Oral

[O27-3] O27-3: Oncology (1)

Chairs: Alan Fotoohi, Sweden / Masami Kawahara, Japan
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[O27-3-1] Towards therapeutic drug monitoring of everolimus in oncology? Results of an exploratory study

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Background

The recommended dosage of everolimus (EVR) in oncology is 10 mg once daily and therapeutic drug monitoring (TDM) of EVR is not mandatory. No trough level (C_0) target has been defined so far. The aims of this study in patients on EVR for breast, renal or neuroendocrine cancer were to: (i) determine whether C_0 is associated with the occurrence of toxicity and efficacy; and (ii) investigate the relationship between CYP3A polymorphisms and C_0.

Methods

Clinical, biological and radiologic data from 54 patients were collected from their medical records. Toxicity was defined by temporary interruption and/or EVR dose reduction and efficacy by progression-free survival as documented in the patients' medical records. C_0 values were dichotomized by ROC curve analysis and the association between exposure and toxicity or efficacy was determined using Cox models (efficacy) or Cox models for repeated events (toxicity). The stability of the results was investigated using bootstraps. The impact of *CYP3A4*22* and *CYP3A5*3* SNPs on C_0 was investigated using the generalized estimating equation.

Results

Forty two patients (77.8%) had breast, 10 (18.5%) renal cell and 2 (3.7%) neuroendocrine cancer. Toxicity (all grades) was reported in 75.9% of the patients (EVR discontinuation in 25.9% patients). A C_0 EVR higher than 26.3 ng/mL (Sen=0.38,Spe=0.88) was associated with a 4-fold increased risk of toxicity (C_0>26.3 ng/mL: HR= 4.12, IC95%=[1.48-11.5], p=0.0067) while a a C_0 EVR lower than 11.9 ng/mL was associated with a 3-fold increased risk of progression (C_0<11.9 ng/mL: HR=3.2, IC95%=[1.33-7.81],p=0.001). A significantly lower C_0 was observed in CYP3A5 expressors (at least one *CYP3A5*1* allele;$intercept_{(expressors)}$ =10.72±1.45 ng/mL, $\beta_{\text{non expressors}}$ = +6.32±2.22 ng/mL, p=0.0044) whereas no association was found between carriers of the *CYP3A4*22* variant and C_0.

Conclusions

A C_0 EVR threshold associated with a 4-fold increased risk of toxicity and with a 3-fold increased risk of progression has been determined. These thresholds have to be confirmed in prospective studies. The *CYP3A5*3* genetic polymorphism seems to have an important influence on EVR exposure (higher than in transplantation).