

Fatal Outcome of Tenofovir Treatment in Chemotherapy-induced Hepatitis B Reactivation Presumably Due to Mitochondria Toxicity: Failure of Compliance with Screening Guidelines and Monitoring during Treatment

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Abstract

Background: The American Gastroenterological Association Institute guidelines on hepatitis B reactivation (HBVr) advocate for screening and treatment with nucleoside analogues. These drugs are known to cause mitochondrial toxicity and monitoring is recommended. Additionally, chemotherapy can cause mitochondrial damage that may enhance nucleosides toxicity. Compliance with these guidelines, however, is unknown. We present a case of fatal outcome of HBVr that could have been prevented with screening.

Case presentation: A 69-year-old female received chemotherapy for invasive breast cancer without prior screening for hepatitis B. She developed abdominal pain and loss of appetite few weeks after finishing chemotherapy. She was found to have elevated liver enzymes (ALT=2000 unit), positive hepatitis B surface antigen and hepatitis B viremia (11×10^7 IU). She was diagnosed with HBVr. She was started on tenofovir although by the time treatment was initiated her symptoms were improving, ALT decreased to 726 unit and hepatitis B viremia dropped to 16×10^4 IU. Few days after starting tenofovir she developed abdominal pain, diarrhea, vomiting, lactic acidosis, cardiomyopathy and eventually expired. The final manifestations and laboratory findings were suggestive of mitochondrial toxicity.

Conclusions: This case suggests that recent chemotherapy may predispose to rapid onset of severe tenofovir toxicity and illustrates the importance of compliance with HBV screening and monitoring for drug toxicity during treatment.

Keywords: Tenofovir treatment; Chemotherapy; Hepatitis B reactivation; Mitochondria toxicity

Introduction

Tenofovir and other nucleoside reverse transcriptase inhibitors have been reported to infrequently cause mitochondrial toxicity and lactic acidemia in HIV patients, usually after a prolonged drug exposure [1-5]. Tenofovir is also often used in the treatment of chronic hepatitis B [6,7]. Hepatitis B virus reactivation (HBVr) following anti-cancer or immunomodulating therapy is increasingly recognized [8-10]. The outcome of HBVr varies between mild disease to acute hepatic failure and death [10]. Therefore, screening such patients with hepatitis B core antibody prior to starting immunomodulating treatment and prophylactic antiviral treatment, preferably with nucleoside analogues, regardless of hepatitis B surface antibody status, is advocated [9]. Compliance with hepatitis B screening prior to such therapy, however, is probably suboptimal. Therefore, HBVr may develop and antiviral treatment is warranted in patients who remain on immunomodulators or chemotherapy [9]. The approach to patients with HBVr who are no longer on chemotherapy is unclear and the benefit of antiviral treatment in these patients is unknown. Current American

Gastroenterological Association Institute guidelines advocate for screening and prophylactic treatment of high-risk patients but do not address patients who develop HBVr [9].

Certain cancer chemotherapies, such as Taxol-based therapy, can be associated with mitochondrial dysfunction [11-13]. The accumulative effects of chemotherapy and nucleoside analogues on mitochondrial function have not been evaluated. We report a case of fatal outcome of HBVr due to failure to comply with screening guidelines. The patient was treated with tenofovir. She developed lactic acidosis and cardiomyopathy and eventually expired. We suspect that the recent chemotherapy may have predisposed to severe tenofovir toxicity, presumably due to pre-existing mitochondrial dysfunction.

Case Report

We present a 69-year-old woman with history of left-sided stage three invasive breast ductal carcinoma, diagnosed in 2017. She underwent left mastectomy and axillary lymph node dissection which revealed that several lymph nodes were involved. She received adriamycin and cytoxan for eight weeks followed by weekly taxol, herceptin and pertuzumab. Screening for hepatitis B was not

implemented. She was noted to be anemic (hg=8.1 gm down from 14.3 gm prior to chemotherapy). She received a transfusion of one unit of blood and chemotherapy was discontinued. ALT at that time was 31 IU and increased to 78 within two days. Over the next two weeks she developed abdominal discomfort and weakness. She was found to have elevated liver enzymes (Figure 1). Hepatitis markers were checked one day later and revealed positive hepatitis B surface antigen and total core antibody with negative core IgM antibody. Hepatitis B viral DNA titer was 11×10^7 IU. Eighteen days later, she developed jaundice and was admitted to the hospital. On admission, the patient was feeling better, her abdominal discomfort nearly resolved, and her appetite improved. The physical examination was unremarkable except for jaundice. Admission laboratory tests revealed that ALT, AST and bilirubin were decreasing, and the hepatitis B viral DNA titer dropped to 16×10^4 IU. She remained asymptomatic and her liver enzymes continued to drop over the next two days. She was started on tenofovir 20 days after the recognition of the HBVr. She was maintained on home medications including atorvastatin, amlodipine, fexofenadine, isosorbide mononitrate, pantoprazole, Montelukast and ondansteron. Within two to three days the patient started to have abdominal pain, nausea and vomiting, and severe weakness; she quickly deteriorated with dyspnea, lethargy and hypotension. She was transferred to the medical ICU and intubated. Chest X-rays were consistent with pulmonary edema and an echocardiogram showed severe global hypokinesis with estimated ejection fraction of 25%-30%. Blood cultures were obtained and she was started on broad spectrum antibiotics for presumed sepsis. Blood cultures were negative. Despite

attempts at resuscitation she remained hypotensive, developed lactic acidosis, progressive multi organ failure and eventually expired nine days after starting tenofovir (Table 1).

