Pharmacokinetic analysis of weekly paclitaxel from patients enrolled in a genotype-driven phase I study: new horizon for conventional chemotherapeutic drugs

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Background

Personalized medicine embody one of the most important challenges in cancer therapy. Moreover, genotype-driven phase Ib studies could represent an innovative strategy for defining the relationship between genotype and maximally-tolerated dose (MTD) and should be taken into consideration to redefine the dose or the treatment modalities with new and conventional cytotoxic drugs for therapy personalization. For instance, the large inter-individual variability in therapeutic effect and in severity of toxicity is a clinically relevant problem in paclitaxel (PTX) treatment and could be related to the genetic characteristics of patients. Indeed, previous studies pointed out the effect of *ABCB1-2677G>T/A* polymorphism on P-gp protein expression and also the correlation with drug clearance, that results lowered in patients carrying the variant allele. On this background, we planned a dose-escalation phase Ib study to assess the recommended dose for weekly PTX monotherapy according to *ABCB1-2677G>T/A* genotype, in epithelial ovarian cancer patients.

Methods

Eligible patients were stratified in 2 groups based on the *ABCB1-2677G>T/A* polymorphism: 'low risk of toxicity' (*ABCB1-2677GG* genotype) and 'high risk of toxicity' (*ABCB1-2677GT; GA, AA, TT, AT* genotypes). PTX was administered as 1-h i.v. infusion every week over 4-week cycles. For both groups, the starting dose was 80 mg/m^2 and was escalated (steps of 10 mg/m^2) if 0/3 or <2/6 pts had a dose limiting toxicity (DLT) (grade 3-4 non hematologic or grade 4 hematologic toxicity during the first 2 cycles of therapy). The MTD was defined as the dose at which <4/10 pts had a DLT. A PK study was performed to clarify the relationship between *ABCB1-2677G>T/A* polymorphism and PTX AUC (area under the plasma concentration-*vs*-time curve) and clearance. For this purpose, the pharmacokinetic profile of the drug was evaluated twice during the first chemotherapy cycle: on the first PTX administration and on the fourth.

Results

So far, 34 patients (9 'low risk' and 25 'high risk' patients) were enrolled in this on-going study. The MTD resulted 120 mg/m^2 in the 'high risk' cohort while, since there were 1/3 DLT at 110 mg/m^2 in the 'low risk' cohort, the group needs to be enlarged up to 6 patients before escalating the dose to the next level. Preliminary pharmacokinetic analysis seems to indicate a non linear PTX pharmacokinetics for doses higher than 100 mg/m^2 probably because of the saturation of elimination processes. Moreover, the correlation between AUC or clearance and genotype seems not to be statistically significant at the dose of 80 or 100 mg/m^2.

Conclusions

In the treatment of advanced ovarian cancer patients with weekly PTX, a dose higher than the current standard dose (80 mg/m^2) can be safely administered. Moreover, this study has become part of a new European Project (HORIZON2020), aimed at creating point-of-care devices for quantification of paclitaxel in small body fluid for real-time therapeutic drug monitoring. Data obtained from this phase I study will be used for the analytical and clinical validation of the new device.