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Kinetic-Pharmacodynamic Model of Chemotherapy Induced Peripheral Neuropathy in Patients with Metastatic Breast Cancer Treated with Paclitaxel, Nab-Paclitaxel or Ixabepilone: CALGB 40502 (Alliance)

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Abstract

Chemotherapy induced peripheral neuropathy (CIPN) is a dose limiting toxicity caused by several chemotherapeutic agents. Currently, CIPN is managed by empirical dose modifications at the discretion of the treating physician. The goal of this research is to quantitate the dose-CIPN relationship to inform the optimal strategies for dose modification. Data were obtained from the Cancer and Leukemia Group B (CALGB) 40502 trial, a randomized phase III trial of paclitaxel vs.

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nab-paclitaxel vs. ixabepilone as first-line chemotherapy for locally recurrent or metastatic breast cancer. CIPN was measured using a subset of the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity (FACT-GOG-NTX) scale. A kinetic-pharmacodynamic (K-PD) model was utilized to quantitate the dose-CIPN relationship simultaneously for the three drugs. Indirect response models with linear and $S_{\max}$ drug effects were evaluated. The model was evaluated by comparing the predicted proportion of patients with CIPN (score 8 or score 12) to the observed proportion. An indirect response model with linear drug effect was able to describe the longitudinal CIPN data reasonably well. The proportion of patients that were falsely predicted to have CIPN or were falsely predicted not to have CIPN was 20% or less at any cycle. The model will be utilized to identify an early time point that can predict CIPN at later time points. This strategy will be utilized to inform dose adjustments to prospectively manage CIPN.

Keywords

CIPN; Paclitaxel; Nab-Paclitaxel; Ixabepilone; K-PD model

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) is a dose limiting toxicity caused by platinum drugs, vinca alkaloids, bortezomib and taxanes (among others) that impairs the quality of life and/or functional status of cancer patients (1,2). CIPN is characterized by numbness, tingling, and discomfort in the hands and feet (1). The mechanism involves early, sustained and progressive dysfunction of the sensory axons while motor function remains unchanged (3,4). CIPN can also have a significant effect on survival, as it can interfere with optimal dosing or necessitate the early discontinuation of effective therapies (1,2).

There are limited options for the prevention or management of CIPN. Many agents have been studied to prevent CIPN but none have been found to be effective, hence the American Society of Clinical Oncology does not recommend their use (3). With regards to the treatment of CIPN after the completion of chemotherapy, the best available data support a moderate recommendation for treatment with duloxetine based on a prospective randomized trial showing a modest improvement in pain severity (3,5).

A number of risk factors for CIPN have been postulated, including dose or schedule, exposure and genetic polymorphisms. For paclitaxel, a dose of 250 mg/m² administered as a 3-hour infusion every 3 weeks was found to cause more grade 3 neuropathy as compared to doses of 210 mg/m² and 175 mg/m² in patients with metastatic breast cancer (6). In another study, the mean cumulative dose for onset of neurotoxicity (grade 2) was 715 mg/m² for paclitaxel in metastatic breast cancer (7). Weekly paclitaxel (80 mg/m²) resulted in higher rate of neuropathy (grade 2 to 4) as compared to paclitaxel (175 mg/m²) administered every 3 weeks for a total of 6 doses in combination with carboplatin for ovarian cancer (8). A recent study of patients treated with paclitaxel on Cancer and Leukemia Group B (CALGB) 40101 showed that a common polymorphism in *FGD4*, a congenital peripheral neuropathy gene, increases the risk of developing CIPN (9). Another study found that women who were

CYP3A4*22 carriers had a higher risk of developing CIPN (10). Higher area under the curve (AUC) of paclitaxel and time above a concentration of 0.05 μM have also been correlated with the severity of CIPN (10,11). Similarly, a higher rate of CIPN was observed in a phase III trial of nab-paclitaxel (260 mg/m^2 q3w) as compared to paclitaxel (175 mg/m^2 q3w). The authors attributed the higher rate of CIPN with nab-paclitaxel to a 49% higher actual delivered paclitaxel dose for nab-paclitaxel as compared to paclitaxel (12). For ixabepilone, based on data collected from phase II and III trials, the rate of ixabepilone induced grade 3 or 4 neuropathy ranged from 1% to 24% with median resolution time of 5 to 6 weeks (13). Despite all of these studies, it remains difficult to predict which patients are at higher risk for CIPN (14).

