Prophylactic Antiviral Therapy in Low-Risk Patients infected with the Hepatitis B Virus with Solid Tumors

Type
Research paper

Keywords
Chemotherapy, tumor, HBV reactivation, Solid malignancies, Prophylactic antiviral therapy

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This study aimed to evaluate the prophylactic antiviral therapy in low-risk patients with the Hepatitis B Virus (HBV) infections during chemotherapy.

Material and methods
From January 2011 to March 2018, HBsAg-positive patients were analyzed in this retrospective study. The HBV reactivation, related hepatitis, chemotherapy delay, and fulminant hepatic failure in low-risk patients between the prophylactic anti-HBV therapy (prophylaxis group) and the non-prophylactic anti-HBV therapy group (control group) were compared.

Results
There were 68 patients in the prophylaxis group and 102 patients in the control group. The result showed that the HBV reactivation was not significantly different between the prophylaxis group and the control group (P=0.741). Three and 5 patients with HBV-related hepatitis were detected in the prophylaxis and control groups, respectively. Moreover, 2 and 4 patients with HBV activation-related chemotherapy delay were detected in the two groups, respectively, without any significant difference (P>0.05). Multivariate analysis showed that HBV DNA titer was associated with HBV reactivation in low-risk patients (P=0.001).

Conclusions
Prophylactic antiviral therapy might not reduce the HBV reactivation of low-risk solid malignancies (non-HCC, non-hematological lymphatic cancer, and HBV DNA titer <100 IU/ml). For low-risk patients, monitoring the HBV DNA titers and liver function tests in the follow-up observations might be an optimal and cost-effective strategy.
**Prophylactic Antiviral Therapy in Low-Risk Patients infected with the Hepatitis B Virus with Solid Tumors**

**Running title:** Prophylactic antiviral treatment in tumor patients

**Abstract**

**Objective:** This study aimed to evaluate the prophylactic antiviral therapy in low-risk patients with the Hepatitis B Virus (HBV) infections during chemotherapy. **Methods:** From January 2011 to March 2018, HBsAg-positive patients were analyzed in this retrospective study. The HBV reactivation, related hepatitis, chemotherapy delay, and fulminant hepatic failure in low-risk patients between the prophylactic anti-HBV therapy (prophylaxis group) and the non-prophylactic anti-HBV therapy group (control group) were compared. **Results:** There were 68 patients in the prophylaxis group and 102 patients in the control group. The result showed that the HBV reactivation was not significantly different between the prophylaxis group and the control group ($P=0.741$). Three and 5 patients with HBV-related hepatitis were detected in the prophylaxis and control groups, respectively. Moreover, 2 and 4 patients with HBV activation-related chemotherapy delay were detected in the two groups, respectively, without any significant difference ($P>0.05$). Multivariate analysis showed that HBV DNA titer was associated with HBV reactivation in low-risk patients ($P=0.001$). **Conclusion:** Prophylactic antiviral therapy might not reduce the HBV reactivation of low-risk solid malignancies (non-HCC, non-hematological lymphatic cancer, and HBV DNA titer $<100$ IU/ml). For low-risk patients, monitoring the HBV DNA titers and liver function tests in the follow-up observations might be an optimal and cost-effective strategy.

**Keywords:** Solid malignancies; Chemotherapy; HBV reactivation; Prophylactic
Introduction

Currently, approximately 30% of the worldwide population is infected or has been infected with the Hepatitis B Virus (HBV) [1] and approximately 350–400 million individuals in the world are HBV carriers [2]. In recent years, the incidence of malignancies has increased every year. In 2012, there were 14.1 million cases of new-onset malignancies worldwide and it is estimated that there will be more than 18 million cases recorded by the end of 2018 [3-4]. Therefore, a large number of hepatitis B patients with malignancies will be noted. Systemic cytotoxic chemotherapy is one of the crucial methods for the treatment of malignancies. During and after chemotherapy, it might disrupt the immune balance of the body and lead to HBV reactivation [5-7]. The clinical manifestations, from the mild elevation of alanine transaminase (ALT) to the deterioration of the liver function, liver failure, and death due to chemotherapy delay might occur after HBV reactivation [8], which in turn, would affect the efficacy of systemic anti-cancer therapy. The guidelines, therefore, recommend prophylactic antiviral therapy for 6–12 months in HBsAg-positive patients with malignancies before chemotherapy [9-10].

