Pharmacokinetic analysis of weekly paclitaxel from patients enrolled in a genotype-driven phase I study

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Background

The great inter-patient variability both in response and toxicity associated to paclitaxel (PTX) limits the potentialities of this powerful cytotoxic agent. Since these differences in the outcome has been already associated even to patients' genetic make-up, genotype-driven phase I studies could represent an innovative strategy for defining the relationship between genotype and maximally-tolerated dose (MTD), in order to redefine the dose or the treatment modalities and to personalize this therapy. 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.
Moreover, the PTX pharmacokinetic studies, due to the lack of adequate technologies and sensible instruments during the second part of the 20th century, are quite inaccurate and have given rise to different uncertainties. In fact, no consensus has been reached about both the linear or non-linear pharmacokinetics of PTX, and a possible autoinduction effect of PTX metabolism after repeated administrations.
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. Secondary aims of this study were to evaluate the pharmacokinetics of PTX and its 6Î±-hydroxylated metabolite (6Î±-OH-PTX) in human plasma and to define the effect of PTX pharmacokinetics on toxicity and response rate.

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 pharmacokinetic study was performed to clarify the relationship between *ABCB1-2677G>T/A* polymorphism and PTX pharmacokinetics parameters. In order to study the autoinduction mechanism, the pharmacokinetic profile of the drug was evaluated twice during the first chemotherapy cycle: on the first PTX administration and on the fourth.

Results

Until now, 37 patients were enrolled (35 patients were evaluable: 10 in the group 1 and 25 in the group 2). For group 2 no DLTs were observed among 10 patients at 120 mg/m^2, while 130 mg/m^2 was not tolerated (2 DLTs in 3 patients). Hence, the MTD resulted 120 mg/m^2 for this group. For group 1, 1 DLT was observed among the first 3 patients at 110 mg/m^2, thus the cohort needs to be enlarged up to 6 patients before to proceed with the dose escalation. Preliminary analyses have showed no significant difference in the pharmacokinetic parameters of both PTX and 6Î±-OH-PTX among the two genotype groups. Moreover, since no statistical differences in PTX C_{max}, t_{max}, AUC_{last}, and Cl ($p>0.05$) between the I and the IV administration has been obtained, it is possible to exclude the PTX metabolism autoinduction. Furthermore, a switching from linear to non-linear PK has been observed when doses higher than 110 mg/m^2 were administered.

Conclusions

Although this dose finding study is still on-going, the safe dose of PTX that can be administered in advanced ovarian cancer patients enrolled in the 'high risk' group has been identified and PTX can be safely administered at doses up to 120 mg/m^2, compared to the standard dose of 80 mg/m^2. Moreover this study partly clarify some open questions about the pharmacokinetics of PTX indicating the dose level of 110 mg/m^2 as the turning point from linear to non-linear behaviour and excluding the possible autoinduction of PTX metabolism.