Poster

[P25-10] P25-10: Oncologic drugs (2)

Chair: Takuya Iwamoto, Japan

Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall)

[P25-10-10] A role of genetic polymorphisms in genes related to sunitinib and SU12662 clearance

Noriko Matsunaga[1], Makiko Yamada[2], Kayoko Sato[3], Kojiro Ohba[4], Hitoshi Sasaki[5], Takashi Kitahara[6]

(1.Nagasaki University Hospital, 2.Nagasaki University Hospital, 3.Nagasaki University Hospital, 4.Nagasaki University Hospital, 5.Nagasaki University Hospital, 6.Nagasaki University Hospital)

Keywords: sunitnib, genetic polymorphism

Background

Sunitinib is an orally administered tyrosine kinase inhibitor that is approved as a systemic therapy for metastatic renal cell carcinoma. The interpatient variability of sunitnib pharmacokinetics (PK) is high, and a large variability in efficacy and toxicity of sunitinib has been reported. Sunitnib and its active N-desethyl metabolites (SU12662) are mainly metabolized by cytochrome P450(CYP)3A4, but also the involvement of CYP3A5 has been suggested. It has been reported that ABCG2 (G family of ABC transporters) C421A polymorphism increases the AUC of sunitinib. It was observed that POR*28 in the gene encoding P450 oxidoreductase(POR) increased CYP3A activity when treated with taclolimus, but it is not yet well understood when treated with sunitnib. Therefore, the aim of this study is to investigate the effect of CYP3A5*3, POR*28 and ABCG2 C421A on the PK of sunitinib and its toxicity.

Methods

This study was a single-institute prospective study that included 16 adult patients who had metastatic renal cell carcinoma, which was treated with sunitinib. Steady-state plasma trough concentrations of sunitinib and SU12662 were measured by HPLC-UV. Genotyping was performed with TaqMan probes using Mx300P real-time PCR instrument. Total sunitinib concentration/dose (C/D) ratio, clinical blood test data and adverse events relationships with CYP3A5*3, POR*28 and ABCG2 C421A polymorphisms were investigated and assessed using Wicoxon rank-sum test and Fisher exact test.

Results

CYP3A5*3 and POR*28 polymorphisms did not significantly changed the total sunitinb C/D ratio. On the other hand, ABCG2 421 C/A polymorphism resulted in the mean total sunitinib C/D ratio to be 1.5 fold higher than that of C/C ($p < 0.001$). Both sunitinib and SU12662 C/D ratios of ABCG2 421 C/A polymorphism were higher than C/C ($p < 0.001$). However, the total sunitinib trough level of ABCG2 C/A patients was not different from that of C/C patients. The platelet count was also no changed between ABCG2 C421A polymorphism. RBC ($p=0.001$), Hb ($p < 0.001$) and Hct ($p < 0.001$) were lower on ABCG2 C/A patients in comparison to C/C patients. In addition, both the incidence of inappetence ($p < 0.001$) and hypertension ($p < 0.001$) in ABCG2 C/A patients were higher than C/C patients.

Conclusions

In metastatic renal cell carcinoma patients, the variability of sunitinib PK could be explained in part by the genetic variation of ABCG2 C421A, but not of CYP3A5*3 and POR*28 polymorphism. Our results indicate that gene polymorphism related to absorption is more effective to sunitnib PK than metabolism. ABCG2 C421A polymorphism had different adverse event even if the total sunitnib trough level were same. Further

investigations are needed to reveal the relationship between ABCG2 polymorphism and adverse effects of sunitinib.