Examining the relationship between paclitaxel exposure and peripheral neuropathy in non-small cell lung cancer

Francis W. Ojara (1,2), Andrea Henrich (1,2), Niklas Hartung (1,6), Markus Joerger (3), Max Roessler (5), Joachim V. Pawel (4), Wilhelm Huisinga (6), Charlotte Kloft (1)

(1) Dept. Clinical Pharmacy & Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany, (2) Graduate Research Training program PharMetrX, Germany, (3) Dept. of Oncology & Haematology, Cantonal Hospital, St Gallen, Switzerland, (4) Pneumology clinic, Asklepios Fachkliniken, Gautig, Germany, (5) CESAR central office, Vienna, Austria and (6) Institute of Mathematics, Universitaet Potsdam, Germany

Background and Objectives

Peripheral neuropathy (PN), a dose-limiting, cumulative adverse event of paclitaxel (PTX) occurs in more than 20% of patients on PTX therapy. PTX dose and exposure (time above plasma concentration of 0.05 μM, $T_{C>0.05\mu M}$) are predictors of PN from statistical tests with a single predictor-PN relation per patient [1,2]. This does not reflect the impact of dose changes on burden of PN within patients. This work aimed at examining the relationship between PTX dose and exposure ($T_{C>0.05\mu M}$ and AUC_{∞}) against PN with 1) a single predictor-PN relations per patient and 2) multiple predictor-PN relations per patient, to ascertain the impact of dose modification on severity of PN.

Methods

- PTX, plus carboplatin or cisplatin was administered every 3 weeks for ≤ 6 cycles to patients in two treatment arms: A (BSA-guided dosing), and B (PK/PD-guided dosing), details published in [3].
- PN symptoms, grades and duration were captured using the common terminology criteria, version 4.0 [4].
- PN grades classified: clinically important (2 and 3), and clinically not important (0 and 1).
- The risk of clinically important PN with change in predictor was examined using binary logistic regression (LR) analysis, as depicted in Figure 1.

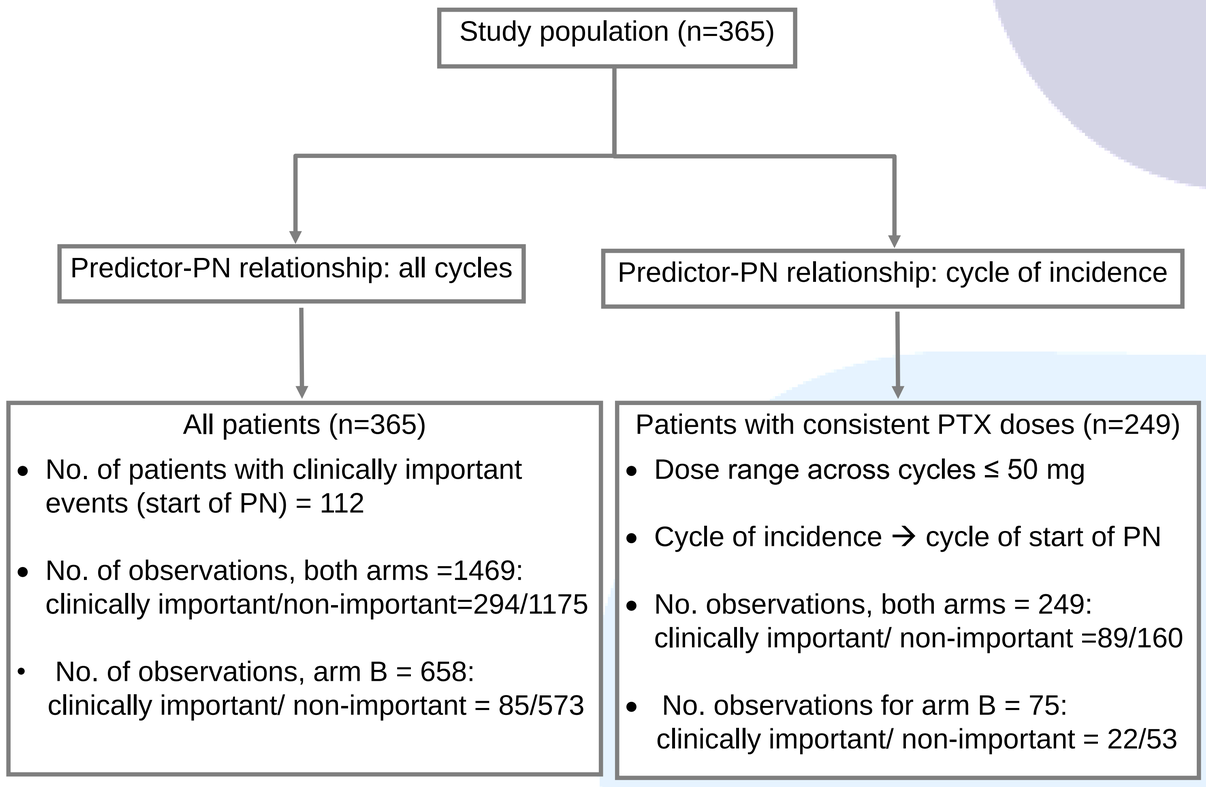

Figure 1: Data composition for binary LR analysis: all cycles and only cycle of incidence.

- Statistical significance evaluated by the likelihood ratio test at α=0.05 (1 degree of freedom).
- Dataset formatted in R 3.3.2, and modelling activities in NONMEM 7.3.

