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Infectious Diseases

## Decrease of dual hepatitis B and C virus infections in children with cancer: changes in risk factors over 30 years

**The frequency of dual hepatitis C and B virus infections and the impact of risk factors were evaluated in a cohort of 420 children with cancer. Multivariate analysis showed that primary cancer diagnosis, duration of therapy, and specific immunoprophylaxis were significant variables influencing the incidence of dual viral hepatitis, whereas other risk factors had no impact in this group.**

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Children with cancer are a group at high risk of dual hepatitis B (HBV) and C (HCV) infection.[1-3] For these children, the major risk factors for acquiring viral hepatitis have been reported to be endemic environment, blood transfusions, major surgical procedures, infection in the family, and frequent medical procedures connected with percutaneous or mucosal invasion.[4-7]

HBV and HCV are the main causes of chronic viral hepatitis and chronic liver disease in children with cancer.[8-9] We analyzed two groups of Polish children with cancer treated in different time periods when different preventive procedures for viral hepatitis infections were available.

A total number of 420 children with cancer were included in the study. All children were treated in one center, followed-up for at least 6 months, and tested for HBV and HCV serum and/or liver specimen markers, including HCV-RNA by RT-PCR. The patients were divided into 2 groups, with regard to period of beginning anticancer therapy and strategy of general prophylaxis (Table 1).

The general strategy to control HBV and HCV infections involved a multi-step procedure, including initiation of blood donor screening for HCV infection; institution of anti-hepatitis B immunization;[10] intensification of universal precautions as standard of care; administration of an educational program for staff, patients, and families; and acquisition of contemporary blood collection equipment. The introduction of this prophylaxis was completed in 1996.

In group I, patients treated before 1997, 110 (44.2%) children had no markers of infections, 53 (21.3%) were infected with HCV only, 33 (13.2%) with HBV only and 53 (21.3%) had dual infection. The cumulative risk of dual infection for all patients was 44.7% (Figure 1A). Patients with leukemia were at 2.5-fold (95%CI=0.99-6.90, $p$ = 0.032) and 5-fold (95%CI = 1.89-14.03, $p$ = 0.0002) higher risks of dual infection than those with lymphomas and solid tumors, respectively. The risk of dual infection was 2.6-fold higher for blood recipients (95%CI = 1.02-7.44, $p$ = 0.028), however the number of units of blood transfused had no impact on the frequency of any infections. There was no influence of surgical treatment on incidence of dual infection, or on any single infection. In children who were included in an immunoprophylaxis program against HBV infection, the risk of chronic HBV and chronic dual infection was 8.1-fold (95%CI=2.01-33.3, $p$ = 0.0001) and 2.8-fold (95%CI=1.41-5.61, $p$ = 0.0001) lower, respectively, than in the other children. In Cox univariate analysis, development of chronic dual hepatitis B and C was related to mean alanine transferase (ALT) value ($p$ = 0.0389), blood transfusions ($p$ = 0.0281), duration of anticancer therapy ($p$ = 0.0011), primary cancer diagnosis ($p$ = 0.0796) and anti-HBV immunoprophylaxis ($p$ = 0.0020), but not to age, gender, living place, mean and peak serum bilirubin level, having undergone surgical procedures, the number of units of blood transfused prior to infection, and infections among relatives. In Cox multivariate analysis, anti-HBV immunoprophylaxis ($p$ = 0.0002), duration of anticancer therapy ($p$ = 0.0092), and mean ALT activity ($p$ = 0.0001) were the only factors significantly related to development of dual hepatitis. The median ALT activity in the dual HBV/HCV group was higher than in all other patients taken together (121 vs 78 IU/L, $p$ < 0.0001). There were no differences in median bilirubin level between the HBV/HCV group and the other patients.

