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Fulminant Hepatic Failure in Non-Hodgkin Lymphoma Patients Treated with Chemotherapy

Lay-Tin Soh, Peng-Tiam Ang, Ivy Sng, Eu-Jin Chua and Yong-Wan Ong

Chemotherapy is the mainstay of therapy for patients with non-Hodgkin lymphoma. Among side-effects associated with the use of chemotherapy, immunosuppression is one which can be potentially fatal. In hepatitis B carriers, immunosuppression permits widespread infection of the hepatocytes and its subsequent withdrawal causes an "immunological rebound" leading to massive necrosis of hepatocytes. 4 patients who died of fulminant hepatitis following chemotherapy are reported. These were patients with positive hepatitis B serology. Caution is advised when treating non-Hodgkin lymphoma in patients from hepatitis B endemic regions.
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INTRODUCTION

DESPITE ADVANCED disease, cure is the common goal sought by all who treat patients with intermediate and high grade non-Hodgkin lymphoma (NHL). This has been made possible because of the significant advances made in treatment of lymphoma over the past 15 years. The treatment of non-Hodgkin lymphoma often involves the use of chemotherapy, which, besides suppressing and eradicating the tumour, compromises the immunity of the patient. In certain groups of patients, this immunosuppression can prove to be fatal. The following is an account of 4 hepatitis B carriers who died from fulminant hepatitis during and after chemotherapy.

Case reports

Case 1. A 55-year-old Chinese man with stage IVB diffuse large cell lymphoma, was treated with MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisolone). The regimen alternates myelosuppressive with non-myelosuppressive agents weekly for 12 weeks. High-dose steroids (prednisolone, 75 mg daily) are given during this time with tailing of dose from week 10. Liver function tests prior to chemotherapy were normal except for a mildly raised alanine transaminase (79 U/l). Evaluation at the end of chemotherapy showed no evidence of residual disease. 3 weeks after cessation of chemotherapy, the patient developed lethargy, generalised malaise, jaundice and tea-coloured urine. He was

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febrile with an enlarged liver. Investigations revealed markedly elevated transaminases and hyperbilirubinaemia. The hepatitis B surface antigen (HBsAg) and hepatitis Be antibody (anti-HBe) were positive. Despite supportive measures, he progressively deteriorated and died of liver failure from fulminant hepatitis. The post-mortem liver biopsy sample showed massive necrosis of the hepatocytes. There was no evidence of lymphoma.

Case 2. A 65-year-old Chinese woman had stage IIA diffuse large cell lymphoma. She was treated with six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) given every 3 weeks. Pulse steroid (prednisolone 50 mg/m^2 daily for 5 days) was given with each cycle. Liver function tests done prior to chemotherapy were normal except for a low albumin (2.7 g/l). 5 weeks after completion of chemotherapy, the patient was admitted with liver failure from fulminant hepatitis. The HBsAg prior to chemotherapy was positive and it remained positive during the fulminant hepatitis period. Anti-HBe was positive.

Case 3. A 29-year-old Chinese man with bulky stage IIB diffuse large cell lymphoma, was treated with MACOP-B. He was a known HBsAg carrier. Liver function tests done prior to chemotherapy were normal except for low albumin (3.5 g/l). 3 weeks after completion of MACOP-B, he was admitted with acute hepatitis which worsened progressively. HBsAg was initially negative at the time of admission but became serologically positive after 4 weeks. His condition deteriorated and he died of liver failure.

Case 4. A 37-year-old Chinese man had bulky stage IIB diffuse large cell lymphoma and was treated with MACOP-B. He was a known HBsAg carrier. The only abnormal liver function test was an elevated alanine transaminase level (102 U/l). In this patient, steroid was tailed more gradually than usual from week 8 (prednisolone; 60 mg daily on week 8, 45 mg daily on week 9, 30 mg daily on week 10 and 20 mg on weeks 11 and 12). At week 12, he presented with symptoms and signs of acute hepatitis. HbsAg tested on admission was negative and the anti-HBe antibody was positive. Despite increasing the steroid dose and supportive measures, the hepatitis pursued a fulminant course and he died after 4 weeks.

DISCUSSION

Acute fulminant hepatitis was the immediate cause of death in these 4 patients with non-Hodgkin lymphoma. This occurred towards the end of or after therapy. Negative serology for Epstein–Barr virus, cytomegalovirus, hepatitis A, hepatitis C and delta viruses and positive serology for hepatitis B virus implicates hepatitis B as the likely aetiological agent. 3 of the patients were known hepatitis B carriers while the last (case 1) was noted to be serologically positive when he presented with acute hepatitis. In addition, the HbsAg which was positive prior to chemotherapy, became negative in cases 3 and 4.

Fulminant hepatitis can result from toxicity. Among the chemotherapeutic agents used, potential hepatotoxins included methotrexate and cyclophosphamide [1]. In the doses given, methotrexate causes hepatic fibrosis but not acute hepatic necrosis. Cyclophosphamide has been reported to cause severe hepatic injury [2]. However, other than these 4 patients, there was no evidence of hepatic injury in the 351 lymphoma patients treated at our department during this period.

This phenomenon of fulminant hepatitis in chronic hepatitis B patients upon withdrawal of immunosuppressive treatment has been reported by a number of authors [3–9]. The phenomenon is not restricted to patients given steroids but also occurs in patients given cytotoxic chemotherapy [3–6].

Lam *et al.* [10] reported that in a HbsAg carrier given steroids, the raised transaminase levels and histology indicate more severe infection and the onset of remission is delayed. Scullard [11] found that in chronic hepatitis B patients who were given prednisolone therapy, there was an increase in the DNA polymerase levels during the treatment period suggesting enhanced HBV replication. This is followed by a fall in the DNA polymerase activity and elevation of transaminases upon withdrawal of steroids. Signelli [12], in his study of 101 patients randomised to steroid, azathioprine and placebo, found that immunosuppression favours the replication of hepatitis B virus in patients with HbsAg-positive chronic active hepatitis.

In these 4 patients, it is likely that the administration of immunosuppressive permits widespread infection of the hepatocytes with hepatitis B virus and upon cessation of immunosuppressive therapy, the return of immunity led to viral attack with destruction of the infected hepatocytes. In our experience, gradual withdrawal of steroid and increase of dose in the event of acute hepatitis do not appear to improve the outcome. Hence, patients who are candidates for cancer chemotherapy should be routinely screened for HbsAg. This is important in countries in the far east and some tropical countries where the prevalence of hepatitis B viral infection can be as high as 20% [13]. In such patients, caution should be exercised during the administration of immunosuppressive therapy.

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