Steroid-Free Chemotherapy Decreases the Risk of Hepatitis Flare-up in Hepatitis B Virus Carriers With Non-Hodgkin's Lymphoma

To the Editor:

Reactivation of hepatitis B virus (HBV) has frequently been observed during the chemotherapy of HBV carriers with non-Hodgkin's lymphoma (NHL).[1,2] This issue is particularly important in HBV endemic areas around the world, in which the HBV carrier rate of the population may be as high as 15% to 20%.

Several lines of evidence suggest that glucocorticoids, ingredients of most first-line chemotherapy for NHL, are important predisposing factors to HBV reactivation: (1) HBV carriers with other solid tumors, who are usually treated by steroid-free chemotherapy, have rarely experienced HBV reactivation. (2) A retrospective Japanese study, comparing steroid-containing versus steroid-free regimens in the treatment of HBV carriers with hematological malignancies, reported a significant higher risk of hepatitis flare-up in the former group.[3] (3) HBV DNA was found to contain a glucocorticoid-responsive element.[4] (4) Glucocorticoids specifically activate HBV gene expression in cultured human hepatoma cells which were transfected by HBV genomes.[5]

Between January 1988 and December 1994, a total of 38 lymphoma patients, whose serum HBsAg (HBV surface antigen) had been prospectively examined to be positive, were treated by a standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen in our institutions. Eighteen patients (47.4%) developed hepatitis during chemotherapy. Among them, 9 patients (23.2%) had serum alanine aminotransferase >500 IU/L, while 3 (7.9%) died of fulminant hepatitis and another 3 died of progressive lymphoma.

During the same period of time, 12 lymphoma patients with positive serum HBsAg were prospectively treated by steroid-free chemotherapy. ACE (doxorubicin 40 mg/m^2, intravenously [IV], D1; cyclophosphamide 650 mg/m^2, IV, D1; VP-16 55 mg/m^2, IV, D1-3), VIM (VP-16 100 mg/m^2, IV, D1,3,5; ifosfamide 1.0 gm/m^2, IV, D1-5; methotrexate 30 mg/m^2, IV, D1,5), and ACO (doxorubicin 55 mg/m^2, IV, D1; cyclophosphamide 750 mg/m^2, IV, D1; vincristine 1.4 mg/m^2, IV, D1) were used in 7, 3, and 2 patients of diffuse aggressive lymphoma, respectively. Only 1 (8.3%) of these 12 patients developed clinical hepatitis during chemotherapy ($P < .05$). Ten patients (83.3%) achieved complete remission, and 8 of them remain disease free at this report with a median follow-up of 34 months.

Our data suggest that steroid-free chemotherapy reduces the risk of hepatitis flare-up in HBV carriers. A larger-scale prospective study comparing steroids-containing and steroids-free chemotherapies in HBV carriers with NHL is mandatory.

Ann-Lii Cheng
Departments of Internal Medicine and Oncology
Cancer Research Center
National Taiwan University Hospital and College of Medicine
Taipei, Taiwan

REFERENCES

1. Lok ASF, Liang RHS, Chiu EKW, Wong KL, Chan TK, Todd D: Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Gastroenterology 100:182, 1991

2. Soh LT, Ang PT, Sng I, Chua EJ, Ong YW: Fulminant hepatic failure in non-Hodgkin's lymphoma patients treated with chemotherapy. Eur J Cancer 28A:1338, 1992

3. Ohtsu T, Sai T, Oka M, Sugai Y, Tobinai K: Activation of hepatitis B virus carriers with hematologic malignancies. Jpn J Clin Oncol 21:360, 1991

4. Tur-Kaspa R, Burk RD, Shaul Y, Shafritz DA: Hepatitis B virus DNA contains a glucocorticoid-responsive element. Proc Natl Acad Sci USA 83:1627, 1986

5. Chou CK, Wang LH, Lin HM, Chi CW: Glucocorticoid stimulates hepatitis B viral gene expression in cultured human hepatoma cells. Hepatology 16:13, 1992