However, there is a lack of clinical research on the need for prophylactic anti-HBV therapy in low-risk patients undergoing cytotoxic chemotherapy (hepatitis B patients with non-hematological lymphatic cancer, non-HCC, and low HBV DNA titers). Thus, this retrospective study aimed to evaluate the prophylactic antiviral therapy in those low-risk patients with HBV-infections during chemotherapy.

Materials and Methods
Patients

From January 2011 to July 2013, HBsAg-positive patients with solid tumors who received chemotherapy in the Cancer Hospital of the Chinese Academy of Medical Sciences and the Tianjin Medical University General Hospital were enrolled in this study. The Ethics Committees of our hospital approved this retrospective study.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with malignancies that were pathologically confirmed; (2) Patients aged ≥18 years; and (3) Patients combined with HBsAg positive; (4) HBV DNA titers <100 IU/ml. Exclusion criteria: (1) Patients with HCC, hematological malignancies, and lymphoma; (2) Patients who had anti-hepatitis C virus antibodies or consumed alcohol excessively [>20g/day]; (3) Patients with acute fulminant hepatitis; and (4) HBV DNA titer was not detected before chemotherapy or HBeAg-positive patients.

Study design and measurements

The patients were divided into the prophylaxis group (prophylactic therapy received before chemotherapy) and the control group (anti-HBV therapy received after HBV reactivation). In the prophylaxis group, the patients were administered anti-HBV drugs orally 1 week before chemotherapy until at least 3 months after the end of chemotherapy: Lamivudine 100mg/day (GKS), Entecavir 0.5mg/day (Bristol-Myers Squibb and Chia Tai Tianqing), and Adefovir Dipivoxil 10mg/day (GKS). Parameters such as HBV reactivation risk, related hepatitis, chemotherapy delay, and severe liver failure caused by hepatitis B reactivation were compared between the two groups.

In the Hepatitis B screening, HBeAg and HBeAb were detected with a radioimmunoassay kit (radioimmunoassay [RIA] enzyme-linked immunosorbent assay
HBsAg and HBsAb were detected with an Abbott HBsAg analyzer and the sensitivity was 0.05 IU/ml. The lower limit of detection for HBV DNA by the Roche Molecular System (Cobas Amplicor HBV monitor test; Roche Molecular Systems, Pleasonton, CA) was 20 IU/ml.

The definition of hepatic events

HBV reactivation is defined as follows: (i) a $\geq 2$ log (100-fold) increase in HBV DNA compared to the baseline level and (ii) an HBV DNA $\geq 3$ log (1,000) IU/mL in a patient with a previously undetectable level in the serum during the follow-up period [10]. HBV-related hepatitis: the serum ALT level (the normal upper limit is 40 IU/L) more than 3-fold and $>100$U/L after HBV reactivation. The chemotherapy delay is defined as more than 8 days of chemotherapy. The abnormal liver function is defined as ALT or AST $>40$ U/L in the liver function tests.

Observational index

The observational index included serum HBeAg, anti-HBeAb, and HBV DNA concentrations and biochemical parameters, such as serum bilirubin, AST, and ALT levels before each chemotherapy session. The patients were followed-up every 3–6 months until death.

Statistical methods

We used the software program SPSS 17.0 (IBM, Chicago, USA) to conduct the statistical analysis. Discontinuous variables were expressed as a percentage (%). Continuous variables were expressed as mean± SD. In this study, a t-test was used for two-group comparisons of a normal distribution. The non-normally distributed
continuous data were compared using non-parametric tests. The counting data were tested by a chi-square test. We used a stepwise forward method and the Logistic model was used in the multivariable analysis of the competing risks. P<0.05 was considered statistically significant.