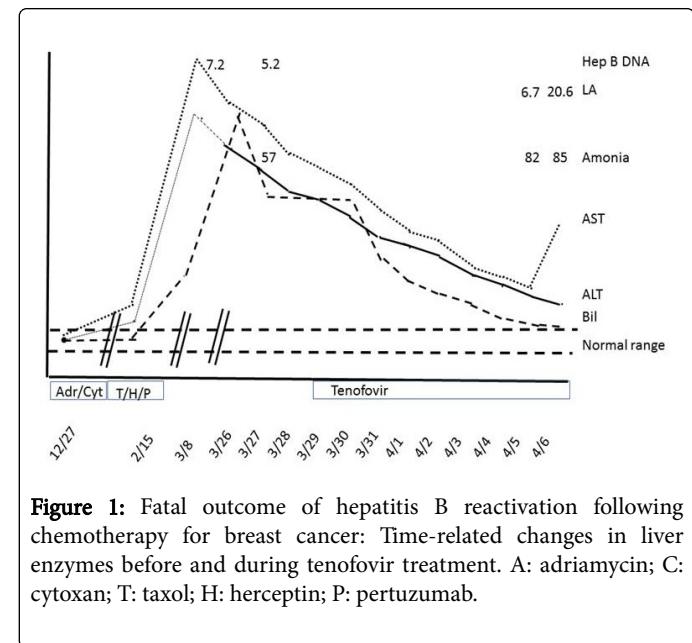


Figure 1: Fatal outcome of hepatitis B reactivation following chemotherapy for breast cancer: Time-related changes in liver enzymes before and during tenofovir treatment. A: adriamycin; C: cytoxan; T: taxol; H: herceptin; P: pertuzumab.

Day of Tenofovir Treatment									
Laboratory test	0	1	2	3	5	6	7	8	9
Albumin (mg/dL)	2.3	2.2	2.2	1.8	2	1.8	1.4	1.1	1.6
Creatinine (mg/dL)	0.99	0.93	0.87	0.85	1.11	1.3	1.83	2.43	2.04
Glucose (mg/dL)	82	102	115	99	86	80	121	39	65
Ammonia level (mcmol/L)	57						69	82	85
Lactic acid (mmol/L)								6.7	20.6
pH								6.95	

Table 1: Hepatitis B reactivation: Laboratory test evolution during tenofovir treatment.

Discussion

Nucleoside analogues are known to cause mitochondrial DNA loss and predispose to lactic acidemia and rarely lactic acidosis with high mortality among HIV infected patients [1-5]. Although stavudine and DDI had the highest association, all nucleoside analogues, including tenofovir have been implicated in mitochondrial DNA damage. These drugs are rarely used in non-HIV infected patients but tenofovir and lamivudine are sometimes used in the prophylaxis and treatment of hepatitis B virus [6,7]. Tenofovir-related toxicity was reported in a patient with cirrhosis [14]. Additionally, lactic acidosis and rhabdomyolysis was reported in another patient during telbivudine and tenofovir treatment for chronic hepatitis B [15]. Our patient did not have pre-chemotherapy HBV screening and developed HBVr as supported by negative IgM core antibody. She probably became symptomatic during immune reconstitution after stopping chemotherapy and began to improve during the immune restoration

phase. Soon after starting tenofovir, she developed symptoms that were suggestive of mitochondrial toxicity [3,5]. Eventually, her condition progressed to severe lactic acidosis, hypoglycemia, and final rise in AST without ALT which implies a muscle source, severe cardiomyopathy with normal echocardiogram two weeks earlier and eventually died. These changes are likely due to mitochondrial toxicity rather than progressive hepatic failure because she was feeling better and liver enzymes were trending down before tenofovir was initiated. Additionally, the nausea, vomiting, abdominal pain, lactic acidosis, severe cardiomyopathy and the drop-in bilirubin are more suggestive of mitochondrial dysfunction rather than progression to fulminant hepatitis or chemotherapy-related cardiomyopathy [5]. She was receiving other medications that may have interacted with tenofovir. Additionally, she may have had a metabolism phenotype that predisposes to higher tenofovir drug levels. Whatever the mechanism may be, this patient probably had pre-existing mitochondrial damage secondary to the recent chemotherapy that predisposed to severe and

earlier nucleoside toxicity or medications interaction. This patient was probably in the restoration phase of HBVr and may not have needed antiviral treatment. Current guidelines, however, focus on HBVr prevention and do not address patients who were not screened and developed HBVr. This case illustrates the importance of compliance with screening guidelines and monitoring for drug toxicity.

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