Because dose is widely recognized as a risk factor, CIPN is usually managed by dose interruptions and/or reductions after CIPN occurs. Recently, an open label randomized trial successfully utilized pharmacokinetically guided paclitaxel dosing in patients with advanced non-small-cell lung cancer to reduce the occurrence of CIPN. (15). Some researchers have postulated that early recognition and initial management through dose interruption or reduction might prevent discontinuation of therapy (16,17). However, there is little emphasis on prevention of CIPN through prospective dose modification by utilizing a patient's own early toxicity data to predict later toxicity. Therefore, there is a definite need for dose individualization to manage CIPN (18).

The longitudinal dose and CIPN data were available from a randomized, phase III trial of weekly paclitaxel compared to nanoparticle albumin bound paclitaxel (nab-paclitaxel) or ixabepilone with or without bevacizumab as first line therapy for locally recurrent or metastatic breast cancer conducted by the Alliance for Clinical Trials in Oncology (CALGB 40502) (19). The aims of the current research were to utilize the data from this trial to: 1) describe the quantitative relationship between dose and patient reported CIPN score; and 2) qualify the model for its intended purpose. In future work, we will aim to: 1) identify an early time point that is predictive of later CIPN scores; and 2) perform simulations to propose a prospective dose modification algorithm to manage CIPN.

Methods

Data

The data were obtained from a randomized, phase III trial that evaluated the efficacy and safety of paclitaxel, nab-paclitaxel or ixabepilone with or without bevacizumab as first line therapy for locally recurrent or metastatic breast cancer patients (19). Each participant signed an Institutional Review Board approved, protocol-specific informed consent in accordance with federal and institutional guidelines. With respect to peripheral neuropathy, patients with Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4) grade 2 pre-existing peripheral neuropathy were excluded from the trial. A chemotherapy cycle consisted of 28 days. Paclitaxel, nab-paclitaxel and ixabepilone were administered intravenously at doses of 90 mg/m^2 over 1 hour, 150 mg/m^2 over 30 minutes, and 16 mg/m^2 over 1 hour, respectively, on days 1, 8 and 15 of each 28-day cycle. Bevacizumab was administered at a dose of 10 mg/kg intravenously on days 1 and 15 of each 28-day cycle for 97% of patients across the three treatment arms (19). Dosing information in each cycle was

available; however, no plasma concentration data were collected. Dose modifications were performed due to hematological toxicity, intolerable Grade 2 or Grade 3 peripheral neuropathy, hypersensitivity reaction or other non-hematologic toxicity. The doses of paclitaxel, nab-paclitaxel and ixabepilone could be reduced to 60 mg/m², 90 mg/m² and 10 mg/m², respectively (19). The baseline demographic characteristics such as age, weight, height, body mass index (BMI), body surface area (BSA), race and use of prior taxanes were available.

Response variable for measuring CIPN symptoms

A validated, patient reported scale (the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity scale (FACT-GOG-NTX) was utilized for assessing CIPN that consisted of 11 items related to physical symptoms and functional limitations, rated on a 5-point Likert scale from 0 (“Not at all”) to 4 (“Very much”), as demonstrated in Supplementary Table 1 (20–22). CIPN was evaluated using the FACT-GOG-NTX at baseline and on day 1 of each chemotherapy cycle. It has been reported that the first four questions pertaining to sensory neuropathy account for the majority of changes in CIPN over time (22), and this was confirmed to be the case for the data from the current trial (Supplementary Figure 1). Therefore, a phenotype was derived by adding the scores from the four FACT-GOG-NTX items related to sensory neuropathy denoted as CIPN score in the manuscript. The CIPN scores ranged from 0–16 with higher scores indicating higher severity. Patients with CIPN scores of > 4 at baseline were considered to already have some degree of CIPN despite meeting eligibility criteria of not having Grade 2 neuropathy by CTCAE. Since the goal of the research was to propose dose adjustments for patients who are at risk for developing CIPN (not for those who already have it), patients with baseline CIPN score > 4 were excluded from model development. The excluded patients accounted for 8% of the total population.

Dose-CIPN score model

A longitudinal dose-response model was developed to quantify the time course of CIPN scores for paclitaxel, nab-paclitaxel and ixabepilone using nonlinear mixed effects modeling. The nonlinear mixed effects modeling was conducted in NONMEM (version 7.2, ICON Development Solutions, Ellicott City, MD) and graphical exploration was performed using R version 3.3.0.

