Hepatitis B—A Major Threat to Childhood Survivors of Leukaemia/Lymphoma

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Summary
This prospective descriptive study was undertaken to determine: the proportion of paediatric oncology patients with prior exposure to hepatitis B at cancer diagnosis; the risk and risk factors for acquisition of hepatitis B infection during chemotherapy; and the development of a prevention policy. Sixty African children were included in this study. At the time of cancer diagnosis, 67.7 per cent had not been exposed to hepatitis B, and none had active infection. After follow-up (median of 20 months; range 4–81 months) 23.3 per cent had active hepatitis B infection, which was subclinical in the majority of cases. The diagnosis of leukaemia/lymphoma posed a major risk factor for the acquisition of active hepatitis B infection (chi-square 7.0; p-value = 0.008), probably due to intensive chemotherapy regimens and severity of immunosuppression. No association with gender, age, place of origin, or number of blood transfusions was found. Patients with leukaemia/lymphoma were at an increased risk for horizontal transmission of hepatitis B. A policy of active surveillance for infective carriers of hepatitis B infection and passive immunization of seronegative immunosuppressed patients must be implemented to limit the endemic infection in paediatric oncology units.

Introduction
The prevalence of active hepatitis B varies worldwide, with a high prevalence of 20 per cent in sub-Saharan Africa, compared to 0.5–2 per cent in western Europe. 1 Hepatitis B is still endemic in South Africa, with reports indicating a prevalence of 15 per cent in the rural population versus 0.97 per cent in the urban setting. 2–5 Horizontal transmission of hepatitis B plays an important role in developing countries. 4 It occurs mainly through body fluids, especially saliva. 6–7 Infective hepatitis B surface (HBsAg) and e-antigens are present in the saliva of immunocompromised children, thereby creating a highly infectious reservoir. 7,8 Furthermore, only 12.5 per cent of immunocompromised children are able to clear HBsAg during the first year of the infection, compared to 90 per cent of healthy children. 9,10 This inability to clear the virus is due to the enhanced viral replication. 9 Immunosuppressive drugs also induce a re-activation of a dormant hepatitis B infection, with the reappearance of HBsAg. 9,10 This infection is usually subclinical. 9,10 Previous antibodies to HBsAg may also disappear or have an inability to prevent recurrence of hepatitis B infection in immunocompromised children. They are, therefore, at risk of developing hepatitis B carrier status. 6,9,11 Children with cancers are frequently admitted to the hospital for prolonged periods in view of problems such as compliance, travel distance, and finance involved in regular attendance. They are often severely immunocompromised secondary to their chemotherapy regimen and subsequently more susceptible to hepatitis B infection. 6,9,9 Risk factors include repeated venepunctures, blood product administration and destruction of mucous membranes secondary to chemotherapy, which allows parenterally transmissible agents to enter the immunocompromised host. 6,12 The exposure risk to hepatitis B during a blood transfusion, however, is low and is estimated at 15.83 per million blood donations. 13,14 Hepatitis B infection plays a significant role in the long-term morbidity of survivors of childhood cancer, with the subsequent risks of cirrhosis and hepatocellular carcinoma. 15

The aim of the study is to document the change in hepatitis B status of children with cancer at primary diagnosis and after receiving immunosuppressive chemotherapy. Furthermore, this study aims to determine possible risk factors that may predispose these children to acquire hepatitis B infection. The endpoint of the study is to formulate a policy regarding the prevention of hepatitis B in the paediatric oncology unit.

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Subjects and Methods

A prospective, descriptive study was done on all children attending the paediatric-oncology outpatient department at Kalafong Hospital during the period 1 October 1998 to 28 February 1999. Serological markers for hepatitis B and C were routinely done on all newly diagnosed paediatric cancer patients, and then repeated during the study period.

The median time period from diagnosis to re-screening was 20 months (range 4–81 months). The demographic data (age, gender, place of origin) of each child was documented on admission, as well as routine liver function studies, number of blood transfusions received per child, and the clinical outcome of each patient.

