The Prophylactic Use of Lamivudine Can Maintain Dose-Intensity of Adriamycin in Hepatitis-B Surface Antigen (HBs Ag)-positive Patients with Non-Hodgkin's Lymphoma Who Receive Cytotoxic Chemotherapy

We investigated the effectiveness of lamivudine to prevent hepatitis flare up due to reactivation of hepatitis-B virus (HBV) in hepatitis-B surface antigen (HBsAg)-positive patients with Non-Hodgkin's lymphoma (NHL) during cytotoxic chemotherapy. HBsAg-positive patients with NHL were identified from the lymphoma database of the Asan Medical Center from January 1995 to August 2002, and their medical records were reviewed. We found that 31 patients were received cytotoxic chemotherapy among 41 NHL patients with HBsAg-positive during same period. We divided them into 2 groups of HBsAg patients with NHL as follows: Group A who received cytotoxic chemotherapy with lamivudine 100 mg daily; Group B without any prophylactic antiviral therapy. There were no significant differences between Group A and B in several clinical variables. Seventeen patients (85%) in group B and one patient (9%) in Group A had hepatitis due to reactivation of HBV ($p<0.001$), with one hepatic failure related death in Group B and none in group A. The mean dose intensity of adriamycin actually delivered was 13.3 mg/m^2/week (80% Relative Dose intensity (RDI)) in Group A and 9.1 mg/m^2/week (55% RDI) in Groups B ($p<0.001$). Our data suggest that the frequency of chemotherapy-related HBV reactivation may be significantly decreased by lamivudine prophylaxis with maintenance of the dosage of adriamycin.

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INTRODUCTION

Reactivation of hepatitis-B virus (HBV) infection in patients receiving cytotoxic chemotherapy for hematologic malignancies is well documented (1-4). The severity of the hepatitis ranges from anicteric hepatitis to severe, progressive hepatic failure that may result in death (1, 2, 5-17). In an endemic area for chronic hepatitis-B infection, reactivation of this virus is a serious cause of morbidity and mortality in patients undergoing cytotoxic chemotherapy.

Possible mechanisms to explain reactivation include enhancement of viral replication leading to an increase in the number of infected hepatocytes. After withdrawal of the immunosuppressive agent and restoration of immunocompetence, activated T lymphocytes may attack the infected hepatocytes, leading to their rapid destruction (18-21).

In Japan, 53% of lymphoma patients with chronic HBV infection developed severe hepatitis during chemotherapy, and this was associated with a high mortality of 24% (16). Another survey in Hong Kong has shown that the rate of HBV reactivation was more likely to develop in patients with Non-Hodgkin's Lymphoma (NHL) than in those with other malignancies, probably reflecting the more immunosuppressive treatment the lymphoma patients received (17).

Because these episodes of hepatitis are preceded by a substantial increase in HBV replication during the immunosuppressive phase, a rational approach to patient management would include the use of specific nucleoside analogues that selectively block HBV replication. Lamivudine is a reverse transcriptase inhibitor of viral DNA polymerase with an excellent profile of safety and tolerability, causing inhibition of viral replication and approved as an antiviral treatment in hepatitis-B virus infected patients (2, 22, 23).

Recently, prophylactic therapy of lamivudine was reported to be effective for the treatment and prevention of hepatitis due to exacerbation of HBV (24, 25). Despite the introduction and use of lamivudine, some HBsAg-positive patients still developed hepatic failure and died (25, 26). This is probably related to the late institution of the nucleoside analogues when hepatitis due to reactivation of HBV has already been

developed (25). Therefore, a better strategy might be to use nucleoside analogues preemptively before the cytotoxic chemotherapy and hence to prevent the enhancement of HBV replication during the early immunosuppressive period (25, 27).

In this study, we analyzed the effectiveness of preemptive use of lamivudine in preventing hepatitis due to exacerbation of HBV in HBsAg-positive patients with NHL during cytotoxic chemotherapy.

PATIENTA AND METHODS

Patients

1,333 adult patients diagnosed as de novo NHL in the Asan Medical Center from January 1995 to August 2002 were included in the study. We identified 41 patients with serological evidence of HBsAg-positive. After exclusion of 10 patients who did not receive cytotoxic chemotherapy as follows: sepsis due to unknown etiology in 1; pneumonia and multiorgan dysfunction syndrome in 2; patient's own refusal in 2; double primary malignancies in 3 (2 patients with underlying hepatocellular carcinoma; 1 patient with non-small cell lung cancer with multiple brain metastasis); and follow-up loss after pathologic diagnosis in 2 patients. We reviewed the medical records and collected the clinical data from 31 patients who were selected from the database of the Asan Medical Center, and who underwent chemotherapy among 41 patients.