Results

The general characteristics

A total of 260 participants were included in this study. Also, 90 patients were excluded due to the following reasons: 42 patients were HBV DNA>100U/ml at the baseline; 44 patients had a lymphoma; 4 patients HBV DNA were not detected at baseline. The follow-up ranged from 7.0 to 80.0 months, the final follow-up was in September 2018, and the median duration was 30 months. 143 patients were negative for HBV DNA and 27 patients had HBV DNA titer > 20 IU/ml, ranging from 21-93 IU/ml, with a median of 36 IU/ml. Nine patients with HBsAg were above the detection limit of 250 IU/ml and 161 patients had an HBsAg quantification of 0.01-240IU/ml. The cohort consisted of 35 breast cancer, 50 lung cancer, 76 gastrointestinal cancer, 2 ovarian cancer, 2 nasopharyngeal carcinomas, 1 synovial sarcoma, 1 urothelial bladder carcinoma, 1 prostatic cancer, 1 testicular seminoma, and 1 parotid carcinoma patients. Eighty-seven patients included in this study advanced palliative chemotherapy and 83 patients included postoperative adjuvant therapy.

Sixty-eight of the 170 patients received prophylactic anti-HBV therapy (prophylaxis group), while there were 102 patients without prophylactic anti-HBV treatment (control group). The age, gender, cancer type, tumor stage, initial treatment plan, and treatment cycle of the patients were similar between the two groups (Table 1).
**IHBV Reactivation, HBV-related hepatitis, and chemotherapy delay**

The results showed that the cumulative HBV reactivation rates were 2.0%, 5.9%, and 6.7% in the control group and 2.9%, 4.4%, and 4.4% in the prophylaxis group at 10, 30, and 60 weeks after the start of chemotherapy, respectively (Fig 1; \( P=0.515 \)).

The HBV reactivation had no significant difference between the two groups (\( P=0.741 \), Fig 2). The cases of hepatitis B reactivation is described in detail in Table 2. The prevention of HBV reactivation was similar among the three antiviral drugs (\( P=0.373 \)). The HBV reactivation also occurred in 9 patients during chemotherapy. HBV reactivation occurred in 1 patient at 12 weeks after chemotherapy (control group). Furthermore, 23 (33.8%) and 40 patients (39.2%) experienced abnormal liver function in the two groups (\( P=0.515 \)). Of these 63 patients with abnormal liver function, 8 (12.7%) were associated with HBV reactivation, 46 (73.0%) with chemotherapy-induced liver injury, and 9 with tumor progression (14.3%). A further analysis displayed 8 cases of HBV activation-related hepatitis, including 3 cases in the prophylaxis group and 5 cases in the control group; the incidence of both groups was also similar (4.4% vs. 4.9%, \( P=0.882 \), Fig 3). There were also, interestingly, 13 and 25 cases of chemotherapy delay in the two groups, \( (P=0.456) \). The correlation between chemotherapy delay and HBV reactivation was 2.9% (2/68) and 3.9% (4/102), respectively, without any significant difference (\( P=0.875 \), Fig 4).

**Risk factor**

Age, gender, tumor type, adjuvant therapy, combined with liver metastasis, HbsAg level, HBV DNA titer, steroid-containing regimen, taxane-based regimen, anthracycline-based regimen, fluorouracil-based regimen, prophylactic anti-HBV therapy, and whether ALT was elevated before chemotherapy were analyzed. The results showed that the taxane-based chemotherapy regimen and HBV DNA titer were
associated with HBV reactivation (11.3% vs. 2.8%, \( P=0.038 \); 29.6% vs.1.4%, \( P<0.001 \)) (Table 3). The above factors (\( P<0.2 \)) were also analyzed by multivariate analysis and the results confirmed that HBV DNA titer was an independent risk factor for HBV reactivation in low-risk patients (HR=20.807, 95% CI: 3.644–118.817, \( P<0.05 \)) (Table 4).