Base Model

Since pharmacokinetic data were not collected, a kinetic-pharmacodynamic (K-PD) model as previously described (23) was utilized to quantitate the time course of dose and CIPN score. A K-PD model allows for the characterization of the time-course of a drug's effects in the absence of pharmacokinetics by using dosing information. CIPN score was treated as a continuous variable. The onset of CIPN occurs gradually, and hence is not a direct effect after dose administration. Therefore, an indirect response model that represents the stimulation of CIPN with the dose of neurotoxic drugs was utilized as the pharmacodynamic model (24). Figure 1 illustrates the structure of the K-PD model. The differential equations are described as follows:

$$\frac{dA}{dt} = -KDE \cdot A \quad (1)$$

$$IR = KDE \cdot A \quad (2)$$

$$\frac{d(\text{CIPN score})}{dt} = K_{in} \cdot (1 + \text{slope} \cdot IR) - K_{out} \cdot \text{CIPN score} \quad (3)$$

$$\text{CIPN score}(0) = \frac{K_{in}}{K_{out}} \quad (4)$$

where A is the amount of the drug in the virtual compartment, KDE represents the elimination rate constant from the virtual compartment, IR is the virtual infusion rate, CIPN score is the response variable, K_{in} and K_{out} are the zero and first order rate constants for the appearance and disappearance of CIPN symptoms, respectively, and slope represents the slope of CIPN score and IR. The baseline CIPN score was estimated and K_{out} was calculated as $K_{in}/\text{baseline CIPN score}$.

Apart from the linear model, the drug effect was also modeled as a S_{max} model described using the following equation:

$$\frac{d(\text{CIPN score})}{dt} = K_{in} \cdot \left(1 + \frac{S_{max} \cdot IR}{SDK_{50} + IR} \right) - K_{out} \cdot \text{CIPN score} \quad (5)$$

where S_{max} is maximum stimulation and SDK_{50} is the IR that produces 50% of maximum stimulation.

Since all three drugs exert their anticancer effects by enhancing tubulin polymerization (25–27), it is likely that the mechanism of development of CIPN is the same for all three drugs. Therefore, a combined model for the three drugs was developed, with slope (equation 3) or SDK_{50} (equation 5) estimated separately for each drug. The between subject variability (BSV) was incorporated on all the parameters. The parameters were assumed to be lognormally distributed; therefore, an exponential structure as described below was utilized to estimate BSV.

$$P_i = \text{tvP} * \exp(\eta_p) \quad (6)$$

where P_i is the parameter in an individual, tvP is the population estimate of the parameter and η_p is the between subject variability. η_p was assumed to be normally distributed with a mean of 0 and a variance of Ω^2 . Inclusion of correlation between the random effects of the parameters was attempted. The residual variability was modeled using an additive error structure. First order conditional estimation with interaction was used for the estimation.

Covariate Model

Exploratory data analysis of covariates including height, weight, age, BMI, BSA, race and use of prior taxane with CIPN score was conducted. No trends were observed in the exploratory data analysis. Furthermore, relationships between random effects of the model parameters and covariates were examined to identify if covariates needed to be included in the model.

Model Qualification

The final model was qualified using goodness of fit plots, individual predictions and precision of the parameter estimates. The precision of the final model parameters was obtained using bootstrapping. For obtaining bootstrap parameter estimates and confidence intervals, 1,000 datasets with the same design (same number of subjects and dose schedule) were generated by random sampling with replacement. The final model was fitted to each of these datasets and the median and the 90% confidence intervals were obtained for the model parameters.

Since we propose to use the individual empirical Bayes estimates for prediction of CIPN, the individual predicted and the observed CIPN scores were compared at C2D1 (cycle 2, day 1), C4D1 (cycle 4, day 1), C7D1 (cycle 7, day 1) and C10D1 (cycle 10, day 1) using the following metrics. The CIPN score was modeled as a continuous variable; thus, the predicted CIPN score can include decimal values. Therefore, the predicted CIPN score was rounded to the nearest integer value for comparison to observed CIPN score. For example, a predicted CIPN score of 7.5 was rounded to 8. The percent concordance and discordance were calculated as described below.