We divided them into 2 groups of HBsAg-positive patients with NHL as follows: Group A who received lamivudine 100 mg daily (n=11); Group B who received cytotoxic chemotherapy without any prophylactic antiviral therapy (n=20).

Laboratory Studies

In accordance with our standard admission protocol, all patients with NHL were screened and tested in serum by commercially available immunoassay kits for hepatitis-B serology (Diasorin, A6K-3® RIA-IRMA Immuno-RadioMetric Assay): [HBsAg, anti-HBs, HBeAg, anti-HBe, antiHBc IgM and IgG]; serum biochemistry [protein, albumin, bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT)]; HCV antibody; and HBV DNA if needed before cytotoxic chemotherapy.

Definition of Hepatitis and Hepatic Failure

For the purpose of this study, "hepatitis" was defined as threefold or greater increase in serum ALT level that exceeded the reference range (>40 IU/L). Icteric hepatitis was defined as serum bilirubin level that exceeded the reference range (<1.2 mg/dL) by twice in the absence of clinical or laboratory features of acute infection with HAV, HCV, delta virus, or other systemic infections, malignant hepatic infiltration (detected

by imaging studies), and alcoholism. "Chronic hepatitis" was defined as presence of persistent elevated liver enzyme and past medical history of overt hepatitis continued for at least 6 months. "Liver cirrhosis" was diagnosed by means of laboratory (hypoalbuminemia and thrombocytopenia less than 150,000 per microliter with or without jaundice) and radiological findings by using of non-invasive abdominal ultrasonography, which was not implicated in intra-abdominal involvement of lymphoma. In our study, hepatic failure was defined as the presence of hepatic encephalopathy and blood coagulopathy (prolonged prothrombin time).

Statistical Analysis

The Fisher's exact test was used to compare the baseline characteristics, hepatic events, and outcomes in patients treated with lamivudine (Group A) to those without any antiviral therapy (Group B), whereas continuous variables were compared by using the Mann-Whitney U test.

Dose intensity (DI) of doxorubicin was evaluated according to the method of Hryniuk and Bush (28). Expression of the actual DI was calcaulated by dividing the actual total dose of doxorubicin in standard CHOP regimen by the time (3 weeks). Calculation was carried out for the whole treatment period and separately for the initial cycles to achieve the maximal response or to determine the progression of disease. Relative dose intensity (RDI) in patients was compared by using independent sample t-test. The rates of survival of group A and B was calculated by using Kaplan-Meier method, censoring at last follow-up and death. 95% confidence intervals for all estimates were also provided where appropriate p-values less than 0.05 were considered to be significant throughout this study. Analysis of the data was performed by using SPSS for Windows V. 10.0 (SPSS inc, Chicago, IL, U.S.A.) statistical software program.

RESULTS

Comparison of Baseline Characteristics of Groups A and B

We found that thirty one patients (19 men and 12 women), aged 18-70 yr (median, 47 yr), who received cytotoxic chemotherapy were HBsAg-positive with NHL between January 1995 and August 2002 at Asan Medical Center. The pathologic subtypes were as follows: diffuse large B cell in 27 (87%) patients, follicular lymphoma in 2 (7%) patients, peripheral T cell lymphoma in 1 (3%) patient, and extranodal NK/T cell lymphoma, nasal type in 1 (3%) patient. The first-line chemotherapy regimens included: CHOP (cyclophosphamide 750 mg/m^2 iv day 1, adriamycin in 50 mg/m^2 iv day 1, vincristine 1.4 mg/m^2 iv day 1, prednisolone 40 mg/m^2 po day 1-5) in 29 (94%) patients; EDAP (etoposide 100 iv mg/m^2 iv day