**Discussion**

Recently, approximately 51.7–72.0% of patients with hematological malignancies and lymphomas developed HBV reactivation if the prophylactic anti-HBV therapy was not administered [11-15]. Prophylactic antiviral therapy is also still required for patients who have been previously infected with HBV while undergoing autologous and allogeneic hematopoietic stem cell transplantation and received Rituximab combined with chemotherapy. Also, approximately 13.0–43.0% of these patients had HBV reactivation during and after chemotherapy [11, 16]. The occurrence of tumors has also recently increased [17-19]. Chemotherapy-induced HBV reactivation was an independent risk factor in hepatitis B patients with solid tumors [20]. Previous studies on solid tumors including patients with hepatocellular carcinoma (HCC) showed that the HBV reactivation risk was significantly higher than that in other solid tumors [21]. Anti-HBV therapy significantly improved the prognosis of patients with hepatitis and HCC [22].

This study found that prophylactic anti-HBV therapy couldn’t reduce the HBV reactivation in hepatitis B patients with low-risk solid malignancies (non-hematological lymphatic cancer, non-HCC, HBV DNA titer < 100 IU/ml). It was previously reported that the higher the score, the higher the risk of HBV reactivation [18]. All patients in the current study were low-risk patients and the overall HBV reactivation risk was 5.9%,
which was similar to the above study [19, 23-25].

Recent studies have also reported that the HBV reactivation risk in solid malignancies treated with Lamivudine for prophylactic anti-HBV therapy was 0–7% [19, 24-25]. Thus, the HBV reactivation risks in the above studies are similar to those in the prophylaxis group. However, the HBV reactivation risk in the control group was significantly lower than in previous studies [6, 19, 25, 26]. The HBV reactivation risk in the non-prophylactic anti-HBV therapy group in previous studies was 16–36%, which was higher than the control group. The reason may be due to the exclusion of patients with hematological lymphatic cancer, high HBV DNA titers, HBeAg-positive, and HCC [19-20, 26-27].

Furthermore, three anti-HBV drugs were used in this study: Lamivudine, Entecavir, and Adefovir Dipivoxil. Previously, Entecavir was superior to Lamivudine in preventing HBV reactivation [28-31]. However, no difference was detected among the three drugs in preventing HBV reactivation in our study, which might be due to the limited sample size.

Single-factor and multivariate analysis of HBV reactivation confirmed that HBV DNA titer is an independent risk factor. Previous studies found that HBV reactivation might be related to HBV DNA titers before chemotherapy [18-20]. In our study, HBV DNA titers were detectable in 15.9% of the patients. Despite the low titer of HBV DNA, the rate of HBV reactivation was significantly increased. Therefore, these patients should be treated with prophylactic antiviral therapy as long as the HBV DNA titer test results are positive.

Health economics is becoming an increasingly critical factor in medical decision-making [32-33]. The current study confirmed that prophylactic antiviral therapy cannot reduce the rate of HBV reactivation in low-risk patients and that antiviral therapy after
HBV reactivation has similar prophylactic effects on chemotherapy delay, hepatitis, and fulminant liver failure. Therefore, from the perspective of cost-efficiency, only follow-ups without prophylactic anti-HBV therapy in low-risk patients can greatly reduce the economic cost of treatment and save medical resources, thereby benefitting both the society and patients.

Limitations: Firstly, the sample size was limited, further RCTs with larger sample sizes are essential for the substantiation of these findings. Secondly, the participants were Chinese, which might not be optimal for populations in other countries. Thirdly, the covalently closed circular DNA (cccDNA) of HBV is considered to be related to HBV reactivation [34]. However, relevant tests were not carried out in the present study, thereby excluding some high-risk groups of HBV reactivation. Therefore, it is necessary to design a rigorous prospective RCT to verify the above conclusions.