$$\begin{aligned} \% \text{ Discordance (Discord1)} \\ = \frac{(\text{Proportion of patients with observed CIPN score} < 8 \text{ but predicted CIPN score} \geq 8)}{\text{Total number of patients}} \times 100 \end{aligned}$$

(7)

$$\begin{aligned} & \% \text{ Discordance (Discord2)} \\ &= \frac{(\text{Proportion of patients with observed CIPN score} \geq 8 \text{ but predicted CIPN score} < 8)}{\text{Total number of patients}} \times 100 \end{aligned}$$

(8)

$$\% \text{ Concordance (Concord1)} = \frac{(\text{Proportion of patients with observed and predicted CIPN score} \geq 8)}{\text{Total number of patients}} \times 100$$

(9)

$$\% \text{ Concordance (Concord2)} = \frac{(\text{Proportion of patients with observed and predicted CIPN score} < 8)}{\text{Total number of patients}} \times 100$$

(10)

A CIPN score cut-off of 8 was selected because it is the midpoint of the range and corresponds to an average score of 2 (an answer of “somewhat”) for the four questions, which would likely have a significant impact on the patient’s quality of life. In an ideal situation, one would want to maximize the proportion of patients in Concord1 and Concord2, while minimizing the proportion in Discord1 and Discord2. An alternative CIPN score cut-off of 12 was also explored because it corresponds to an average score of 3 (an answer of “quite a bit”) for the four questions, which would certainly have a significant impact of the patient’s quality of life.

To compare CIPN severity amongst the three drugs, CIPN scores were simulated using the population parameters with doses of 90 mg/m² (paclitaxel), 150 mg/m² (nab-paclitaxel) and 16 mg/m² (ixabepilone) administered on day 1, 8 and 15 for 7 cycles in a patient with a BSA of 1.8 m².

Results

The analyzable population for the CALGB 40502 trial was 783 patients (19). However, patients with baseline CIPN>4, no baseline CIPN information, or inaccurate dosing history were excluded from the dataset, and hence the revised dataset for our analysis included 653 patients with 4799 observations. Nevertheless, the results of our analysis are representative of the overall population enrolled in the trial since the proportion of patients with CIPN across the three treatment arms in the original dataset and the revised dataset are similar.

Table 1 shows the demographics of the population used for model development, which are not different than the total population (data not shown). The number of patients in the paclitaxel, nab-paclitaxel and ixabepilone arms were 234, 215 and 204, respectively. The distributions of the baseline age, weight, height, BMI, BSA, race and the use of prior taxane were similar among the three treatment arms. The baseline CIPN score ranged from 0–4, with ~ 65% of the patients having a CIPN score of 0 at baseline.

The time course of CIPN and number of patients remaining in the trial for the paclitaxel, nab-paclitaxel and ixabepilone arms are shown in Figure 2. There appears to be significant variability in CIPN scores, but on average, CIPN scores increased with time and then reached a plateau in all treatment arms. This may be due to dose reductions or treatment discontinuation. Only 17% of patients discontinued therapy due to adverse events, including peripheral neuropathy (19). On a median level, CIPN score after 6 cycles was ~4 for paclitaxel and ~6 for nab-paclitaxel and ixabepilone. CIPN scores from approximately 55% (128/234) of patients were available for paclitaxel through 6 cycles, while 44% (95/215) and 45% (92/204) of the patients had CIPN scores through 6 cycles available in the nab-paclitaxel and ixabepilone arms, respectively.

As reported by Rugo *et al*, dose reductions were more frequent and occurred earlier for patients receiving nab-paclitaxel, with 31% of patients having been dose-reduced by cycle 2, and 45% by cycle 3 compared with 9% (cycle 2) and 15% (cycle 3) for paclitaxel, and 6% (cycle 2) and 15% (cycle 3) for ixabepilone. Only 28% of patients were still receiving full-dose nab-paclitaxel at the start of cycle 5 compared with 76% for paclitaxel and 65% for ixabepilone (19). The reasons for dose modifications or drop out for individual patients were not available. The dose modifications could have been due to toxicities other than neuropathy, and treatment discontinuation was primarily due to disease progression, death, or adverse events (19).