1-4, dexamethasone 40 mg/m^2 po day 1-5, cytosine arabinoside 1,000 mg/m^2 continuous intravenous infusion, cisplatin 25 mg/m^2 iv days 1-4) in 1 (3%) patient; and proMACE-cytaBOM (prednisolone 60 mg/m^2 per po days 1-14, adramycin 25 mg/m^2 iv day 1, cyclophosphamide 650 mg/m^2 iv day 1, etoposide 120 mg/m^2 iv day 1, cytosine arabinoside 300 mg/m^2 iv day 8, methotrexate 120 mg/m^2 iv day 8, leucovorin 15 mg po day 9, bleomycin 5 units/m^2, vincristine 1.4 mg/m^2 iv day 8) in 1 (3%) patient. The number of course of cytotoxic therapy ranged from 2-13 (median 5). As a rule, we did not modify the dose of steroid like other chemotherapeutic agents, irrespective of underlying liver function of patients who received cytotoxic chemotherapy.

There were no differences between Group A and Group B in sex, age, underlying liver disease, stage, IPI (International Prognostic Index) score, B symptom, hepatic involvement of NHL, HBV serology, HBV DNA, and precore mutant (Table 1).

Hepatitis due to Exacerbation of HBV after Cytotoxic Chemotherapy

Seventeen patients (85%) in Group B and one patient (9%) in Group A had hepatitis due to reactivation of HBV, with one hepatic failure related death in Group B and none in Group A. Five patients in Group B started to receive lamivudine after stabilization of first attack of hepatitis flare-up, and none of them experienced hepatitis due to reactivation HBV from the beginning of lamivudine treatment. After cytotoxic chemotherapy, there were significantly more episodes of hepatitis due to exacerbation of HBV in Group B than in Group A ($p<0.001$).

Comparison of hepatitis flare-up between patients positive for HBeAg and those positive HBeAb (anti-HBe)

There were no statistical differences between patients with HBeAg and those with anti-HBe in sex, age, underlying liver disease, stage, IPI score, B symptom, hepatic involvement of NHL (Table 2).

Table 1. Baseline characteristics of Group A and B

	Group A (n=11)	Group B (n=20)	p
Use of lamividine	Yes	No	
Median age (yr) (range)	44 (29-68)	47.5 (18-70)	0.649
Sex			0.705[†]
Male	6 (55%)	13 (65%)	
Female	5 (45%)	7 (35%)	
Immunophenotype			0.591*
B cell	10 (91%)	19 (95%)	
T cell	1 (9%)	1 (5%)	
Stage			1.000*
1/2	7 (64%)	12 (60%)	
3/4	4 (36%)	8 (40%)	
IPI score			1.000*
Low/low intermediate	7 (64%)	12 (60%)	
High intermediate/high	4 (36%)	8 (40%)	
B symptom			0.106*
Yes	3 (27%)	3 (15%)	
No	8 (73%)	17 (85%)	
Hepatic involvement of lymphoma			0.158*
Yes	3 (27%)	4 (20%)	
No	8 (73%)	16 (80%)	
Underlying liver disease			0.749*
Asymptomatic	3 (27%)	4 (20%)	
Chronic hepatitis	6 (55%)	10 (50%)	
Liver cirrhosis	2 (18%)	6 (30%)	
Hbe Ag/Ab			0.056*
+/-	7 (64%)	5 (25%)	
-/+	4 (36%)	15 (75%)	
HBV-DNA			0.452[†]
+	5 (45%)	6 (30%)	
-	6 (55%)	14 (70%)	
Precore mutant			0.383*
Yes	1 (9%)	5 (25%)	
No	10 (91%)	15 (75%)	

*: Fisher's exact analysis, [†]: Pearson chi-square test.

Table 2. Baseline characteristics of patients with HBeAb (anti-HBe) and those with HBeAg

	Anti-HBe	HBeAg	p-value
Age (yr)			1.000*
<60	15 (79%)	9 (75%)	
≥60	4 (21%)	3 (25%)	
Sex			
Male	12 (63%)	7 (58%)	1.000[†]
Female	7 (37%)	5 (42%)	
B symptom			1.000*
Yes	6 (32%)	3 (25%)	
No	13 (68%)	9 (75%)	
Immunophenotype			
B cell	18 (95%)	11 (92%)	1.000*
T cell	1 (5%)	1 (8%)	
Stage			
1/2	9 (47%)	6 (50%)	1.000[†]
3/4	10 (53%)	6 (50%)	
IPI score			
Low/low intermediate	11 (58%)	8 (67%)	0.717*
High intermediate/high	8 (42%)	4 (33%)	
Hepatitis/Hepatic failure			0.060*
Yes	14 (74%)	4 (33%)	
No	5 (26%)	8 (67%)	
Lamivudine prophylaxis			0.056*
Yes	4 (21%)	7 (58%)	
No	15 (79%)	5 (42%)	
Underlying liver disease			0.652*
Asymptomatic	4 (21%)	3 (25%)	
Chronic hepatitis	9 (47%)	7 (58%)	
Liver cirrhosis	6 (32%)	2 (17%)	
Hepatic involvement			1.000*
Yes	4 (21%)	2 (17%)	
No	15 (79%)	10 (83%)	

*: Fisher's exact analysis, [†]: Pearson chi-square test.

