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ORIGINAL ARTICLE

Reactivation of Hepatitis B after Irinotecan

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ABSTRACT

Objective: *To analyse the incidence of hepatitis B reactivation following treatment with irinotecan-based combined chemotherapy and the outcomes of patients with hepatitis B reactivation.*

Patients and Methods: *A prospective phase II study investigating the response to irinotecan, leucovorin, and 5-fluorouracil in 34 patients with stage IV colorectal cancers. All patients had hepatitis B virus status checked at baseline.*

Results: *Three patients were identified to be hepatitis B virus carriers. Two of the patients had hepatitis B reactivation after chemotherapy commenced, while the third patient, who was given lamivudine before commencement of chemotherapy, did not have any adverse hepatic event.*

Conclusions: *In view of the increasing use of irinotecan as palliative treatment for advanced colorectal cancer, further studies on the probable causal relationship between irinotecan and reactivation of hepatitis B infection are recommended. The prophylactic use of lamivudine in patients at risk might be beneficial.*

Key Words: *Chemotherapy, Hepatitis*

INTRODUCTION

Chemotherapy-induced chemical hepatitis is not uncommon in patients receiving certain chemotherapeutic agents such as methotrexate, etoposide, and dactinomycin. Other causes of impaired liver function include tumour progression, concurrent medications, bacterial infections, and hepatitis viral infection. In Hong Kong, more than 10% of the adult population are chronic hepatitis B virus (HBV) carriers. Therefore, reactivation of hepatitis B infection should not be overlooked. Previous studies of chemotherapy-induced reactivation of hepatitis B infection have mainly focused on patients with haematological malignancies. In one study of Chinese patients with lymphoma, 47% of HBV carriers developed reactivation during chemotherapy, resulting in a 5% mortality rate.[1] A recent study among local patients with various cancers who received chemotherapy found that approximately 20% of HBV carriers developed reactivation.[2] Another study of local patients with breast cancer who mainly received cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU) or an anthracycline-containing regimen detected a 41% rate of reactivation of hepatitis B infection.[3]

A prospective phase II study testing irinotecan-based combined chemotherapy was performed at the Queen Mary Hospital and patients with advanced stage colorectal cancer were recruited into the study. The incidence of hepatitis B reactivation and the outcome of these patients were analysed.

PATIENTS AND METHODS

A prospective phase II study testing the FOLFIRI regimen (irinotecan 180 mg/m^2 on day 1, leucovorin 200 mg/m^2 on days 1 and 2, 5-FU bolus 400 mg/m^2 on days 1 and 2, and 5-FU infusion 600 mg/m^2 on days 1 and 2) was performed from August 2000 to June 2001. Thirty four patients with stage IV colorectal cancers were recruited to the study. All patients had HBV status checked at baseline.

Based on the definition of Yeo et al, hepatitis was defined as 3-fold or greater increase in serum alanine aminotransferase (ALT) that exceeds the upper limit of normal (ULN), i.e., 53 U/L, or an absolute increase of ALT to more than 100 U/L when compared with the baseline prechemotherapy value.[4] According to Lok et al, hepatitis was attributed to reactivation or

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exacerbation of chronic hepatitis B when there was reappearance of HBV DNA or hepatitis B e antigen (HBeAg) in the serum, or a sudden increase (>10-fold) in serum HBV DNA level, with no evidence of hepatotoxic drugs or systemic infections.[1] At the Queen Mary Hospital, the Digene II test (Digene, Maryland, USA) is used to measure the HBV DNA level. Its lower detection limit is 0.142 MEq/mL (i.e., 0.142 x 10^6 copies/mL). An HBV DNA level of > 0.142 MEq/mL is evidence of active hepatitis B viral replication.

RESULTS

Three patients were identified to be HBV carriers (hepatitis B surface antigen [HBsAg] seropositive) before treatment. They had grossly normal baseline liver function test (LFT), although 2 had very mildly elevated aspartate aminotransferase (AST). The progress of these 3 HBsAg-positive patients during treatment were reviewed and reported as follows.

Patient 1

A 65-year-old man received a diagnosis of advanced rectosigmoid carcinoma complicated by ascites peritoneal, and liver metastases in November 2000. At baseline, he had very mild elevation of AST at 47 U/L (normal range, 20-48 U/L). He had a baseline HBV DNA test done in a private hospital in November 2000 and was found to have 2.264 x 10^6 copies/mL in his serum before commencement of chemotherapy. He was treated with 2 cycles of FOLFIRI in December 2000 and his LFT became deranged with an elevation of ALT and AST to 101 U/L and 193 U/L, respectively, (Figure 1). This was initially treated as chemotherapy-induced hepatitis and, after a short delay, the third cycle was resumed. However, his HBV DNA was subsequently shown to be elevated to 82.970 MEq/mL (82.970 x 10^6 copies/mL), which was an approximately 36-fold increase in serum HBV DNA, and was evidence of hepatitis B reactivation. Daily lamivudine 100 mg was started and his LFT returned to normal soon afterwards. He completed 8 cycles of chemotherapy and achieved static disease without adverse hepatic events.