The times to the first occurrence of CIPN for paclitaxel, nab-paclitaxel and ixabepilone based on different CIPN thresholds are shown in Figure 3. Regardless of the CIPN threshold, patients on paclitaxel had CIPN later than the patients on nab-paclitaxel and ixabepilone. The median time to CIPN ≥ 8 was 238, 135 and 147 days for paclitaxel, nab-paclitaxel and ixabepilone, respectively. The percent of patients with CIPN ≥ 8 were 41% (96/234), 48% (103/215) and 47% (95/204) for paclitaxel, nab-paclitaxel and ixabepilone, respectively.

The K-PD model with linear drug effect yielded population parameter estimates that are summarized in Table 2. The rate of appearance of CIPN symptoms was estimated to be 0.0084 units/day, such that the average patient would take 119 days to increase their score by 1 point. The baseline CIPN score was estimated to be 0.5 units. The slopes were estimated to be 0.882 units/mg/day, 0.826 units/mg/day and 9.74 units/mg/day for paclitaxel, nab-paclitaxel and ixabepilone, respectively. As mentioned earlier, IR (which is derived from the elimination rate constant (KDE) and the amount in the virtual compartment) drives the changes in CIPN score. Therefore, to interpret the slope estimates with respect to changes in CIPN score, distributions of IR for each drug were generated. The 2.5th, 50th and 97.5th percentiles of the IR derived from the virtual compartment were 0.53 mg/day, 8.65 mg/day

and 22.23 mg/day for paclitaxel, respectively (Supplementary Figure 2). The CIPN scores for corresponding infusion rates were calculated to be 0.7, 4.3 and 10.3 using the following equation.

$$\text{CIPN score} = \text{baseline CIPN score} \cdot (1 + \text{slope} \cdot \text{IR}) \quad (11)$$

Similarly for nab-paclitaxel, the CIPN scores for infusion rates of 1.13 mg/day, 14.41 mg/day and 29.83 mg/day were 1, 6.9, 13.7, respectively. For ixabepilone, the CIPN scores for infusion rates of 0.05 mg/day, 1.05 mg/day and 3.31 mg/day were 0.7, 5.6 and 16.6, respectively.

The KDE, which represents the elimination rate constant from the virtual compartment, was estimated to be 0.0086/day, 0.0122/day and 0.0047/day for paclitaxel, nab-paclitaxel and ixabepilone, respectively. KDE may be interpreted as a parameter that is analogous to the elimination rate constant (K_{el}) of a pharmacokinetic model. It has been reported that the half-life ($0.693/K_{el}$) of ixabepilone (52 hours, (26)) is longer as compared to paclitaxel (13.7 hours, (28)) and nab-paclitaxel (23.2 hours, (29)). Therefore, it is expected that the KDE will be lower for ixabepilone. This indicates that once drug administration is stopped, the CIPN score will decline more slowly for a patient treated with ixabepilone as compared to patients treated with paclitaxel or nab-paclitaxel. The BSV was estimated on all of the parameters. The shrinkage was less than 40% on the random effects of the parameters except for K_{in} . Plots of random effects of the parameters versus covariates did not depict any trends and therefore further covariate evaluation was not conducted (Supplementary Figure 3).

The K-PD model with linear drug effect had a reasonable goodness of fit by the usual plots (Supplementary Figure 4). The individual predicted versus observed CIPN score plot showed reasonable agreement between the observed and predicted CIPN scores. The conditional weighted residuals versus population predicted CIPN score or time did not show bias. Figure 4 shows the individual patient CIPN score versus time profiles for representative individuals treated with paclitaxel (Figure 4A), nab-paclitaxel (Figure 4B) and ixabepilone (Figure 4C). These plots depict that the model is able to reasonably describe the trend in time course of CIPN score at an individual level. As is evident from the plots, there is substantial variability in peak CIPN, time to peak CIPN score and decrease in CIPN symptoms after cessation of dose. However, the individual predictions were able to capture the different trends in observed CIPN score with dose.

A S_{max} model as described in the methods section was also explored. However, the parameter estimate for SDK_{50} for paclitaxel was estimated to be outside the range of model derived IR, which is unreasonable and not interpretable. The mean maximum response (R_{max}) was predicted to be 20, which is outside the range of observed CIPN score. Also, the shrinkage on the random effects of the parameters was more than 50%. Therefore, the model with linear drug effect was selected as the best one to describe the data.