A 5-ml sample of blood was taken from each patient on each occasion. The serum was tested for hepatitis B surface antigen (HBsAg) and hepatitis B e-antigen (HBeAg) by means of a rapid ICT Diagnostics screening test (donated by Schering-Plough). Radioimmunoassays (Austria R 11-125, Ausab R RIA, RIA Corab R, Abbott Laboratories) were used to determine the HBsAg, antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigens (anti-HBc), respectively. HBeAg and antibody to HBeAg (anti-HBe) were detected using the HBeAg/anti-HBe immunoradiometric assay (Sorin Biomedical Diagnostics, Italy).

Results

Evidence of previous exposure to hepatitis B

Figure 1 illustrates the percentage of subjects in (a) the leukaemia/lymphoma group and (b) the solid tumour/histiocytosis X group who showed signs of exposure to hepatitis B at cancer diagnosis and during/after chemotherapy. Fourteen children (23.3 per cent) had evidence of hepatitis B markers on first admission to the paediatric oncology unit. Eleven children had anti-HBs, while two children had anti-HBs and anti-HBc or anti-HBe, respectively. One child had only anti-HBc. Forty-six children (76.7 per cent) had no evidence of previous exposure to hepatitis B infection.

Evidence of hepatitis B markers increased to 43.3 per cent at re-screening. Twelve children, who were initially seronegative for hepatitis B, tested positive for HBsAg and developed antibodies to the highly immunogenic HBcAg. Four of these children had evidence of a recent infection with an IgM response to HBcAg. Two children who had anti-HBs (one with anti-HBe as well) lost their antibodies and became HBsAg positive. The number of children with active hepatitis B infection increased from 0 per cent initially to 23.3 per cent at re-screening. Twelve children were in the leukaemia/lymphoma group and two children were diagnosed with solid tumours.

Thirty-six children (56.6 per cent) still had no evidence of exposure to hepatitis B.

Possible risk factors predisposing to active hepatitis B infection

The following risk factors were investigated: cancer diagnosis, number of blood transfusions received, age, gender, and place of origin.

The study group was divided into a leukaemia/lymphoma group (n = 33) and a solid tumour/histiocytosis X group (n = 27). Thirty-six per

cent of the children with leukaemia/lymphoma developed active hepatitis B infection (HBsAg positive), while only 7 per cent of the solid tumour/histiocytosis X group became HBsAg positive (chi-square 7.0; \( p = 0.008 \)). Children with either leukaemia/lymphoma in this study group, therefore, had an increased risk to acquire active hepatitis B infection (odds ratio: 5.21; 95 per cent CI, 1.13–24.02; logistic regression).

The children in the leukaemia/lymphoma group received a median of six blood transfusions per patient (range 0–27 transfusions/patient), compared to a median of one transfusion per patient (range 0–14 transfusions/patient) in the solid tumour/histiocytosis X group. None of the patients with histiocytosis X received any blood transfusions (Fig. 2). This difference proved to be statistically significant between the two groups of patients (\( p = 0.023 \), two-tailed \( p \)-value for normal approximation). Blood transfusions per se did not pose a major risk factor for the acquisition of hepatitis B infection (odds ratio: 1.06; 95 per cent CI, 0.99–1.14).

The median age of the study group was 7.5 years (range 1–16 years) (Table 1). The median age of the leukaemia/lymphoma groups was 9 years (range 2–16 years), compared to 6 years (range 1–15 years) in the solid tumour/histiocytosis X group. There was no difference in the median age between the two groups (\( p = 0.1334 \)). Furthermore, age was not a risk factor for the development of active hepatitis B infection (odds ratio: 1.00; 95 per cent CI, 0.84–1.19).

The male to female ratio was 1.7:1 (Table 1). Gender was not a risk factor for the acquisition of hepatitis B infection (odds ratios: 1.05; 95 per cent CI, 0.26–4.27).

Sixty-three per cent of children were of rural origin, which appeared to be slightly protective against exposure to hepatitis B infection, although this was not statistically significant (odds ratio: 0.58; 95 per cent CI, 0.14–2.45) (Table 2).

