamivudine group.

There were no statistically significant differences in terms of age, stage, type of surgery, pathology of tumor, VMS, LFT, or liver ultrasonography between the two groups. In addition, both the indications for chemotherapy and the chemotherapeutic regimens were similar.

Biochemical, virological, and clinical outcomes in the two groups of patients (Table 2)

The prophylactic lamivudine group

The median number of chemotherapy cycles the patients received in total was 6 (range: 4–8). Five patients (23.8%) developed hepatitis during chemotherapy; none of these five patients had hepatitis because of HBV reactivation. These cases were instead due to the chemotherapeutic drugs. The severity of hepatitis was mild in three patients (14.3%) and severe in two patients (9.5%). Disruption of chemotherapy occurred in four patients (19.0%), none of these disruptions were due to HBV reactivation. One patient (4.8%) had chemotherapy prematurely terminated because of a chemotherapeutic drug allergy, and three patients (14.3%) completed chemotherapy with delays; one of the delays was due to pneumonia.

The antiviral agent was well tolerated and was not associated with any unexpected effects or additional toxicity.

The control group

The median number of chemotherapy cycles was 6 (range: 1–8). Six patients (28.6%) developed HBV reactivation during the study period without the occurrence of clinical hepatitis. However, three of the 21 patients (14.3%) developed hepatitis, all resulting from chemotherapeutic drugs. The severity of hepatitis was mild in two patients (9.5%) and moderate in one patient (4.8%). Disruption of chemotherapy occurred in two patients (9.5%) without the occurrence of HBV reactivation. One patient (4.8%) had

Table 1 Comparison between the 'prophylactic lamivudine' and 'control' groups

	'control' group		'prophylactic lamivudine' group		*P*-value
	No.	%	No.	%	
Total no. of patients	21	–	21	–	
No. of females	21	100	21	100	
Median age (range)	43(20–62)	–	45(29–64)	–	0.696[a]
Stage					
I	4	19.0	10	47.6	0.174[b]
II	14	66.7	8	38.1	
III	1	4.8	2	9.5	
IV	2	9.5	1	4.8	
Type of surgery					
Breast-conserving surgery	11	52.4	11	52.4	1.000[b]
Mastectomy	8	38.1	8	38.1	
Tumor pathology					
Histology					
Invasive ductal carcinoma	17	81.0	16	76.2	1.000[b]
Noninvasive ductal carcinoma	4	19.0	5	23.8	
Immunohistochemistry					
ER status					
Negative	6	28.6	9	42.9	0.520[b]
Positive	15	71.4	12	57.1	
PR status					
Negative	6	28.6	12	57.1	0.118[b]
Positive	15	71.4	9	42.9	
CerbB-2 status					
Negative	17	81.0	15	71.4	0.719[b]
Positive	4	19.0	6	28.6	
Median ki67 (range)	0.35(0.00–0.90)	–	0.39(0.00–0.80)	–	0.480[a]
Median P53 (range)	0.21(0.00–0.90)	–	0.15(0.00–0.85)	–	0.485[a]
Median TOPO (range)	0.13(0.00–0.60)	–	0.13(0.00–0.45)	–	0.395[a]
Viral marker status					
HBsAb					
Negative	20	95.2	19	90.5	1.000[b]
Positive	1	4.8	2	9.5	
HBeAg					
Negative	18	85.7	19	90.5	1.000[b]
Positive	3	14.3	2	9.5	
HBeAb					
Negative	4	19.0	3	14.3	1.000[b]
Positive	17	81.0	18	85.7	
HBcAg					
Negative	13	61.9	14	66.7	1.000[b]
Positive	3	14.3	2	9.5	
Missing	5	23.8	5	23.8	
HBcAb					
Negative	1	4.8	0	0	1.000[b]
Positive	20	95.2	21	100	
HB-PreS1-Ag status					
Negative	15	71.4	13	61.9	0.744[b]

