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ORIGINAL ARTICLE

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Preemptive use of interferon or lamivudine for hepatitis B reactivation in patients with aggressive lymphoma receiving chemotherapy

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Abstract The hepatitis B virus (HBV) reactivation rate among hepatitis B virus surface antigen (HBsAg)-positive patients undergoing chemotherapy ranges from 21 to 35% with a mortality rate of 4–41%. The risk is significantly evident in patients with aggressive lymphoma, which is highly responsive to standard chemotherapy with cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone (CHOP) achieving a complete response rate of 60–80% and 5-year survival rate of 30–50% with only 1% of treatment-related mortality. α-Interferon and lamivudine were given as preemptive treatment for HBV reactivation in HBsAg-positive patients treated for aggressive lymphoma consecutively from 1994 to 1997 and 1998 to 2001, respectively, in our institution. The outcome of 77 HBsAg-positive patients treated for aggressive lymphoma at our institution from 1990 to 2001 was studied. Of these patients, 53 did not receive prophylaxis while 13 received subcutaneous α-interferon 3×10^6 U thrice weekly and 11 received oral lamivudine 100 mg/day simultaneously with chemotherapy. Seventeen patients in the non-prophylactic group experienced HBV reactivation (32%), seven of whom progressed to fatal fulminant hepatitis (41%), which is associated with 13.2% of the mortality rate among the non-prophylactic patients. None of the 24 patients in the prophylactic group had grade III or IV toxicity or elevated ALT level greater than fivefold exceeding 200 IU/l suggestive of clinical hepatitis that required dose reduction or delayed chemotherapy. Thus, preemptive use of α-interferon or lamivudine in HBsAg-positive lymphoma patients undergoing chemotherapy may be a promising approach to prevent HBV reactivation that carries a risk of delayed treatment or even fatal outcome.

Keywords Lymphoma · Lamivudine · Interferon · HBV

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Introduction

Reactivation of hepatitis B virus (HBV) replication has been described in chronic HBV carriers diagnosed with leukemia, nasopharyngeal cancer, and choriocarcinoma and transplant recipients who were treated with cytotoxic or immunosuppressive agents, with a reactivation rate of 21–35% and mortality of 4–41% [15, 18, 34, 46]. However, the most commonly reported cases are patients with lymphoma [4, 17, 18, 20, 24, 30, 32, 43, 47, 49].

Aggressive non-Hodgkin's lymphoma is highly responsive to anthracycline-containing combination chemotherapy. The most appropriate standard therapy is cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone (CHOP), which could achieve a complete remission rate of 60–80% and long-term disease-free survival rate of 30–50% [3]. Myelosuppression, gastrointestinal bleeding, neurotoxicity, pneumonia, and mucositis are frequent treatment-induced toxicities but rarely lead to mortality, which was reported to be 1%, usually due to granulocytopenia and subsequent infection [14, 16]. Thus, hepatitis B virus surface antigen (HBsAg)-positive patients with aggressive lymphoma undergoing chemotherapy are often encountered with a significant risk of HBV reactivation that could not only delay the treatment course but also lead to a fatal outcome.

Interferon had been studied and used extensively as the best treatment option for chronic HBV infection before the development of newer nucleoside analogues, although the exact mechanism is not yet well understood [11, 13, 19, 23, 28, 42]. Lamivudine has shown promising results in the treatment of chronic hepatitis B infection, but much concern about resistance calls for further caution [2, 10, 12, 21, 31, 35]. Thus, even though great improvements in effectively eradicating HBV have been achieved in the

past 5 years, the roles of α-interferon and nucleoside analogue therapy in the treatment and prevention of HBV reactivation in cancer patients or transplant recipients who are HBsAg-positive patients remain to be defined [26].

The management of HBsAg-positive lymphoma patients during and after cytotoxic or immunosuppressive therapy is a challenging task. Measures to prevent HBV reactivation in these patients have not been established. Removal of steroids from the chemotherapy regimen was suggested to be beneficial but was not well defined [6, 7]. There are few reports on predictable effective treatment for HBV reactivation among HBsAg-positive lymphoma patients. Moreover, Taiwan is an endemic area for HBV infection with a prevalence rate of 15–20% [5]. A high percentage of lymphoma patients at risk for HBV reactivation is often encountered in daily practice. We reviewed the HBsAg-positive lymphoma patients treated at our institution from 1990 to 2001 and present a retrospective study on the effect of non-prophylaxis and preemptive treatment with interferon or lamivudine for HBV reactivation.