Evidence of clinical hepatitis B infection

Seven of the 14 children, who developed an HBs-antigenaemia during chemotherapy, had evidence of clinical hepatitis, with hepatomegaly and jaundice, in the presence of raised aminotransferases (defined as an elevated AST with a five-fold increase above the upper limit of normal).16 Five of the children developed hepatotoxicity, induced by chemotherapeutic agents (Table 3). These children tested negative for all markers of hepatitis A, B and C during these episodes. Two children, however, developed active hepatitis B infection, coinciding with clinical jaundice, hepatomegaly, and raised aminotransaminases. One child had evidence of hepatitis A infection at the same time. Both these children subsequently developed carrier status, defined as HBsAg-positive for a period longer than 6 months.16 Routine liver biopsies were not done in any of these children, as none of them showed clinical or laboratory evidence of ongoing hepatic necrosis (defined as

![Fig. 2. Number of blood transfusions in each diagnostic group. ST/HX: solid tumour/histiocytosis X (n = 27); L/L: leukaemia/lymphoma (n = 33)]](image-url)
a three-fold increase in transaminases above the upper limit, lasting for at least 6 consecutive months or more.\textsuperscript{16}

\textbf{Discussion}

None of the children in this study had active hepatitis B at initial screening, which is in keeping with the low prevalence of urban South Africa (0.97 per cent).\textsuperscript{4} During the course of treatment, 23.3 per cent of these children developed active hepatitis B infection, which is higher than that reported from other paediatric oncology units, where comparable rates were 6–12 per cent.\textsuperscript{12} This may be explained by the higher prevalence of hepatitis B in sub-Saharan Africa.\textsuperscript{1}

Leukaemia/lymphoma is a significant risk factor in the development of active hepatitis B infection. This is probably due to the severity of immunosuppression induced by the disease itself and the more intensive chemotherapy regimens, leading to an increased need for blood transfusions and invasive procedures compared to children with either solid tumour or histiocytosis X. Infected blood products are not deemed a significant risk factor as the overall presence of HBs-antigen among donors is approximately 0.5 per cent.\textsuperscript{14} Furthermore, the South African Blood Transfusion Service have been actively screening for hepatitis B since 1984,\textsuperscript{14} and none of the children developed hepatitis C, which probably indicates that blood products \textit{per se} are not the main method of transmission. The incubation period for hepatitis C, however, is prolonged in immunocompromised children, and these children will therefore have to be re-screened at a later stage.\textsuperscript{17}

Age and sex do not play a significant role in the acquisition of hepatitis B in this study, which is supported by a study from Ghana.\textsuperscript{18} However, in the general paediatric population, the development of acute hepatitis B infection increases with age, with a peak age for infection between 2 and 4 years.\textsuperscript{2} The median age of the HBsAg-positive group in our study was 9 years, which is older than expected from above data. This lends weight to the argument that horizontal transmission probably occurs in the paediatric oncology unit, rather than in the community.

The development of chronic hepatitis B infection is inversely related to age.\textsuperscript{10} Acquisition of hepatitis B infection at a young age is associated with a much higher rate of carrier status, and correlates with the development of complications such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma.\textsuperscript{2} Two children with documented carrier status, 8 and 11 years respectively, were older than expected from the above-mentioned data. This emphasizes the fact that immunocompromised children are a high-risk group, where predictors of subsequent morbidity are different from those of the general paediatric population. However, both these patients also lost their initial antibodies to hepatitis B, which is in accordance with the literature. The subsequent infection may have been due to re-activation or re-infection.\textsuperscript{9} These children may, therefore, have had an increased risk of developing carrier status since they were probably infected at a young age.