In conclusion, prophylactic nucleoside analogs (anti-HBV) therapy during chemotherapy might not reduce HBV reactivation risk in hepatitis B patients with low-risk solid malignancies (non-hematological lymphatic cancer, non-HCC, and low HBV DNA titers). Therefore, from the perspective of cost-efficiency, the reexamination of HBV DNA titer and liver function is recommended. Anti-HBV therapy, especially HBV DNA titer negative, is administered after HBV reactivation occurs.

**Conflict of Interest statement**

None of the authors had any personal, financial, commercial, or academic conflicts of interest separately.

**Acknowledgements**
We are particularly grateful to all the people who have helped with our article.

Funding

None

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Figure legends:

Fig 1. Cumulative reactivation rate in the prophylaxis and control groups

Fig 2. Hepatitis B virus (HBV) reactivation in the prophylaxis and control groups

Fig 3. Hepatitis B virus (HBV)-related hepatitis in the prophylaxis and control groups

Fig 4. Hepatitis B virus (HBV)-related chemotherapy disruption in the prophylaxis and control groups
### Table 1 Baseline Characteristics of Patients with HBsAg*-positive Solid Tumor

| Variables                        | Prophylaxis group N=68 (%) | Control group N=102 (%) | P       |
|----------------------------------|----------------------------|-------------------------|---------|
| Age (years)                      |                            |                         | 0.958   |
| Mean                             | 52.6                       | 52.5                    |         |
| SD                               | 10.4                       | 10.7                    |         |
| Gender                           |                            |                         | 0.851   |
| Male                             | 35 (51.5%)                 | 51 (50%)                |         |
| Female                           | 33 (48.5%)                 | 51 (50%)                |         |
| Tumor type                       |                            |                         | 0.584   |
| Breast cancers                   | 16 (23.5%)                 | 19 (18.6%)              |         |
| Lung cancers                     | 22 (32.4%)                 | 28 (27.5%)              |         |
| Gastrointestinal cancers         | 26 (38.2%)                 | 50 (49.0%)              |         |
| Other cancers                    | 4 (5.9%)                   | 5 (4.9%)                |         |
| Tumor stage                      |                            |                         | 0.755   |
| Stage I-III                      | 32 (47.1%)                 | 51 (50.0%)              |         |
| Stage IV                         | 36 (52.9%)                 | 51 (50.0%)              |         |
| Adjuvant Chemotherapy            |                            |                         | 0.802   |
| Yes                              | 34 (50.0%)                 | 49 (48.0%)              |         |
| No                               | 34 (50.0%)                 | 53 (52.0%)              |         |
| HBsAg Level                      |                            |                         | 0.159   |
| >250IU/ml                        | 6 (8.8%)                   | 3 (2.9%)                |         |
| <250IU/ml                        | 62 (91.2%)                 | 99 (97.1%)              |         |
| HBV DNA Status                   |                            |                         | 0.072   |
| Positive                         | 15 (22.1%)                 | 12 (11.8%)              |         |
| Negative                         | 53 (77.9%)                 | 90 (88.2%)              |         |
| Baseline ALT* (U/L)              |                            |                         | 0.437   |
| Mean                             | 22.1                       | 23.9                    |         |
| SD                               | 12.1                       | 15.6                    |         |
| Baseline liver metastasis        |                            |                         | 0.086   |
| Yes                              | 23 (33.8%)                 | 48 (47.1%)              |         |
| No                               | 45 (66.2%)                 | 54 (52.9%)              |         |
| Chemotherapy regime              |                            |                         | 0.683   |
| Anthracycline-based              | 2 (6.9%)                   | 4 (3.9%)                |         |
| Fluorouracil-based               | 24 (35.3%)                 | 40 (39.2%)              |         |
| Taxane-based                     | 10 (14.7%)                 | 21 (20.6%)              |         |
| Anthracycline +Taxane            | 12 (17.6%)                 | 15 (14.7%)              |         |
| Other                            | 20 (29.4%)                 | 22 (21.6%)              |         |
| Cycles of chemotherapy           |                            |                         | 0.950   |
| Mean                             | 6.5                        | 6.5                     |         |
| SD                               | 2.8                        | 2.7                     |         |
| Duration of follow-up (months)   |                            |                         | 0.657   |
| Mean                             | 38.7                       | 36.9                    |         |
| SD                               | 23.7                       | 23.9                    |         |