Patients and methods

Of the 519 patients diagnosed with aggressive lymphoma at National Cheng Kung University Hospital, Tainan, Taiwan from 1990 to 2001 88 (17%) were HBsAg positive. Nine patients were excluded due to not receiving chemotherapy, one was coinfected with hepatitis C virus, and one was diagnosed with triple cancers. The retrospective study included 77 patients, 51 male and 28 female, with a median age of 49 years at diagnosis. Most patients had stage III (35%) and stage IV (29%) disease. Of the patients, 44% had an elevated lactic dehydrogenase (LDH) level and 47% had B symptoms. All patients were treated with an anthracycline-based regimen, e.g., cyclophosphamide, epirubicin, vincristine, and prednisone (CEOP), bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone (BACOP), doxorubicin, cyclophosphamide, vindesine, and bleomycin (ACVB), methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD), methotrexate, doxorubicin, cyclophosphamide, prednisone, and bleomycin (MACOP-B), prednisone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, and methotrexate (PACEBOM), of which CEOP was the most frequently used. Five were treated with a non-steroid-containing regimen. A median of six cycles of chemotherapy was performed. The median follow-up time was 2 years. The clinical characteristics of the patients with aggressive lymphoma and the HBsAg-positive patients included in the study are presented in Table 1.

Preemptive treatment for HBV reactivation in HBsAg-positive patients using α-interferon 3×10^6 U subcutaneously thrice weekly at the beginning of chemotherapy and discontinued 4–8 weeks after completion of chemotherapy was given to 13 patients consecutively from 1994 to 1997; lamivudine 100 mg/day orally at the start of chemotherapy and discontinued 4 weeks after completion of chemotherapy was given to 11 patients consecutively from 1998 to 2001. Informed consent was obtained from every patient. Possible side effects at each visit or admission during the whole course of treatment were recorded. Alanine aminotransferase (ALT) and aspartate transferase (AST) levels prior to and after each cycle of chemotherapy and at regular follow-up visits were documented. HBV reactivation was defined as an elevation of the ALT level by a fivefold or greater increase that exceeded 200 IU/l (normal: <40 IU/l) after excluding other common causes of ALT elevation including other viral hepatitis, drug-induced hepatitis, and alcoholic hepatitis. Time, duration, peak ALT level, and peak bilirubin level were monitored during HBV reactivation. The patients were followed up monthly for the first 6 months, every 3 months for the next 6 months, and then annually when complete remission was reached.

Table 1 Clinical characteristics of all patients with aggressive lymphoma treated at our institution from 1990 to 2001. *HBsAg* hepatitis B virus surface antigen, *CEOP* cyclophosphamide, epirubicin, vincristine, and prednisone

HBsAg status	Negative	Positive	
		Included	Excluded
Patients (*n*)	431	77	11
Male (%)	246 (57)	49 (64)	7
Female (%)	185 (43)	28 (36)	4
Age at diagnosis			
Median	55	49	50
Range	20–83	18–90	24–70
Clinical stage			
I (%)	90(21)	7(9)	2
II (%)	121(28)	21(27)	2
III (%)	74(17)	27(35)	3
IV (%)	146(34)	22(29)	4
Elevated LDH (%)	211(49)	34(44)	5
B symptoms (%)	223(52)	36(47)	4
Chemotherapy regimen: CEOP (%)	215(50)	51 (66)	0

Results

Seventy-seven HBsAg-positive patients were treated for aggressive lymphoma in our institution from 1990 to 2001. Of the patients, 53 did not receive prophylaxis for HBV reactivation while 13 patients were given preemptive interferon and 11 lamivudine during systemic chemotherapy. The patients were followed up for a median of 2 years ranging from 2 months to 10 years.

In the non-prophylactic group, clinical hepatitis occurred in 17 patients (32%) who had a median age of 39 years (range: 18–70). Clinical hepatitis occurred within 1 month of the first dose of chemotherapy in eight patients. Three patients received non-steroid-containing chemotherapy. Of the patients, 7 died of fulminant hepatitis, 16 from disease progression, and there was 1 unrelated death. One patient in the non-prophylactic group developed hepatoma 5 years after complete remission of lymphoma and survives to date after hepatectomy.