Table 1 continued

	'control' group		'prophylactic lamivudine' group		*P*-value
	No.	%	No.	%	
Positive	6	28.6	8	38.1	
Median HBV-DNA quantitation (copies/mL)	3.99×10^6 ($<1.00 \times 10^3$–8.28×10^7)	–	6.16×10^6 ($<1.00 \times 10^3$–9.80×10^7)	–	0.110[a]
Liver function tests (range)					
Median ALT (U/L)	14.6(6.0–27.0)	–	22.3(7.0–96.0)	–	0.130[a]
Median TBIL (μmol/L)	16.7(6.4–44.1)	–	13.6(5.6–21.6)	–	0.302[a]
Median ALB (g/L)	43.1(26.0–51.0)	–	44.8(42.0–50.6)	–	0.283[a]
Median PT (s)	11.8(10.1–23.9)	–	11.3(10.0–13.4)	–	0.940[a]
Liver ultrasonography					
Normal	19	90.4	15	71.4	0.155[b]
Fatty liver	1	4.8	3	14.3	
Liver cyst	0	0	3	14.3	
Liver hemangioma	1	4.8	0	0	
Type of chemotherapy					
Neoadjuvant	1	4.8	2	9.5	0.560[b]
Adjuvant	14	66.7	17	80.9	
Neoadjuvant + Adjuvant	4	19.0	1	4.8	
Salvage	2	9.5	1	4.8	
Chemotherapeutic regimen(s)					
Anthracyclin based	1	4.8	2	9.5	0.257[b]
Taxane based	4	19.0	7	33.3	
Anthracycline + taxane based	16	76.2	10	47.7	
Others	0	0	2	9.5	

[a] Mann–Whitney U test

[b] Fisher's exact test

Table 2 Morbidity and mortality in the 'prophylactic lamivudine' and 'control' groups during the study period

	'control' group		'prophylactic lamivudine' group		*P*-value
	No.	%	No.	%	
Overall morbidity					
Occurrence of HBV reactivation	6	28.6	0	0	0.021[b]
Occurrence of hepatitis	3	14.3	5	23.8	0.697[b]
Hepatitis attributable to HBV reactivation	0	0	0	0	0.697[b]
Hepatitis attributable to other causes	3	14.3	5	23.8	
Chemotherapeutic drugs	3	14.3	5	23.8	
Severity of hepatitis					
Mild (ALT $\leq 2 \times$ UNL)	2	9.5	3	14.3	0.576[b]
Moderate (ALT $> \times 2$ and $\leq \times 5$UNL)	1	4.8	0	0	
Severe (ALT $>5 \times$ UNL)	0	0	2	9.5	
Disruptions of Chemotherapy	2	9.5	4	19.0	0.663[b]
Premature termination	1	4.8	1	4.8	1.000[b]
Hepatitis, all cases	0	0	0	0	1.000[b]
Poor tolerance	1	4.8	0	0	
Other causes	0	0	1	4.8	
Chemotherapeutic drug allergy	0	0	1	4.8	
Completed chemotherapy with delay of $\geq$8 days	1	4.8	3	14.3	0.606[b]

Table 2 continued

	'control' group		'prophylactic lamivudine' group		*P*-value
	No.	%	No.	%	
Hepatitis, all cases	1	4.8	2	9.5	0.606[b]
Hepatitis due to HBV reactivation	0	0	0	0	
Other causes	0	0	1	4.8	
Pneumonia	0	0	1	4.8	
Median no. of chemotherapy cycles received (range)	6(1–8)	–	6(4–8)	–	0.860[a]
Overall mortality					
All cases	1	4.8	0	0	1.000[b]
Cases due to HBV reactivation	0	0	0	0	1.000[b]
Cases due to progressive malignant disease	1	4.8	0	0	

[a] Mann–Whitney U test

[b] Fisher's exact test

chemotherapy prematurely terminated because of poor tolerance and that patient died from the progressive malignant disease 8 months later, giving an overall mortality rate of 4.8%. One patient (4.8%) completed chemotherapy with delays because of hepatitis attributable to chemotherapeutic drugs.

Patients who developed HBV reactivation during the study period then received lamivudine, which was tolerated well by all, and no unexpected effects or additional toxicity occurred.

Comparison of outcomes between the two groups

In the prophylactic lamivudine group, there was significantly less HBV reactivation (0 vs. 28.6% in the control group, $P = 0.021$). However, the incidence of hepatitis, the severity of hepatitis, the disruptions of chemotherapy and the overall mortality were not statistically different between the groups ($P = 0.697$, 0.576, 0.663, and 1.000, respectively).

Discussion

Chemotherapy-induced HBV reactivation may cause varying degrees of liver damage, thereby disrupting chemotherapy and compromising the cancer prognosis. Therefore, it is important to deal with the clinical problem of HBV reactivation to get the maximum potential benefit from chemotherapy.

Several strategies employing lamivudine have been proposed to deal with chemotherapy-induced HBV reactivation. Initially, lamivudine had been used to treat patients who developed ALT elevation attributable to HBV reactivation during chemotherapy [13–16]. However, this approach, the therapeutic strategy, has been reported to lead to fatal reactivation [10, 15, 17]. Even for those who do recover from this complication, their cancer prognosis may be impaired because of the disruption of chemotherapy.

