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

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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$_{C>0.05}$) 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$_{C>0.05}$ and AUC$_C$) 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.

Results (cont.)
• With all cycles, risk of PN decreased by 10% for 10 mg increase in dose, odds ratio, OR (95% CI): 0.898 (0.835 - 0.969), (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)

Results
• No difference in distribution of dose and T$_{C>0.05}$ between clinically important and clinically not important PN (Figures 2 and 3).

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$_{C>0.05}$ and AUC$_C$ 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.

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References

Study population (n=365)

All patients (n=365)
• No. of patients with clinically important events (start of PN) = 112
• No. of observations, both arms = 1469;
clinically important/non-important = 284/1175
• No. of observations, arm B = 658;
clinically important/non-important = 85/573

Patients with consistent PTX doses (n=249)
• Dose range across cycles ≤ 50 mg
• Cycle of incidence → cycle of start of PN
• No. of observations, both arms = 249:
clinically important/non-important = 89/160
• No. of observations for arm B = 75:
clinically important/non-important = 22/53

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.