Simulations were conducted using the mean population parameters at the doses studied in the trial for paclitaxel, nab-paclitaxel and ixabepilone to compare the neurotoxicity between

different drugs. On average, nab-paclitaxel resulted in higher neuropathy as compared paclitaxel and ixabepilone, but the 90 % confidence intervals are too wide to draw any statistical conclusions (Figure 5). Nevertheless, this observation is consistent with the observed data, as the nab-paclitaxel arm had a higher proportion of patients experiencing Grade 2 or greater CIPN by CTCAE compared to paclitaxel and ixabepilone (19). In addition, the rate of decline in CIPN score was faster for nab-paclitaxel as compared to paclitaxel and ixabepilone, as expected based on the higher KDE of nab-paclitaxel.

Model evaluation was also done using the individual predicted CIPN scores at C2D1, C4D1, C7D1 and C10D1 (Figure 6). The percent of subjects in Discord1 and Discord2 (discordant pairs) was 20% or less at all time points. More importantly, the proportion of patients in Discord1 was 10% or less in all cycles, indicating that the probability of the model to incorrectly predict that a patient will develop severe CIPN (i.e. false positive) is less than 10%.

Discussion

Paclitaxel and nab-paclitaxel are taxane derivatives that are indicated for the treatment of a variety of cancers including metastatic breast cancer (25,27). Ixabepilone is a semisynthetic analogue of epothilone B that is also indicated for the treatment of metastatic breast cancer (26). A phase III trial was conducted to compare the efficacy of either nab-paclitaxel or ixabepilone to paclitaxel administered once per week (19). All three drugs are labeled to be given every 3 weeks, but weekly dosing is commonly used and has been demonstrated to have an overall survival benefit compared to every three week dosing (30). Although the primary objective of the clinical trial was to assess efficacy, several safety assessments including longitudinal measurement of CIPN scores were also conducted. CIPN is the dose-limiting toxicity of these chemotherapeutic agents. The sensory neuropathy was measured by physician assessment using the CTCAE v4 (19). The percent of patients with grade 2 sensory neuropathy by CTCAE were 54%, 46% and 47% for nab-paclitaxel, paclitaxel and ixabepilone, respectively at any time course of the treatment (19). The dose modifications in the trial were conducted based on CTCAE grades. The neurotoxicity was also assessed using a patient reported outcome (the FACT-GOG-NTX scale). It has been reported that there is significant inter-observer disagreement in scoring CIPN with CTCAE with a tendency to underscore CIPN severity (31–33). Therefore, we used the FACT-GOG-NTX scale to quantify the dose-CIPN relationship.

There is no clear evidence as to whether or not bevacizumab influences CIPN. Since 97% of the patients in this trial were treated with bevacizumab, the contribution of bevacizumab could not be assessed and the contribution (if any) will be similar across treatment arms. Since pharmacokinetic data were not collected, a K-PD indirect response model with linear drug effect was used to characterize the dose-CIPN score relationship. K-PD model has been previously used successfully to describe longitudinal PK-PD relationship when pharmacokinetic information is not available (34–36). As proposed by Jacqmin et al., infusion rate from the virtual compartment was utilized to drive the response instead of the amount of drug in the virtual compartment (23). Data from all three treatment arms were combined for the development of the K-PD model. Since paclitaxel, nab-paclitaxel or

ixabepilone all presumably cause CIPN by the same mechanism of tubulin polymerization (37,38), a combined model was deemed reasonable. In addition, combining the model also allowed for wide range of CIPN scores to be included for a better estimation of K_{in} which is a drug independent parameter. Paclitaxel contains cremophore EL as a formulation vehicle, while nab-paclitaxel is the albumin bound nanoparticle formulation of paclitaxel, without cremophore EL (27). It is not clear how the formulation or vehicle might impact the neurotoxicity of the drugs (39); therefore, paclitaxel and nab-paclitaxel were treated as separate drugs for the analysis. The drug specific parameters, KDE and slope, were estimated separately for each of the three drugs.