None of the patients in the preemptive interferon or lamivudine group experienced an elevation of ALT level greater than fivefold suggestive of clinical hepatitis. Four died of disease progression and there were two unrelated deaths in the preemptive interferon group, while all patients in the preemptive lamivudine group survive. The survival was not adversely affected by the administration of lamivudine or interferon (Table 2).

The patients who were treated with interferon experienced influenza-like illness consisting of fever, chills, malaise, and anorexia, but no dose reduction or discon-

Table 2 Incidence of clinical hepatitis, fulminant hepatitis and outcome

Patients (*n*)	Non-prophylaxis	Preemptive treatment	
		α-Interferon	Lamivudine
HBsAg-positive	53	13	11
Steroid-containing chemotherapy	48	13	11
Clinical hepatitis (%)	17 (32)	0	0
Follow-up time			
Median	2 years		
Range	2 months–10 years		
Outcome			
Fatal fulminant hepatitis (%)	7 (13)	0	0
Disease progression (%)	16 (30)	4 (30)	0
Unrelated death	1	2	0
Hepatoma	1	0	0
Survival (%)	29 (55)	7 (54)	11 (100)

tinuation of treatment was noted. The duration of interferon treatment was comparable with those administered for chronic HBV infection that usually lasted 12–24 weeks. Patients who were given lamivudine did not experience any discomfort that necessitated discontinuation or dose reduction. Preemptive use of interferon or lamivudine for HBV reactivation in our series did not affect the dosage or the delivery schedule of chemotherapy.

Discussion

The HBV prevalence rate of 17% among our series was comparable to the general population in Taiwan [5]. The HBV reactivation rate of 32% in non-prophylactic patients with 41% who progressed to fulminant hepatitis resulted in a mortality rate of 13.2% for the non-prophylactic group. All patients receiving prophylaxis underwent chemotherapy as scheduled without dose reduction and did not experience clinical hepatitis. A similar relapse rate with disease progression was noted between the non-prophylactic group and the interferon group, while a longer follow-up duration of the lamivudine group is required to determine further relapse rate.

Our series showed comparable results with several other studies that had reported the HBV reactivation rate, the incidence of fulminant hepatitis, and the mortality rate due to fulminant hepatitis among HBsAg-positive patients who underwent chemotherapy for lymphoma [7, 9, 27, 30, 32, 33, 49]. The HBV reactivation rate ranged from 20 to 78%, and the mortality rate of chemotherapy-induced HBV hepatitis ranged from 7 to 30%. The incidence of fulminant hepatitis among patients who developed HBV reactivation ranged from 6 to 71% (Table 3). Effective management of HBV reactivation in these groups of patients was seldom reported, but three recent series documented encouraging results with few occurrences or no incidence of HBV reactivation with prophylactic measures [27, 36, 39] (Table 4).

Factors proposed as the possible causes of HBV reactivation were use of glucocorticoid-containing combination chemotherapy, chemotherapy-associated immunosuppression, pretreatment viral load, and precore mutation of HBV [35, 36, 37, 38, 39, 44]. As increased HBV replication in hepatocytes noted after long-term administration of prednisolone in chronic HBV carriers was postulated to be due to a glucocorticoid-responsive element in HBV DNA, the Taiwan Cooperative Group (TCOG) proposed omission of glucocorticoids in chemotherapeutic regimens to prevent HBV reactivation and

Table 3 Incidence of HBV reactivation, fulminant hepatitis, and mortality rate due to fulminant hepatitis among HBV carriers undergoing systemic chemotherapy for lymphoma

Previous series	HBV carriers included (*n*)	Incidence		Mortality rate due to HBV-related fulminant hepatitis (%)
		HBV reactivation (%)	Fulminant hepatitis (%)	
Lok [30]	27	67	11	7
Nakamura [33]	70	63	41	26
Markovic [32]	10	78	60	30
Yeo [49]	78	20	0	0
Dai [9]	13	46	17	8
Lim [27]	35	36.8	71.4	14
Cheng [7]				
Steroid-free regimen	25	38	0	0
Steroid-containing regimen	25	73	6	8
Leaw (our series)	77	32%	41%	9%