Patient 2

A 64-year-old man received a diagnosis of cancer of the rectum with pulmonary metastases in February 2001. Baseline LFT was normal. He received the first cycle of FOLFIRI uneventfully. His LFT was deranged with an ALT of approximately 5 x ULN (262 U/L) and AST of 3 x ULN (123 U/L) on the first day of the

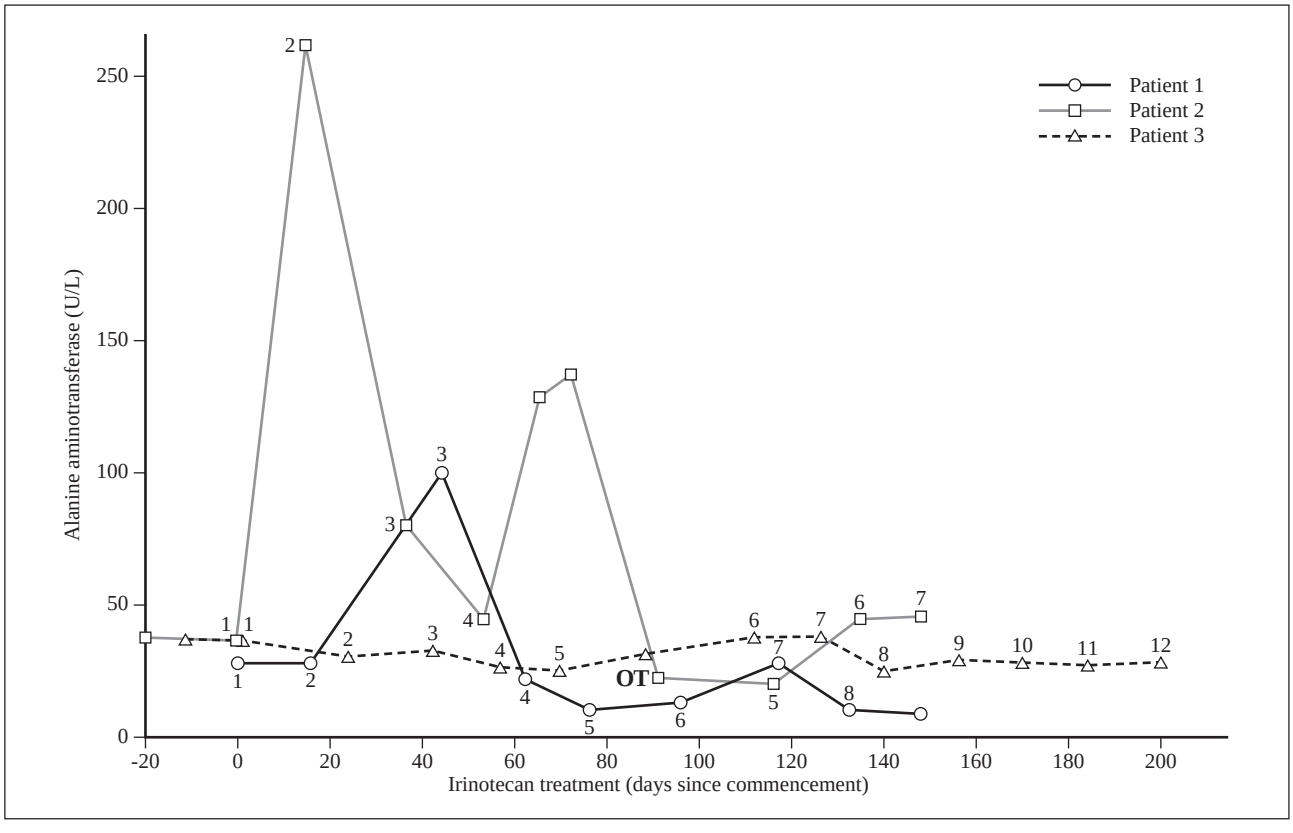

Figure 1. The variation of alanine aminotransferase level in 3 hepatitis B virus carriers during treatment with irinotecan-containing chemotherapy. The numbers represent the chemotherapy cycle. OT refers to the abdominoperineal resection received by patient 2.

second cycle of chemotherapy (Figure 1). The second cycle of chemotherapy was then truncated. A hepatologist was consulted and daily lamivudine 100 mg was started. HBeAg was later confirmed to be present in the serum and HBV DNA was elevated to 2.7 MEq/mL, which was compatible with reactivation of hepatitis B infection. His LFT gradually returned to normal after lamivudine started and the third cycle of FOLFIRI was given. However, his LFT was again deranged after the fourth cycle (Figure 1). Further chemotherapy was halted. A repeat computed tomography scan showed complete response for his pulmonary metastases but a persistent rectal primary tumour. He then underwent an abdominoperineal resection. Histopathology showed a complete pathological response with no residual carcinoma. Postoperatively, he was given 3 more cycles of FOLFIRI as adjuvant therapy with concurrent lamivudine. No further episodes of liver derangement occurred. He was progression-free for approximately 7.5 months before the disease relapsed.