It is important to note that data from only one dose level were available, but due to variability in BSA and significant number of dose reductions in the trial in all the treatment arms, there was a wide range of doses allowing the estimation of the slope parameters. The difference in slope between the three drugs is due to differences in the virtual infusion rate (IR), which reflect the variation in dose range between the three drugs. The median IR for ixabepilone is ~ 1 mg/day while for paclitaxel and nab-paclitaxel, median IR is ~9 mg/day and ~15 mg/day, respectively (Supplementary Figure 2). Similarly, the median dose for ixabepilone was 16 mg/m² as compared to 90 mg/m² for paclitaxel and 150 mg/m² for nab-paclitaxel. The median IR is ~9- fold higher for paclitaxel and ~15 fold higher for nab-paclitaxel as compared to ixabepilone; thus, the slope estimates for paclitaxel and nab-paclitaxel are smaller compared to ixabepilone. Even though there was information on CIPN responses at a wide range of doses, a S_{max} model was not considered appropriate since it is unknown whether the doses evaluated in this trial are high enough to enable capturing the S_{max} part of the dose-response curve.

Furthermore, since slope is a hybrid parameter reflecting both drug potency and clearance, we compared the potency of the three drugs by using relative clearance based on the FDA label or the literature. The clearances of paclitaxel, nab-paclitaxel and ixabepilone are 7.53, 24.6 and 20 L/h/m², respectively (26, 28–29). Thus relative clearance of nab-paclitaxel and ixabepilone compared to paclitaxel is 3.3-fold and 2.7-fold, respectively. Since slope ~ potency * relative clearance, the potency of paclitaxel, nab-paclitaxel and ixabepilone is 0.882, 0.253 and 3.66, respectively. Thus, nab-paclitaxel appears to be the most potent, followed by paclitaxel and ixabepilone.

During model development, plots of random effects against covariates did not show any trends. Prior taxane could be one of the expected covariates on the baseline CIPN score; however, based on the inclusion criteria, the interval between completion of adjuvant or neoadjuvant taxane therapy and start of the trial was >12 months. Therefore, any CIPN that may have occurred due to prior taxane therapy would have likely resolved before the trial began. Since the eventual aim is to use individual post hoc parameters to propose dose individualization strategies to manage CIPN, the focus was on the individual predictions. On an individual level, the model was reasonably able to capture the various time courses in the observed data (by visual inspection) and showed 20% or less discordant pairs, indicating good predictive power.

There are several limitations to our approach. First, the model links dosing information in each subject to the CIPN score. The drug exposures obtained at the doses would be a more reasonable driver for the CIPN scores and may explain some of the variability in the parameters, but pharmacokinetic samples were not collected in this trial. Second, the K-PD model is most suitable in cases where the underlying PK of the drug is linear and follows a one compartment model. Since the PK of all three drugs in this trial are best described by two compartment models, the drug independent model parameters (K_{in} and K_{out}) may have some bias in estimation while the drug specific parameters (slope and KDE) are likely reliably estimated, as concluded by Jacqmin and colleagues. Third, the model can be applied to the dosing regimen and the patient population studied in the trial and cannot be extrapolated to different dosing regimens and patient populations, as the baseline risk and sensitivity to development of CIPN may be different. Fourth, a sum of qualitative data elements was treated as a continuous outcome, and the appropriate threshold for CIPN score that can be related to clinically significant neuropathy is subjective. A patient with a score of 8 might, for example, have a score of 2 on each of the four questions. This would correspond to numbness or tingling in the hands and feet, as well as discomfort in the hands and feet “somewhat” during the past 7 days (between day 21 and day 28 of the previous cycle). However, the validity of the model is maintained even if one chooses a higher threshold for severe CIPN, i.e. CIPN score ≥ 12 (Supplementary Figure 5). Fifth, data on germline polymorphisms that have previously been identified as risk factors for neuropathy were not available from this data set at the time of model development (but DNA were collected and this is an area of future work). Finally, patients who discontinued therapy for reasons other than CIPN could not be observed for incidence of CIPN. This type of missing data due to dropout is most likely uninformative rather than informative, but the possibility that it could have introduced bias into the model cannot be excluded.

We were also not able to identify any baseline covariates that could help to identify patients at high risk for developing CIPN. Therefore, we plan to use early CIPN data from each subject to predict CIPN at later time points in the same subject using the developed model as prior knowledge. Using a patient’s own data to predict their later time course of CIPN will negate the effects of any covariates that could influence the CIPN trajectory. This is also an approach that a treating physician could realistically use to guide dose adjustments in a patient who they are following over time.