Rural children in this study did not have a higher rate of hepatitis B exposure or acquisition. This may indicate that the hepatitis B transmission occurs mainly in the paediatric oncology unit. The presence of an HBe-antigenaemia in 100 per cent of the children with active hepatitis B infection is significant, and indicates a high risk of infectivity, active viral replication, and continuous hepatocyte damage.\textsuperscript{6} Furthermore, the presence of the HBe-antigen enhances HBs-antigen secretion in saliva.\textsuperscript{8} This data is substantiated by a report from India, where 59 per cent of active hepatitis B patients retained the HBe-antigen.\textsuperscript{9} The large number of HBe-antigen positive children is of epidemiological

\begin{table}[h]
\centering
\caption{Aetiology of elevated transaminases in children with active hepatitis B infection}
\begin{tabular}{lllll}
\hline
Case no. & Age (years) & Implicated chemotherapeutic agent & Hepatitis A & Hepatitis B & Hepatitis C \\
\hline
4 & 11 & Nil & IgM-positive & HBsAg-positive & Negative \\
6 & 4 & Methotrexate, AZT & Negative & Negative & Negative \\
12 & 13 & Methotrexate & Negative & Negative & Negative \\
13 & 14 & Adriamycin & Negative & Negative & Negative \\
21 & 8 & Methotrexate & Negative & Negative & Negative \\
26 & 6 & Methotrexate & Negative & Negative & Negative \\
50 & 8 & Nil & Negative & HBsAg-positive & Negative \\
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Hepatitis (defined as an increase in aspartate aminotransferase, or AST, of more than five times the upper limit of normal) was seen in seven of the 14 children who were HBsAg-positive. A drug-induced hepatitis was observed in 5/7 cases, and hepatitis B-induced hepatitis was observed in 2/7.
importance, since these children form a reservoir of infectious carriers.

The majority of the children in the study group (86 per cent) developed subclinical hepatitis B infections, which is in accordance with previous reports.8,9 The treatment of active hepatitis B infection in children with underlying cancer is controversial. Various anti-viral agents have been used to treat chronic hepatitis B in children without cancer, however, only Interferon-alpha has proven effective.19 Use of Interferon-alpha in children with cancer has no beneficial effect against chronic hepatitis B infection, since these children have a low risk of developing cirrhosis, due to their immunotolerant state.6 Interferon-alpha may also be detrimental to the treatment of their underlying cancer, especially leukaemia and lymphoma. There is also no proven adverse effect of hepatitis B on the primary malignancy.6

Previous vaccination to hepatitis B at an early age might have prevented the high prevalence of hepatitis B infection. Routine hepatitis B vaccination of a narrow cohort of newborn infants has only been introduced in the Republic of South Africa since 1994.20 The older median age of the children in this study group has therefore excluded them from exposure to vaccination. The selection of such a narrow cohort for vaccination has delayed the more rapid development of herd immunity and immunization. If vaccination had been offered to two cohort groups initially, including the 5-year-olds it may have protected this high-risk group.20

Conclusions

The majority of children attending this paediatric oncology unit had no protective antibodies against hepatitis B on first diagnosis and are at risk of acquiring this infection. The current risk is 23.3 per cent. Paediatric oncology units in the developing world require a preventative strategy that is both cost-effective and relevant to the health risks of that particular area. It is therefore advisable that South Africa initiates a vaccination strategy against hepatitis B virus infection among black children in Soweto. BMJ 1986; 292: 1440–49.

Active surveillance of all oncology patients is important, and continued screening for active hepatitis B must be done regularly to identify any carriers. Active immunization of susceptible individuals, such as seronegative visitors to the unit, must be considered. Furthermore, all healthcare professionals working in oncology units must have protective vaccination against hepatitis B. The active immunization of children with cancer remains controversial, and must be considered once they are in remission.

A further measure that may decrease the transmission of hepatitis B, is the routine use of disposable bone-marrow needles which is currently not the practice due to cost.21 Passive immunization with anti-HBs hyperimmunoglobulins is an expensive alternative to halt endemic hepatitis B infection in paediatric oncology units, especially in the high-risk patients with underlying leukaemia or lymphoma, but must be undertaken in high-risk environments.

The following policy changes regarding hepatitis B are suggested as a result of this study.

- Active surveillance of the antibody status of all children in the unit.
- Three-monthly surveillance for carrier status in all children with HBs- and HBe-antigenaemia.
- Passive immunization of all seronegative children in the unit at 3-monthly intervals.
- Implementation of the use of disposable bone marrow needles.

References

12. Tabor E, Gerety RJ, Mott M, Wilbur J. Prevalence of hepatitis B...