HBsAg*: hepatitis B surface antigen, ALT*: alanine transaminas
| Patient No. | Age, Y | Sex | Tumor           | Chemo-therapy | Prophylaxis | ALT* | HBV DNA* | Time reactivation | ALT** | HBV DNA** | Antiviral Treatment | Outcome          |
|------------|--------|-----|-----------------|---------------|-------------|------|----------|-------------------|-------|-----------|-------------------|------------------|
| 1          | 53     | M   | Gastric cancer  | SOX           | No          | 34   | Negative | 40w               | 36    | 3.5*10^3 | Entecavir         | Died of Tumor    |
| 2          | 38     | M   | Gastric cancer  | SOX           | No          | 58   | 84       | 13w               | 62    | 6.8*10^3 | Entecavir         | Alive and well   |
| 3          | 47     | F   | Breast Cancer   | EPI+PTX       | No          | 12   | 23       | 7w                | 83    | 3.4*10^3 | Entecavir         | Alive and well   |
| 4          | 59     | F   | Breast Cancer   | PTX+ Heceptin | No          | 18   | 39       | 4w                | 22    | 5.8*10^3 | Entecavir         | Died of Tumor    |
| 5          | 47     | M   | Lung cancer     | DOC           | Yes         | 41   | 93       | 3w                | 238   | 5.4*10^3 | Entecavir added  | Died of Tumor    |
|            |        |     |                 |               |             |      |          |                   |       |           | to 1.0mg          |                  |
| 6          | 48     | M   | Colon cancer    | XELOX         | Yes         | 20   | Negative | 3w                | 97    | 5.4*10^3 | Entecavir         | Alive and well   |
| 7          | 56     | F   | Breast cancer   | EPI+PTX       | No          | 31   | 21       | 17w               | 177   | 4.8*10^3 | Entecavir         | Alive and well   |
| 8          | 50     | F   | Breast cancer   | EPI+DOC       | Yes         | 41   | 39       | 11w               | 171   | 6.2*10^3 | Entecavir added  | Died of tumor    |
|            |        |     |                 |               |             |      |          |                   |       |           | to 1.0mg          |                  |
| 9          | 36     | F   | Breast cancer   | EPI+PTX       | Yes         | 25   | 23       | 6w                | 74    | 4.3*10^3 | Entecavir         | Alive and well   |
| 10         | 56     | M   | esophageal cancer | PTX+DDP     | No          | 32   | 45       | 4                 | 144   | 2.0*10^3 | Entecavir         | Died of tumor    |

Abbreviation:* before chemotherapy the level of ALT and HBV DNA; ** at the time of reactivation the level of ALT and HBV DNA.
# Table 3: Analysis of Potential Risk Factors of HBV Reactivation

