External evaluation of a PK/PD model describing the time course of paclitaxel and neutropenia in patients with advanced non-small cell lung cancer

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Background and Objectives
Paclitaxel (PTX) exhibits complex pharmacokinetics (PK) with high interindividual variability, as well as severe toxicity, namely neutropenia, which makes PTX an appealing drug for dose individualisation. In [1], the concentration-time course of PTX and the resulting neutropenia were previously described by a PK/pharmacodynamic (PD) model. Based on this model, a dose individualisation algorithm was developed. Subsequently, a clinical trial (CEPAC-TDM, EUDRACT: 2010-023688-16) was performed to evaluate whether the developed dosing algorithm was able to reduce grade 4 neutropenia without reducing treatment efficacy. The aim of the work here presented is to externally validate the previously described PK/PD model using the data collected from the CEPAC-TDM study.

Methods
Patients in the CEPAC-TDM study received PTX once every 3 weeks for up to 6 cycles in a 3 h infusion in a dose of either:
- Arm A: 200 mg m² (n = 183) or
- Arm B: according to the published algorithm [1] (n = 183). The first dose was individualised based on sex and age. Subsequent doses were adapted based on the grade of neutropenia and on the time above the threshold plasma concentration of 0.05 μmol/L. (T >0.05; T >0.05 was estimated using the developed PK/PD model (Fig 1). In both arms patients received cisplatin or carboplatin in addition and doses of both drugs were reduced in case of severe toxicity.

Results

- Overall, higher doses of PTX were administered in both sexes in the conventional Arm A (median dose Arm A: 368 mg; Arm B: 285 mg).
- Comparable exposure and neutrophil-time course were observed between sex in Arm B. However, a more profound reduction of neutropenia was achieved in Arm B compared to Arm A for females than for males (Fig 2).

Discussion and Conclusions
- Population prediction of the PTX plasma concentration are slightly underpredicted which might partly cause the overprediction of the PD model.
- The PK/PD model will be refined to take into account bone marrow exhaustion.
- The refined PK/PD model will be used to fine-tune the proposed 3-weekly dosing algorithm.

References:

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