Among 19 patients with anti-HBe prior to chemotherapy, flare-up hepatitis developed in 14 patients (74%) and four patients (33%) experienced hepatitis due to HBV reactivation in 12 patients with HBeAg before cytotoxic chemotherapy (p=0.060). The proportions of patients receiving prophylactic lamivudine therapy were 20% (4 of 19) in the patients with anti-HBe, as compared with 58% (7 of 12) in those with HBeAg (p=0.056). Six of fourteen patients with anti-HBe were identified as precore mutant HBV.

Comparison of Dose Intensity of Adriamycin and Survival of Group A and B

Dose reduction of adriamycin was required in patients who developed hepatitis flare-up and abnormal liver function at initial presentation among 29 patients who were treated by using standard CHOP regimen as the first line chemotherapy (Table 3); as a consequence, the mean DI of adriamycin actually delivered was 13.3 mg/m²/week in Group A and 9.1 mg/m²/week in Group B, which represented 80% RDI in Group A and 55% RDI in Group B (p<0.001) (Fig. 1). Survival rate of Group A was higher than that of Group B. However, the statistical difference of survival rates between Group A and

Table 3. Relative dose intensities (mg/m²/week) of adriamycin given at each chemotherapy cycles

Cycle number	Relative dose intensity (mg/m²/week)		
	With Lamivudine (RDI)	Without Lamivudine (RDI)	*p*-value
1 (n=29)	13.28±0.60 (80%)	10.87±0.62 (65%)	0.296
2 (n=25)	13.12±0.38 (79%)	8.14±1.10 (49%)	<0.001
3 (n=23)	12.55±1.22 (75%)	9.26±1.50 (56%)	0.524
4 (n=15)	13.80±0.59 (83%)	9.81±1.30 (59%)	0.112
5 (n=11)	13.79±0.69 (83%)	7.49±2.74 (45%)	0.081

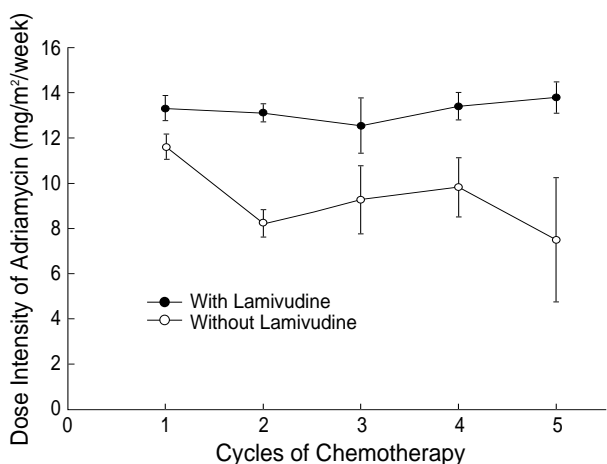N: Number of evaluable patients; RDI: Relative dose-intensity.

Fig. 1. Comparison of dose intensity of adriamycin between Group with lamivudine and Group without lamivudine.

Group B was not significant (p=0.691) (Fig. 2).

DISCUSSION

With the more widespread use of chemotherapy, the possibility of HBV reactivation is becoming an increasing problem that may adversely affect the final outcome of treatment. Cytotoxic chemotherapy for malignancy, particularly among HBsAg-positive patients, may induce acute exacerbation of hepatitis-B and also fulminant hepatic failure, especially when chemotherapy is withdrawn (1-17). However, it is not possible to predict the occurrence and the clinical severity of HBV reactivation in a single patient. HBV reactivation is a particularly important clinical issue in areas such as Korea, where HBV infection is endemic. The HBV carriers among the general population is around at 5.1% in Korea (29).

