Exposure-response and pharmacogenomics of tyrosine kinase inhibitors

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Scope of the lecture:

Molecular targeted therapies with oral tyrosine kinase inhibitors (TKIs) have been increased in cancer therapy. These small molecules are mainly used at a fixed dose according to the dosage and administration of package insert. Fixed dosing may ignore the possible need for dose individualization, and may indeed result in suboptimal treatment or excessive toxicity considering the high inter-individual variability in the pharmacokinetics (PK) of these therapies. To overcome these clinical problems, therapeutic drug monitoring (TDM) and genotyping of PK factors have been explored for individualized pharmacotherapy for oral tyrosine kinase inhibitors. Among oral tyrosine kinase inhibitors, we have been focusing on sunitinib, erlotinib and sorafenib[1)]. Sunitinib has been used for treating advanced renal cell carcinoma (RCC), but patients, especially Asian patients, often show poor adherence due to frequent adverse events such as thrombocytopenia and hand-foot syndrome. In this symposium, I will talk about the 1) pharmacogenomics of sunitinib and other TKIs, emphasizing the ethnic differences of the *ABCG2* c.421C>A polymorphism, and 2) exposure-response relationship of sunitinib.

Learning objectives:

1) Pharmacogenomics of sunitinib

We previously experienced an RCC patient with many severe adverse events, such as facial acne, hypothyroidism and thrombocytopenia, early after the start of sunitinib therapy[2)]. PK analyses revealed that this patient had been exposed to 2.5-fold-higher sunitinib compared with another 4 patients, and that the genotype of the *ABCG2* c.421C>A polymorphism in this patient was a homozygous variant, whereas the other patients were heterozygous or wild type. These relationships were also confirmed in more Japanese patients[3)]. Furthermore, a population pharmacokinetic analysis also demonstrated that the *ABCG2* c.421C>A genotype is a predictive covariate for the oral clearance of sunitinib[4)]. These pharmacogenomic studies, together with *in vitro* and *in vivo* sunitinib transport studies, revealed that sunitinib is a substrate of ABCG2 and loss of its function due to *ABCG2* c.421C>A can lead to an increase in systemic exposure to sunitinib.

Sunitinib-related toxicity was more frequently observed in Asian patients than in non-Asian ones. In contrast to Asian patients, the impacts of the *ABCG2* c.421C>A genotype on sunitinib efficacy and toxicity were not identified in European patients. Interestingly, *ABCG2* c.421C>A appears to be more common in Asians (allele frequency, 26.6-35.0%); on the other hand, this allele is very rare in sub-Saharan African (1.0%) and Caucasian populations (7.4-11.1%). These results suggest that *ABCG2* c.421C>A is one of the reasons for the ethnic difference in sunitinib pharmacokinetics and toxicity.

2) Exposure-response relationship of sunitinib

We carried out a retrospective, observational clinical study of 21 patients with RCC[5)]. Sunitinib was administered for 4 weeks of a 6-week cycle for the first cycle. We evaluated the association of sunitinib-induced toxicities and clinical outcomes with the trough total sunitinib concentration in a steady state during the first cycle. The median sunitinib concentration was 91.8 ng/mL (range, 49.8-205 ng/mL). There was an association between

total sunitinib concentration and the severity of thrombocytopenia, anorexia, and fatigue. Patients with ≥100 ng/mL sunitinib (n=8), compared with patients with < 100 ng/mL (n=13), had a greater incidence of Grade≥3 toxicities. Patients with < 100 ng/mL sunitinib had significantly longer time to treatment failure and progression-free survival time than patients with ≥100 ng/mL. These findings suggest that therapeutic drug monitoring of sunitinib could be useful for avoiding severe toxicities. Dose reduction might be needed, especially when the total sunitinib concentration is ≥100 ng/mL, to avoid unnecessary early discontinuation of treatment.

References:

1) Terada et al., Management of dose variability and side effects for individualized cancer pharmacotherapy with tyrosine kinase inhibitors. Pharmacol. Ther., 152, 125-134 (2015)

2) Mizuno et al., *ABCG*2 421C>A polymorphism and high exposure of sunitinib in a patient with renal cell carcinoma. Ann. Oncol., 21, 1382-1383 (2010)

3) Mizuno et al., Impact of genetic variation in breast cancer resistance protein (BCRP/ABCG2) on sunitinib pharmacokinetics. Drug Metab. Pharmacokinet., 27, 631-639 (2012)

4) Mizuno et al., The effect of *ABCG2* genotype on the population pharmacokinetics of sunitinib in patients with renal cell carcinoma. Ther. Drug Monit., 36, 310-316 (2014)

5) Noda et al. Assessment of sunitinib-induced toxicities and clinical outcomes based on therapeutic drug monitoring of sunitinib for patients with renal cell carcinoma. Clin. Genitourin. Cancer, 13, 350-358 (2015)