
Oral

[O25-1] O25-1: Biomarkers for transplantation

Chairs: Mercè Brunet, Spain / Hirofumi Jono, Japan

Mon. Sep 25, 2017 1:30 PM - 2:30 PM Main Hall (1F)

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[O25-1-3] Biomarkers for steady state concentration prediction of cyclosporine A by pharmacometabolomics and gene polymorphism

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Keywords: biomarker, cyclosporine A, pharmacometabolomics, gene polymorphism

Background

Cyclosporine A (CsA) is an immunomodulatory agent used in standard immunosuppressive regimens in kidney transplantations. However, following oral administration, absorption is incomplete and the blood concentration varies greatly between individuals. Then, how to predict the steady state concentration (C_{min}) of CsA is urgent. Pharmacometabolomics is a new discipline, through assaying the small molecules in biological samples to define metabolomic signatures for predicting drug pharmacokinetics. On the other side, gene polymorphism is a robust tool on the research of drug metabolic differences equally.

Methods

High pressure liquid chromatography-mass spectroscopy (UPLC-MS)-based metabolic profiling was performed on 133 kidney transplant patients by measuring the levels of 1,761 metabolite ions in whole blood samples. C_{min} in whole blood of CsA were measured by UPLC-MS. Genotypes were determined by real-time PCR. 133 patients were divided into two different genotype groups of CYP3A4*1/ CYP3A5*1 and CYP3A4*1/ CYP3A5*3. Principal component analysis (PCA) and partial least squares (PLS) modeling was conducted with data relating to metabolites to predict individualized C_{min} of CsA

Results

We developed two formulas that can be used to predict the C_{min} of CsA from the resultant PLS model. In CYP3A4*1/ CYP3A5*1 group, $C_{min} = -0.09 \cdot \text{valeryl carnitine} + 0.14 \cdot \text{PE (16:0/18:1)} + 0.11 \cdot \text{PC (16:0/16:0)} + 0.14 \cdot \text{PE (18:0/18:1)}$, the prediction power ($R^2=0.308$) was 38% of that of the PLS model. And in CYP3A4*1/ CYP3A5*3 group, $C_{min} = 0.13 \cdot \text{PC (14:0/24:0)} + 0.04 \cdot \text{(Threoninyl-Glycine)} - 0.01 \cdot \text{SM (d18:0/24:1(15Z)(OH))} + 0.03 \cdot \text{PE (16:0/18:1)}$, the prediction power ($R^2=0.488$) was 42% of that of the PLS model.

Conclusions

Here, according to kidney transplantation, we discovered seven new biomarkers in the whole blood samples that can predict individualized C_{min} of CsA in different genotype groups. Furthermore, the validity of these biomarkers should be tested on larger groups.