In group II, the patients treated after 1997, 149 (87.1%) children had no markers of viral infection; 10 (5.85%) were infected with HBV only, including 3 with HBV infection acquired before the anti-cancer therapy; 10 (5.85%) with HCV only, and 2 (1.2%) patients had dual infection. The incidence of dual HBV/HCV infections decreased very significantly from 53/249 in group I to 2/171 group II ($p$ = 0.0000)

**Table 1. Main characteristics of the study population.***

| | *Group I* | *Group II* |
|---|---|---|
| Period of inclusion | 1974-1997 | 1997-2003 |
| Number of patients | 249 (53) | 171 (2) |
| Gender male:female | 148:101 | 91:80 |
| Mean age at diagnosis 95% CI (years) | 7.7/3.2-12.2 | 7.2/2.3-12.1 |
| Mean follow-up 95% CI (months) | 189/168-210 | 37/19-55 |
| HBV immunoprophylaxis | 184 (30) | 171 (2) |
| Diagnosis | | |
| Leukemias | 129 (40) | 73 (1) |
| Lymphomas | 47 (7) | 22 (0) |
| Solid tumors | 73 (6) | 76 (1) |

**The number in brackets indicates the number of patients with dual HBV/HCV infection.*

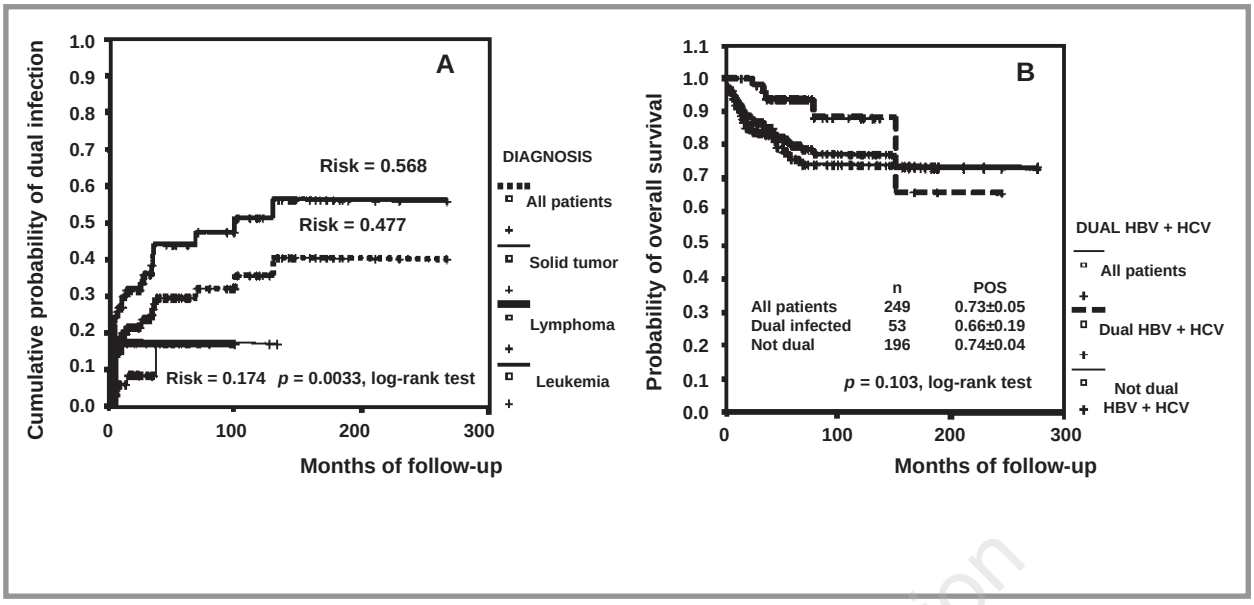


**Figure 1. Kaplan-Meier plots and log-rank comparisons of: (A) cumulative risk of dual HBV/HCV infection with regard to primary diagnosis; (B) influence of dual HBV/HCV infection on probability of overall survival (OS).**

(OR=22.85, 95%CI = 5.35-137).

Our results show that, over the last 30 years, children with cancer were at high risk of dual, and possibly multiple, viral hepatitis in an endemic environment in Poland, although this seems to be of limited relevance to overall survival (Figure 1B). Predisposing factors for dual HBV/HCV infection in children with cancer, evaluated by uni- and multivariate analysis, were lack of immunoprophylaxis against HBV infection and diagnosis of leukemia, combined with duration of anticancer therapy and its frequent complications. The introduction of active-passive immunoprophylaxis against viral hepatitis B, together with a general prophylaxis strategy, reduced the incidence of dual HBV/HCV infections, and were key factors in decreasing the incidence of viral hepatitis in children with cancer, whereas classical risk factors, such as blood transfusions and surgical procedures did not predict risk of dual infection. Due to the general prophylaxis strategy, the number of new infections in the Department is steadily decreasing. It seems that in these conditions, hospital should no longer be regarded as an endemic environment of hepatotropic viruses.

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