Table 4 Prophylactic therapy for HBV reactivation in HBsAg-positive patients undergoing chemotherapy. *P* prophylaxis, *NP* non-prophylaxis

	Rossi [36] P	Shibolet [39]		Lim [27]		Leaw (our series)	
		NP	P	NP	P	NP	P
Patients (*n*)	20	5	13	19	16	53	24
Outcome							
HBV reactivation	2	2	0	7	0	17	0
Fatal fulminant hepatitis	0	0	0	5	0	7	0
Median follow-up time (months)	6	-	21	-	-	24	24
Survival (%)	-	-	77	-	-	55	75

documented the possible role of steroids in HBV reactivation. However, a HBV reactivation rate of 37.5% was still noted among patients receiving non-steroid-containing regimens, while three of five patients in our series who received non-steroid-containing regimens experienced clinical hepatitis [7, 22, 44]. Thus, further studies on other possible causes of HBV reactivation are needed. Decreased T-cell function specific for HBV clearance noted during chemotherapy causes augmented HBV replication that would result in an exaggerated immunological response to clear the HBV-infected hepatocytes upon restoration of the viral-specific T lymphocytes after withdrawal of the immunosuppressive agents; thus, rapid liver damage ensues [45, 48]. The patients in our series experienced clinical hepatitis at a later point in time or after chemotherapy, which is consistent with the hypothesis. The pretreatment level of serum HBV DNA has also been proposed as the most important factor for exacerbation of HBV after intense immunosuppression [25]. Mutant HBV at the precore region has been associated with HBV reactivation with a fulminant course [9].

Interferon for chronic HBV therapy, usually lasting for 12–24 weeks, has been the most effective agent for HBV eradication to reach a success rate of 25–50% before the development of lamivudine, even though its role in the treatment and prevention of HBV reactivation in HBsAg-positive patients undergoing chemotherapy has not been well documented [11, 42]. Our series demonstrated that interferon given for a duration comparable to that for chronic HBV simultaneously with chemotherapy caused minimal and tolerable side effects and may be beneficial in preventing HBV reactivation without altering the treatment dosage or schedule. Further studies may be necessary to evaluate its role as an alternative for preemptive treatment of HBV reactivation in HBsAg-positive lymphoma patients.

Lamivudine, a well-tolerated reverse transcriptase inhibitor, has achieved remarkable results in treating chronic HBV infection or fulminant hepatitis [10, 21, 23, 26, 31]. Encouraging results of lamivudine therapy for HBV reactivation in HBsAg-positive lymphoma patients undergoing chemotherapy were also noted in several pilot studies, but the efficacy in such settings is still being studied [1, 8, 29, 40, 41, 45, 48]. The effectiveness of lamivudine as preemptive treatment for HBV reactivation among lymphoma patients and transplant recipients has been investigated in several preliminary studies where promising results were reported [12, 27, 36, 39, 41]. An ongoing TCOG randomized phase III clinical trial on preemptive lamivudine treatment for HBsAg-positive lymphoma patients is currently underway [7].

The issue of drug-resistant mutant selection and the risk of lamivudine withdrawal hepatitis has been raised as the occurrence of resistance of 15%, 38%, 49%, and 67% at 1 year, 2 years, 3 years, and 4 years, respectively, for chronic HBV carrier was noted, even though without associated deterioration or rapid progression in liver disease [31, 35, 41]. However, there was no previous literature documenting such issues in HBsAg-positive lymphoma patients undergoing chemotherapy. No patients in our series experienced lamivudine withdrawal hepatitis or resistance. Newer nucleoside analogues such as adefovir, entecavir, emtricitabine, and telbivudine have been developed to overcome lamivudine resistance, but further randomized trials are still awaited to determine the efficacy and safety of their roles for prevention of HBV reactivation in patients undergoing chemotherapy [26, 31].

Conclusion

The importance of preventing HBV reactivation in lymphoma patients undergoing chemotherapy could not be overemphasized, as there is still no reliable means of predicting an individual's risks of developing HBV reactivation or its severity. Preemptive interferon or lamivudine therapy treatment may reduce the risk of HBV reactivation and fatal outcome during and after completion of chemotherapy for HBsAg-positive lymphoma patients who could be cured of their underlying malignancies.

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