Patient 3

A 48-year-old man received a diagnosis of cancer of the transverse colon with liver and multiple lymphadenopathy in April 2001. He underwent palliative segmental colectomy and resection of 1 of the liver metastases in a private hospital and was then referred to the Queen Mary Hospital for further management. In view of the experience of the previous 2 patients, he was given daily lamivudine 100 mg as prophylaxis for hepatitis B reactivation. He received 12 cycles of FOLFIRI without any hepatic compromise (Figure 1) during the period of chemotherapy.

DISCUSSION

Approximately 10% of the local population are hepatitis B carriers. Chemotherapy-induced reactivation of hepatitis B infection is one of the known complications among HBsAg-seropositive patients. This can result in varying degrees of hepatic insult, from transient elevation of aminotransferase levels to fulminant hepatic failure.[5] It is postulated that potent cytotoxic therapy causes immunosuppression and hence reactivates HBV replication, permitting widespread infection of hepatocytes. Upon cessation of chemotherapy, there is an immune rebound resulting in rapid destruction of infected hepatocytes and massive liver necrosis. The higher risk of chemotherapy-induced hepatitis B reactivation among haematological patients might be related to the immunosuppressive nature of the disease or the use of high-dose cytotoxic drugs and steroids. Certain chemotherapeutic agents have been found to be associated with a higher risk of reactivation. A prospective study of patients with cancer showed that the use of anthracyclines and vinca alkaloids are risk factors for hepatits B reactivation.[2] A recent analysis of HBV reactivation among HBsAg seropositive patients with cancer showed that anthracycline-containing chemotherapy and lymphoma were the only 2 factors significantly associated with hepatitis B reactivation.[4] Although it is usually reversible for mild hepatitis after prompt management, a delay or reduction of dosage of chemotherapy is often required. A prospective study of breast cancer patients showed a significant association between HBV reactivation and premature discontinuation or delay of chemotherapy.[3]

Colorectal cancer is the third leading cause of cancer death in Hong Kong according to the Hong Kong Cancer Registry, 2000. Up to half of these patients may develop advanced disease after the initial diagnosis. Numerous novel agents have been studied recently to improve the survival of these patients. Irinotecan is one of the agents proven to be beneficial for patients with metastatic colorectal cancer. To our knowledge, no report has been published on the association between the use of irinotecan and hepatitis B reactivation. In our FOLFIRI study, the incidence of hepatitis B reactivation among HBsAg-seropositive patients was noted and is reported here.

The prevalence of HBV carriers was approximately 9% (3 patients) among the 34 patients with colorectal cancer who were recruited into the FOLFIRI study. All of these patients had relatively normal baseline LFTs before chemotherapy. The first 2 patients developed hepatitis B reactivation after 2 cycles and 1 cycle of FOLFIRI respectively. The chemotherapy schedule was delayed or truncated for both patients. Lamivudine was started and their liver function gradually improved. Chemotherapy was resumed for both patients and the response was uneventful. In view of the adverse reaction for these 2 patients, prophylactic treatment with lamivudine was started before administration of chemotherapy for the third patient. He received a total of 12 cycles of FOLFIRI without any interruption and his LFT remained grossly normal. He achieved a partial response.

From this retrospective review on the incidence of hepatitis B reactivation in a prospective study using irinotecan-containing combined chemotherapy, a probable association between hepatitis B reactivation

and the use of irinotecan is suggested. Since the number of patients was small in this trial, it is hard to be conclusive. Lamivudine is a nucleoside analogue and a potent inhibitor of HBV reverse transcription. It has been shown to be effective as treatment and prophylaxis for reactivation of hepatitis B infection among patients who receive chemotherapy.[6-8] A recent phase II study by Yeo et al suggested that prophylactic lamivudine (100 mg 7 days before the commencement of chemotherapy and 8 weeks after completion of chemotherapy) was protective for HBV reactivation in cancer patients receiving chemotherapy.[4] The prophylactic use of lamivudine in our third patient also seemed to be protective against hepatitis B reactivation by irinotecan. In contrast, morbidity and mortality were seen among patients who received lamivudine only after the onset of hepatitis.[9-11] There is often a need to delay or to reduce the dose of chemotherapeutic agents, which might hamper the beneficial effect of the treatment. The second patient had a second surge of liver enzyme levels after starting lamivudine, and this hindered the chemotherapy being given on schedule.

In view of the increasing use of irinotecan as palliative treatment for advanced colorectal cancer, further studies on the probable causal relationship between irinotecan and reactivation of hepatitis B infection are recommended. It is likely that lamivudine is a potential drug for the treatment of hepatitis reactivation. The appropriate time of commencement and duration of use should be promptly investigated to allow colorectal cancer patients who are HBV carriers to receive maximum benefits from this novel chemotherapeutic agent while the risk of reactivation is minimised.

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