OPPORTUNISTIC VIRAL INFECTIONS AFTER PAEDIATRIC TRANSPLANTATION

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Av
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I. Kullberg-Lindh C, Ascher H, Krantz M, Lindh M.
Quantitative analysis of CMV DNA in children the first year after liver transplantation.
Pediatr Transplant 2003;7: 296-301

II. Kullberg-Lindh C, Ascher H, Saalman R, Olausson M, Lindh M.
Epstein-Barr viremia levels after pediatric liver transplantation as measured by real-time polymerase chain reaction. Pediatr Transplant 2006;10(1):83-89.

III. Kullberg-Lindh C, Olofsson S, Brune M, Lindh M.
Comparison of serum and whole blood levels of cytomegalovirus and Epstein-Barr virus DNA. Transplant Infect Dis 2008; 10; 308-315.

IV. Kullberg-Lindh C, Mellgren K, Friman V, Ascher H, Lindh M.
Opportunistic viral infections after paediatric stem cell transplantation.
Submitted.

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ABSTRACT

Background: Opportunistic viral infections can cause considerable morbidity and mortality in organ and stem cell transplanted (SCT) patients, mainly due to iatrogenic T cell dysfunction. Whereas in SCT patients, in general the immunosuppressive treatment can be discontinued after 6-12 months, for the majority of organ transplanted patients, the need for treatment is life-long.
Aims: This thesis focuses on infections with cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus (AdV) and human herpes virus type 6 (HHV-6) in liver and stem cell transplanted children and on the value of quantitative viral DNA measurements. The aims were to (i) investigate the incidence and clinical picture of CMV and EBV infection the first year after liver transplantation and the usefulness of DNA quantification for identifying these infections, (ii) to compare serum and whole blood as material for the analyses and (iii) to describe infections with CMV, EBV, AdV and HHV-6 and their risk factors, identification and outcome in SCT patients during the first 6-12 months after transplantation.
Methods: Serum samples, drawn the first year after transplantation from 18 liver transplanted children were retrospectively investigated for CMV DNA by a quantitative PCR from Roche (CA Monitor), and from 24 liver transplanted children for EBV DNA by real time TaqMan PCR. In the comparison of sample materials, clinical samples (10,641 for CMV and 2,855 for EBV) drawn mainly from transplant patients, were surveyed as regards to viral DNA levels in whole blood and serum. In the study of SCT children, serum samples from 47 consecutively transplanted children were retrospectively investigated with analysis of viral DNA by TaqMan PCR and related to risk factors in a multivariate analysis.
Results: Any CMV marker was found in 83 % of the liver transplanted patients. Symptomatic infection was found in 22% and was associated with significantly higher CMV DNA levels (paper I). More than half of the liver transplanted patients in paper II were EBV naïve at transplantation, probably due to low median age, but 92 % had markers of EBV infection within 1 year. Symptomatic infection was found in 21%: 3 patients with post transplantation lymphoproliferative disease (PTLD) and 2 with hepatitis. In these 5 patients, the EBV DNA levels were significantly higher than in the patients with asymptomatic infection. In paper III, CMV DNA levels were only 0.2 log higher in WB as compared to serum, while EBV DNA levels were 1.5 log higher in WB than in serum. Out of 47 SCT children (paper IV), 47% developed CMV DNAaemia, 19% at levels > 10^4 Geq/mL, and 45% developed EBV DNAaemia, but only 6 % > 10^4 Geq/mL. CMV DNAaemia did not develop if neither donor nor recipient had CMV IgG. ATG and total body irradiation were independent risk factors for high CMV and EBV DNA levels. HHV-6 DNA and AdV DNA were each present in 28% of the SCT patients, in the majority in low or moderate levels. Three children died from CMV, EBV and AdV complications, representing 21 % of the total mortality after SCT, and all these 3 cases were retrospectively found to have very high viral DNA levels in serum.
Conclusion: Quantification of viral DNA levels contributes to a better basis of understanding of post transplant viral infections, and is critical for taking the right actions in terms of balancing immunosuppression and antiviral measures. As sample material, serum and whole blood seemed equally useful for CMV, while for EBV whole blood was more sensitive but less specific.

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