The rate of hepatitis B and C virus infections and the importance of HBV vaccination in children with acute lymphoblastic leukemia

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Aim: The aim of the study was to evaluate the rate of hepatitis B and C virus infection and emphasize the importance of hepatitis B virus (HBV) vaccination in leukemic children.

Methods: One hundred and sixty children who were treated for acute lymphoblastic leukemia (ALL) at Hacettepe University Faculty of Medicine, Pediatric Hematology Unit were included in the study. They were 71 (44.4%) girls and 89 (55.6%) boys with a mean age of 6.45 ± 3.87 years.

Results: Of these 160 children, 22 (13.8%) were anti-HBs-positive and 138 (86.2%) were anti-HBs-negative at the diagnosis of ALL. Among the 138 anti-HBs-negative children, 67 (41.9%) were vaccinated for HBV during maintenance chemotherapy, and 71 (44.3%) could not be vaccinated. Two (2.9%) vaccinated and 22 (30.9%) unvaccinated children developed HBV infection during the follow-up period (P < 0.001). Among 160 children treated for ALL, 24 (15.0%) had HBV, three (1.9%) had hepatitis C virus (HCV) infections, and 29 (18.1%) had toxic hepatitis. The majority of patients with HBV or HCV infections had high risk (HR) protocol, whereas most of the patients with toxic hepatitis had low risk (LR) protocol, especially St Jude Total XIII LR protocol.

Conclusion: Viral hepatitis and toxic hepatitis were observed more commonly in the HR and LR group, respectively, of ALL patients. This could be explained by intensive chemotherapy and more heavy blood product administration in the HR group and the chemotherapeutic agents of methotrexate and 6-mercaptopurine, basic drugs used in the LR group. In respect to protection from these complications, periodic liver function tests, serological tests for HBV and HCV, and vaccination for HBV should be performed for all children with ALL.

Key words: hepatitis B virus infection, hepatitis C virus infection, HBV vaccination, acute lymphoblastic leukemia, children

INTRODUCTION

HEPATITIS WITH ELEVATION of aminotransferase levels is common during the treatment of children with acute lymphoblastic leukemia (ALL). Toxic hepatitis may result from chemotherapeutic agents, especially methotrexate (Mtx) and 6-Mercaptopurine (6-MP). In addition to chemotherapy, hepatitis B and C virus infections, occasionally leukemic infiltration, bacterial infections and antibiotics used during febrile neutropenia periods, are also responsible for the elevation of hepatic transaminases. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are more common in children with ALL than in the general population because of transfusions given during the treatment and the immunosuppressive effect of the chemotherapy.1-3 The aim of this study was to evaluate the hepatitis B or C virus infections of children treated for ALL in our center and to emphasize the importance of HBV vaccination in leukemic children.

METHODS

BETWEEN MARCH 1991 and January 2001, 204 children were treated for ALL at Hacettepe University Faculty of Medicine, Pediatric Hematology Unit. One hundred and sixty children who were still in remission status comprised the study group. Of these 160 children with ALL, 71 (44.4%) were girls and 89 (55.6%) were boys. The mean age of the children was 6.45 ± 3.87 years (range: 0.5–15 years). Eighty-seven patients (54.4%) received modified St Jude Total XI protocol,4,5 whereas 73 (45.6%) received modified St Jude Total XIII protocol (Table 1).4 In March 1997, St Jude
Total XI protocol was changed to St Jude Total XIII protocol in our center. Therefore, before March 1997 the patients received St Jude Total XI protocol and after March 1997 the patients received St Jude Total XIII protocol. St Jude Total XIII protocol is still used in our center. Among the 87 patients who received St Jude Total XI protocol, 30 (34.5%) had low risk (LR) and 57 (65.5%) had high risk (HR) protocols. Among the 73 patients who received St Jude Total XIII protocol, 40 (54.8%) had LR and 33 (45.2%) had HR protocols. The mean follow-up period, which extended from the diagnosis of ALL to the last follow-up examination, was 51.22 ± 23.50 months (range: 30–145 months) for all of the patients. Hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs), anti-hepatitis B core antibodies (anti-HBc), and anti-hepatitis C antibody (anti-HCV) were studied by the ELISA method (Axsym Diagnostics, Abbott Park, IL). Hepatitis C virus RNA in serum and plasma was detected by PCR assay (TaqMan; Perkin Elmer/Applied Biosystems, Foster City, CA). Serological markers for HBV and HCV and liver function tests were performed at diagnosis and at 3-month intervals during the follow-up period. Children seronegative for HBV were vaccinated according to our institutional vaccination protocol.7 Serological markers for HBV were repeated six weeks after the vaccination. Anti-HBs >10 IU/L was defined as a protective antibody level.