Because of the serial monitoring of HBV DNA levels and liver function (ALT), it is now recognized that viral replication occurs 1–2 weeks before clinical hepatitis flare-up in cancer patients [26–28], which raises the possibility of using lamivudine for the prevention of HBV reactivation before the administration of chemotherapy, that is, a prophylactic strategy, because increased viral replication is the critical event in this case. Over the past decade, it has been recognized that HBV reactivation and its associated fatality during chemotherapy can be prevented effectively by using prophylactic lamivudine. However, the studies were based mainly on patients with lymphoma [18–21]. For patients with breast cancer, there have been few studies regarding the prophylactic strategy [12, 22–24]. In an early study by Yeo et al.[23], 31 patients who received lamivudine as a preventive treatment had a significantly reduced incidence of HBV reactivation (from 31.1 to 6.5%), together with a decrease in hepatitis from all causes from 59 to 12.9%. Furthermore, disruption of chemotherapy was also significantly reduced, and it appeared that lamivudine could prevent reactivation-associated mortality. However, this was a retrospective study.

Recently, a prospective study for breast cancer patients was conducted [25]. This study was the first to assess a deferred preemptive lamivudine strategy; that is, based on HBV DNA surveillance, patients received lamivudine only after a significant rise in their HBV DNA level during chemotherapy. This strategy was used for patients in the control group in this study. However, the use of deferred preemptive strategy did not significantly decrease the incidence of HBV reactivation. Neither the incidence of hepatitis nor the number of disruptions of chemotherapy was significantly different between the two groups. Only in the duration of lamivudine use during chemotherapy was

there a difference, which was significantly shorter in the deferred preemptive group. Concerning the cost of therapy and the fact that prolonged lamivudine treatment may cause resistant strains of HBV [29, 30], it is recommended that the use of deferred preemptive lamivudine based on HBV DNA surveillance could be a comparable alternative to prophylactic use in preventing chemotherapy-induced HBV reactivation and its associated morbidity.

This conclusion seems to make some sense in light of the results of the above study. However, that study had some limitations because it was not a randomized controlled study (which may allow spurious causality or bias to some extent), and it only studied HBsAg± patients who required postoperative adjuvant chemotherapy. Moreover, patients were referred to receive lamivudine only after a significant rise in their HBV DNA during chemotherapy, which neglected patients with elevated baseline HBV viral levels who did not show a significant rise in HBV DNA. According to the deferred preemptive strategy, patients would not receive lamivudine in this condition. However, it is well-known that an increasing HBV viral level is one of the risk factors associated with the development of cirrhosis and hepatocellular carcinoma [31–33]. Moreover, an increased serum HBV-DNA level impairs the rate of HBeAg seroconversion in HBeAg seropositive patients; HBeAg seropositive is also associated with the liver diseases mentioned above [30, 34–38]. Furthermore, one patient in the control group of this study developed HBV reactivation 2 months after the completion of her chemotherapy, which would have been prevented if she were using prophylactic lamivudine and which increased the risk of developing the above conditions. In addition, concern over prolonged prophylactic lamivudine treatment, which may be associated with an increased likelihood of treatment-emergent HBV variants with YMDD mutations, seems to not be as serious as the authors thought. No one in this study developed a lamivudine-resistant mutant during the study period. Meanwhile, Ling et al. [39] has shown that only lamivudine treatment exceeding 6 months in duration will increase the emergence of HBV variants with YMDD mutations. If breast cancer patients—who require 4–6 cycles of chemotherapy in total, with each cycle generally lasting 21 days—complete chemotherapy without disruption, they will take lamivudine from 126 to 168 days during chemotherapy. This amounts to 4–5 months of treatment, which in theory will not increase the risk of resistant strains of HBV developing. Considering the above arguments, there is currently no evidence that the deferred preemptive strategy is superior to the prophylactic strategy.

This study is the first formal prospective, randomized controlled clinical study of HBsAg+ breast cancer patients using prophylactic lamivudine during chemotherapy. The results suggest that the use of prophylactic lamivudine significantly decreased the incidence of HBV reactivation in the study population during the study period. Although no improvements in the incidence of hepatitis, the severity of hepatitis, the number of chemotherapy disruptions or overall mortality were observed in this study because of the small sample size, the benefits of prophylactic lamivudine may translate into an anticancer advantage that may only become evident with a larger sample size and long-term follow-up.

In summary, prophylactic lamivudine treatment should be considered for breast cancer patients who are known to be HBsAg+ and are referred for chemotherapy.

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