Survival analysis to the occurrence of adverse events in pediatric liver transplant patients


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Background
Tacrolimus is associated with the risk of adverse events (AE). Therapeutic drug monitoring of tacrolimus trough concentrations (C₀) is performed in daily routine to reduce the probability of AE and optimize therapy. Nonetheless, AE to tacrolimus occur in detriment of patient’s quality of life. The aim of this study was to identify clinical, biochemical and peritransplant variables related to the risk of most frequent and serious AE to tacrolimus in a retrospective cohort study in pediatric liver transplant patients.

Methods
A retrospective study was carried out including first liver transplant patients in the period 2010-2012 surviving at least 2 months post transplantation. Most frequent and serious AE were registered including nephrotoxicity, hypomagnesemia, post-transplant lymphoproliferative disease, tremor and hypertension. AE free survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Risk factors were identified by including clinical, laboratory parameters and recipient/donor variables in a multivariate Cox regression model over a period of 2 years. Allelic discrimination assays were used for genotyping polymorphisms in CYP3A5 in donors and recipients.

Results
72 patients (63% girls) were studied with a mean age and weight of 5.3 years (S.D.5.4) and 21.0kg (S.D.18.9), respectively. Forty-eight patients experienced at least one AE, including (number of patients) hypomagnesemia (n=30), nephrotoxicity (n=12), hypertension (n=3), PTLD (n=2) and tremor (n=1) as first event. All patients received tacrolimus and 72% received basiliximab as induction therapy. Multivariate analysis showed that C₀ (per 1 g/L increase, HR, 1.25, 95%CI, 1.21-1.39, p<0.0001) and CYP3A5 expressers recipients (expressers vs. non expressers, HR, 2.05, 95%CI, 1.03-4.06, p<0.05) were independent predictors of AE. A threshold of 7.15 ng/ml was described for tacrolimus toxicity, determined with ROC curve analysis. Moreover, CYP3A5 expressers required higher doses of tacrolimus than non-expressers (Mann-Whitney, p<0.0001).

Conclusions
In a pediatric transplant population, an increase of 1 ng/ml in C₀ indicates that the risk of suffering an adverse event increases 25%. Moreover, patients who express CYP3A5 have a 105% increased risk of experiencing an adverse event compared to non-expressers. Prospective studies are important to confirm these results.

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