Serum transaminase elevation >300 IU/L was accepted as severe toxic hepatitis,8 and serum transaminase elevation was also detected in viral hepatitis. We performed the differential diagnosis of toxic and viral hepatitis as follows: negative serological markers for HBV and HCV associated with elevated transaminases during chemotherapy suggested a diagnosis of toxic hepatitis. If cessation of chemotherapy resulted in a gradual drop in the elevated transaminases, this was diagnostic for toxic hepatitis. However, in the cases of viral hepatitis, positive serological markers for HBV or HCV and elevated transaminases, especially alanine aminotransferase (ALT) elevation, were both necessary for the diagnosis. ALT is highly liver-specific, whereas aspartate aminotransferase (AST) can also be elevated after injury to other organs. Marked increases in aminotransferase activities, especially ALT elevation, best reflect the degree of liver cell injury. After the diagnosis of viral hepatitis had been established, cessation of chemotherapy was not enough for transaminases to return to normal.

The diagnosis of acute hepatitis B is based on the detection of HBsAg and AntiHBc-IgM. During the initial phase of infection, the markers of HBV replication (HBe Ag and HBV–DNA) were also present. Past HBV infection was diagnosed by the detection of anti-HBs and AntiHBc-IgG. Immunity to HBV infection after vaccination was determined by the presence of anti-HBs only. The diagnosis of chronic HBV infection was based on the detection of HBsAg. Additional tests for HBV replication (HBe Ag and HBV–DNA) were also present to determine if the patient should be considered for antiviral therapy. HbsAg-positive, but HBV replication markers (HBe Ag and HBV–DNA) negative individuals were described as inactive HbsAg carriers. If positive serological markers for HBV and HCV had persisted for more than six months, the diagnoses of chronic hepatitis B and C infections were established.

Additionally, liver biopsy was performed to confirm the diagnosis of chronic hepatitis B and C infections. Histopathological confirmation of the diagnosis was established, especially before the beginning of antiviral treatment including lamivudine and interferon therapies. Since 10 of the 24 patients with HBV infection and all three with HCV infection developed chronic hepatitis B and C infections, they underwent liver biopsy and received antiviral treatment.

Table 1

|               | St Jude Total XI |               | St Jude Total XIII |               | Total n |
|---------------|------------------|---------------|--------------------|---------------|---------|
|               | LR n = 30 (%)    | HR n = 57 (%) |                   | LR n = 40 (%)  | HR n = 33 (%) |         |
| Toxic hepatitis | 6/30 (20.0%)     | 8/57 (14.0%)  | 14/40 (35.0%)      | 1/33 (3.0%)   | 29      |
| HBV infection  | 4/30 (13.3%)     | 15/57 (26.3%) |                   | 5/33 (15.2%)  | 24      |
| HCV infection  | –                | 1/57 (1.8%)   |                   | 2/33 (6.1%)   | 3       |

HBV, hepatitis B virus; HCV, hepatitis C virus; HR, high risk; LR, low risk.
Hepatitis REVEALED BY a marked transaminase elevation may be seen in patients with leukemia.\textsuperscript{8–11} Especially, HBV and HCV infections may cause viral hepatitis in leukemic children who are heavily transfused after the onset of their hematological disease. In developing countries where HBV and HCV infections are common in the general population of the country, such as Turkey, children with ALL will be at a greater risk for HBV and HCV infections. In Turkey the prevalence of HBV infection is put at 5.4–8.2\% in different nationwide surveys.\textsuperscript{12,13} The prevalence of HBV infection in our study (15.0\%) is higher than that of the general population in the country. However, it has been reported in different studies from Turkey that the prevalence of HCV infection is 0.5–2.4\% and in our study the prevalence of HCV infection is 1.5\%, which is almost equal to that of the general population in our country.\textsuperscript{14,15} Kocabas et al.\textsuperscript{16} reported that HBV and HCV
HBV or HCV infection rate in leukemic children  

In conclusion, chemotherapy-related hepatotoxicity might vary principally with the intensity of Mtx and 6-MP treatment. The effect of chemotherapy-related hepatotoxicity on the liver seems to be reversible and does not result in chronic liver disease. However, HBV and HCV infections occur on the basis of the severity of immunosuppression and the amount of administered blood products, which were much more common in HR ALL patients. Additionally, HBV or HCV infections may cause chronic hepatitis and the patients should be followed up for this respect. Periodic liver function tests and serological tests for HBV and HCV should be performed for leukemic children to monitor for these complications.

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