| Characteristics                  | Patients with HBV reactivation | Patients without HBV reactivation | P     |
|----------------------------------|---------------------------------|-----------------------------------|-------|
|                                  | N=10 (%)                        | N=160 (%)                         |       |
| Age (years)                      |                                 |                                  |       |
| ≤65                              | 7 (70.0%)                       | 91 (56.9%)                       | 0.521 |
| >65                              | 3 (30.0%)                       | 69 (43.1%)                       |       |
| Gender                           |                                 |                                  | 1.000 |
| Male                             | 5 (50.0%)                       | 81 (50.6%)                       |       |
| Female                           | 5 (50.0%)                       | 79 (49.4%)                       |       |
| Tumor type                       |                                 |                                  | 0.758 |
| Gastrointestinal cancers         | 4 (40.0%)                       | 72 (45.0%)                       |       |
| Other cancers                    | 6 (60.0%)                       | 88 (55.0%)                       |       |
| Live metastasis                  |                                 |                                  | 0.907 |
| Yes                              | 4 (40.0%)                       | 67 (41.9%)                       |       |
| No                               | 6 (60.0%)                       | 93 (58.1%)                       |       |
| Adjuvant Chemotherapy            |                                 |                                  | 0.490 |
| Yes                              | 6 (60.0%)                       | 78 (48.8%)                       |       |
| No                               | 4 (40.0%)                       | 82 (51.2%)                       |       |
| HBsAg Level                      |                                 |                                  | 0.09  |
| >250IU/ml                        | 2 (20.0%)                       | 7 (4.4%)                         |       |
| <250IU/ml                        | 8 (80.0%)                       | 153 (95.6%)                      |       |
| HBV DNA Status                   |                                 |                                  | <0.001|
| Positive                         | 8 (80.0%)                       | 19 (11.9%)                       |       |
| Negative                         | 2 (20.0%)                       | 141 (88.1%)                      |       |
| Baseline ALT* (U/L)              |                                 |                                  | 0.116 |
| >40U/L                           | 3 (30.0%)                       | 20 (12.5%)                       |       |
| ≤40U/L                           | 7 (70.0%)                       | 140 (87.5%)                      |       |
| Steroid-containing treatment     |                                 |                                  | 0.200 |
| Yes                              | 7 (70.0%)                       | 75 (46.9%)                       |       |
| No                               | 3 (30.0%)                       | 54 (33.1%)                       |       |
| Taxane-based                     |                                 |                                  | 0.038 |
| Yes                              | 7 (70.0%)                       | 55 (34.4%)                       |       |
| No                               | 3 (30.0%)                       | 105 (65.6%)                      |       |
| Anthraclycline-based             |                                 |                                  | 0.125 |
| Yes                              | 4 (40.0%)                       | 31 (19.4%)                       |       |
| No                               | 6 (60.0%)                       | 129 (80.6%)                      |       |
| Fluorouracil-based               |                                 |                                  | 0.742 |
| Yes                              | 3 (30.0%)                       | 64 (40.0%)                       |       |
| No                               | 7 (70.0%)                       | 86 (60.0%)                       |       |
| Prophylactic anti-HBV            |                                 |                                  | 0.741 |
| Yes                              | 3 (30.0%)                       | 65 (40.6%)                       |       |
| No                               | 7 (70.0%)                       | 95 (59.4%)                       |       |
| Factor                                | B    | HR   | 95% CI          | P    |
|---------------------------------------|------|------|-----------------|------|
| Taxane-based (Yes/No)                 | 0.948| 2.581| 0.350-19.034    | 0.352|
| Anthracycline-based (Yes/No)          | 0.604| 1.830| 0.298-11.252    | 0.515|
| ALT increased Baseline (Yes/No)       | 0.786| 2.194| 0.384-12.529    | 0.377|
| HBsAg (≤250 IU/ml/>250 IU/ml)         | -0.894| 0.409| 0.037-4.540     | 0.467|
| HBV DNA titer (20-100U/<20)           | 3.035| 20.807| 3.644-118.817   | 0.001|
Cumulative Reactivation Rate(%)

Control

Prophylaxia

$P=0.515$
$P = 0.741$

Incidence of HBV Reactivation Rate (%)

- Prophylaxis: 4.41% (3/68)
- Control: 6.86% (7/102)
HBV-Relative Hepatitis (%)}

Prophylaxis
Control

4.41% (3/68)
4.90% (5/102)

P = 0.882
$P = 0.734$

- **Prophylaxis**: 2.94% (2/68)
- **Control**: 3.92% (4/102)