Patients with hematological malignancies may be at increased risk of HBV reactivations, as corticosteroid are more often components of their chemotherapy regimen compared with patients with other solid malignancies who received chemotherapy not containing corticosteroid. Indeed, the presence of corticosteroids among the protocol drugs is considered the most important predisposing factor for HBV reactivation following chemotherapy (16, 30). In a retrospective study of 105 HBV carriers with malignant lymphoma, 22 (21%) developed hepatic failure and six (27%) of them died from hepatic failure following cessation of cytotoxic treatment (1).

DI is a very important determinant of the response of NHL. DeVita et al. (31) reported a close association between DI and survival time. Kwak et al. (32) reported a significant correlation between the relative DI for cyclophosphamide or adriamycin and survival time in patients with diffuse large cell lymphoma. In fact, dose of chemotherapy in cases of HBsAg-positive patients may sometimes be affected and modified by underlying liver function, regardless of hepatic involvemet
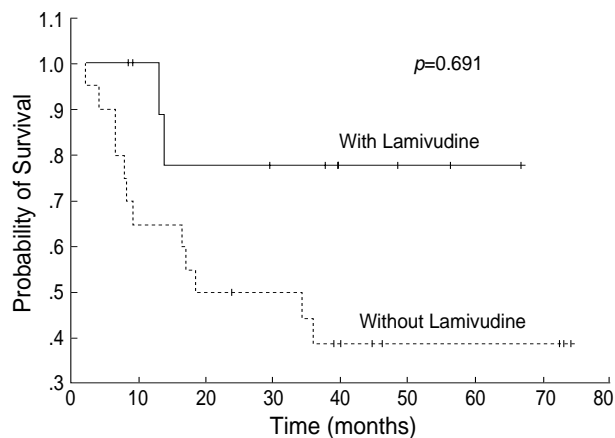

Fig. 2. Overall survival of Group A and B (*p*=0.691), Black solid line: survival curve of lamivudine group. Dotted line: survival curve without lamivudine prophylactic group.

of lymphoma. The hepatotoxicity of chemotherapy needs special caution. Also, as 24 of 31 HBsAg-positive patients (77%) in our study had impaired liver function test before therapy, the use of cytotoxic agents such as adriamycin, which depends on hepatic metabolism, demands special attention. Hepatitis-B flare-up after chemotherapy and abnormal liver function at initial presentation may also cause reduced dose-intensity of adriamycin as shown in Fig. 1. Survival rate of Group A which maintained relatively higher dose intensity of adriamycin by help of lamivudine was better than that of Group B although the result was statistically not significant (p=0.691). Lamivudine has been used more extensively, and has proven effective both as a treatment and as a secondary prevention of chemotherapy-related HBV reactivation (25, 33).

Our results showed that higher proportion of hepatitis flare-up developed in patients with anti-HBe (74%, 14 of 19) compared with those with HBeAg (33%, 4 of 12). This results suggested that the lower proportion of lamivudine prophylaxis involved the increased risk of hepatitis flare-up in patients with anti-HBe (20%, 4 of 19), as compared with patients who were HBeAg positve (58%, 7 of 12) and the lower proportion of hepatitis flare-up induced by active lamivudine prophylaxis in patients with HBeAg. In six cases with anti-HBe who experienced hepatitis due to HBV reactivation, the virus was thought to have precore mutation. This results also suggested precore mutant plays an important role in HBV reactivation in NHL who received cytotoxic chemotherapy (26, 34).

Furthermore, the development of chronic hepatitis may preclude the subsequent completion of the treatment schedule for the hematological malignancies. The toxicity profiles of lamivudine is particularly favorable because it does not overlap with those of other antiviral agents, making this agent particularly suitable for a simultaneous use with chemotherapy. Our results suggest that lamivudine may be used safely along with supporting DI of adriamycin.

In conclusion, the present study suggests that lamivudine can be given safely in association with chemotherapy without causing significant adverse effects, a reduction of the dosage or the efficacy of cytotoxic drugs. The frequency and the severity of chemotherapy-related HBV reactivation may be significantly decreased by lamivudine prophylaxis.

Because our results have limitation that there is no serial follow-up of several serologic markers during and after cytotoxic chemotherapy as a single institutional retrospective non-randomized study, well-designed, prospective multicenter trials are needed with serial quantification of HBV-DNA, liver function evaluation, several serologic markers and serial documentation of liver histology.

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