Results

Predictors against PN grades: all cycles

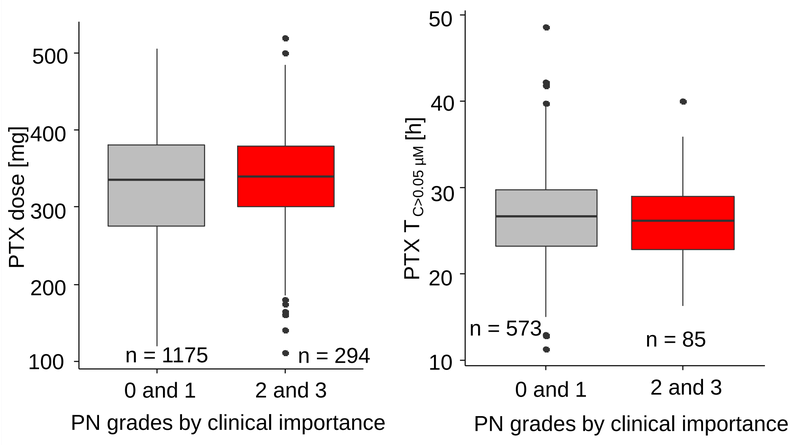

Figure 2: PTX dose against PN grades.

Figure 3: PTX $T_{C>0.05\ \mu M}$ against PN grades (arm B).

- No difference in distribution of dose and $T_{C>0.05\ \mu M}$ between clinically important and clinically not important PN (Figures 2 and 3).

Results (cont.)

Predictors against PN grades: cycle of incidence

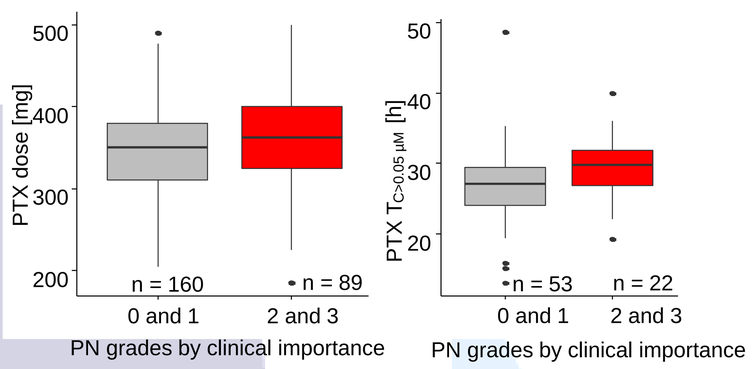

Figure 4: PTX doses against PN grades.

Figure 5: PTX $T_{C>0.05\ \mu M}$ against PN grades (arm B).

- Clinically important PN grades are associated with higher doses and $T_{C>0.05\ \mu M}$ (Figures 4 and 5).
- With all cycles, risk of PN decreased by 10% for 10 mg increase in dose, odds ratio, OR (95% CI): 0.898 (0.835 - 0.989), (Table 1) but increased by 5% for 10 mg increase in dose, OR (95% CI): 1.05 (1.00-1.11) for only cycle of incidence (Table 2)

Table 1: Parameter estimates of binary LR analysis with all cycles considered

Parameters	Estimates (95 % confidence interval)				
	All patients		Arm B patients		
	Base	PTX dose [mg]	Base	PTX $T_{C>0.05\mu M}$ [h]	PTX AUC_{∞} [μmol.h/mL]
OFV	1090.5	1078.6	397.7	396.5	395.2
Predictor effect (θ_1) [unit^{-1}]	-	-0.0110 (-0.0181, -0.00335)	-	0.0351 (-0.116, 0.00460)	-0.0857 (-0.232, 0.0605)
Variance in predictions (ω^2)	40 (13.3, 66.7)	51.6 (21.3, 81.9)	56.4 (21.0, 91.8)	57.3 (22.0, 92.6)	58.5 (21.8, 95.2)

OFV: objective function value, θ_1: change in log (odds of clinically important PN with a unit change in predictor), ω^2: between subject variability in predicted – true response.

Table 2: Parameter estimates of binary LR analysis with only cycle of incidence considered

Parameters	Estimates (95 % confidence interval)				
	All patients		Arm B patients		
	Base	PTX dose [mg]	Base	PTX $T_{C>0.05\mu M}$ [h]	PTX AUC_{∞} [μmoles.h/mL]
OFV	323.5	319.1	98.4	95.0	96.8
Predictor effect (θ_1) [unit^{-1}]	-	0.00518 (0.0002, 0.0102)	-	0.0768 (-0.0104, 0.164)	-0.108 (-0.0719, 0.228)
Odds ratio (95% CI)	-	1.01 (1.000, 1.01)	-	1.08 (0.989, 1.18)	1.11 (0.931, 1.33)

OFV: objective function value, θ_1: change in log (odds of clinically important PN with a unit change in predictor), ω^2: between subject variability in predicted - true response.

- In both cases $T_{C>0.05\mu M}$ and AUC_{∞} were not statistically significant predictors.

Discussion and Conclusions

- Relationship between dose and exposure with PN was quantified by binary LR analysis.
- Negative dose-PN relationship with all cycles arises from 1) dose reductions due to PN in the trial [3], and 2) chronic nature of PN.
- Positive dose-PN relation with data from cycle of incidence → need to consider chronic nature of PN during analysis.
- $T_{C>0.05\ \mu M}$ and AUC_{∞} were not statistically significant predictors: PK/PD-guided dosing → overall, low exposure in arm B.
- Markov models and time to event models will be explored next.
  - → Dependency between observed grades in the same patient
  - → Account for time course in change of PN grades

References

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For additional information, please contact
Francis Williams Ojara
francis.ojara@fu-berlin.de

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