Conclusion

In summary, the dose - CIPN score relationship for paclitaxel, nab-paclitaxel and ixabepilone was successfully quantified and qualified using a K-PD model. The model will be utilized to identify an early time point that is predictive of the later time course of CIPN in individual patients. This strategy will be utilized to recommend a dose adjustment algorithm to minimize the severity of CIPN that patients with metastatic breast cancer develop while being treated with these drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Diagrammatic representation of the K-PD model. $A(t)$: the amount of drug in the virtual compartment at time t , KDE: elimination rate constant from the virtual compartment, $IR(t)$: the virtual infusion rate at time t , K_{in} : the zero order rate for the appearance of CIPN symptoms and K_{out} : the first order rate constant for the disappearance of CIPN symptoms.

Figure 2.
Observed time course of CIPN score for paclitaxel, nab-paclitaxel and ixabepilone. The numbers on the top represent the number of observations at each cycle.

Figure 3.
Time to first CIPN based on different CIPN score cut-offs.

Figure 4A.

Model predicted time course of representative subjects for paclitaxel. Solid black circles represent observed data; blue and black lines represent individual and population predicted CIPN score, respectively. Numbers in red represent dose administered on day 1, 8 and 15 of a cycle.

Figure 4B.

Model predicted time course of representative subjects for nab-paclitaxel. Solid black circles represent observed data; blue and black lines represent individual and population predicted CIPN score, respectively. Numbers in red represent dose administered on days 1, 8 and 15 of a cycle.

Figure 4C.

Model predicted time course of representative subjects for ixabepilone. Solid black circles represent observed data; blue and black lines represent individual and population predicted CIPN score, respectively. Numbers in red represent dose administered on days 1, 8 and 15 of a cycle.

Figure 5.

Model predicted time course of CIPN score for paclitaxel (90 mg/m²), nab-paclitaxel (150 mg/m²) and ixabepilone (16 mg/m²) administered for 7 cycles to a typical patient with BSA of 1.8 m². The solid black vertical line denotes day of last dose. The solid red, blue and black lines are mean predicted CIPN scores and the dotted lines denote 90% confidence intervals derived from bootstrap.

Figure 6.

Model evaluation using individual post-hoc parameter estimates for CIPN cutoff of 8. Red squares, blue circles and black triangles represent paclitaxel (PAC), nab-paclitaxel (NPAC) and ixabepilone (IXA), respectively. Discord1&2: Discordant pairs (Discord1: Observed CIPN score < 8 while predicted CIPN score is ≥ 8; Discord2: Observed CIPN score ≥ 8 while predicted CIPN score is < 8); Concord1&2: Concordant pairs (Concord1: Both observed and predicted CIPN score ≥ 8; Concord2: Both observed and predicted CIPN score < 8).

Table 1

Demographic characteristics of the analysis population whose data were used to develop the model (n= 653).

	Treatment Arms		
	Paclitaxe	Nab-Paclitaxel	Ixabepilone
	90 mg/m ² on days 1, 8 & 15 every 28 days	150 mg/m ² on days 1, 8 & 15 every 28 days	16 mg/m ² on days 1, 8 & 15 every 28 days
Total number of patients enrolled (n=783)	275	267	241
Number of patients excluded (n=130)	41	52	37
Number of patients included in the analysis (n=653)	234	215	204
Height (cm), mean $\pm$ SD	162.6 $\pm$ 7.8	162.7 $\pm$ 6.8	163.0 $\pm$ 7.6
Weight (kg), mean $\pm$ SD	78.4 $\pm$ 19.0	78.5 $\pm$ 20.3	78.1 $\pm$ 18.1
BMI (kg/cm ²), mean $\pm$ SD	29.7 $\pm$ 7.3	29.6 $\pm$ 7.1	29.4 $\pm$ 6.4
Baseline BSA (m ²), mean $\pm$ SD	1.87 $\pm$ 0.24	1.87 $\pm$ 0.25	1.87 $\pm$ 0.23
Age (years), mean $\pm$ SD	57.2 $\pm$ 10.7	56.6 $\pm$ 11.3	56.5 $\pm$ 10.1
Prior taxane therapy (No. of patients (%))	90 (38.5 %)	83 (38.6 %)	82 (40.2 %)
Race			
White (No. of patients (%))	183 (78.2%)	170 (79.1%)	174 (85.3%)
Black (No. of patients (%))	35 (14.9%)	32 (14.9%)	21 (10.3%)
Other (No. of patients (%))	16 (6.8%)	13 (6.0%)	9 (4.4%)
Baseline CIPN Score			
0 (No. of patients (%))	150 (64.1%)	139 (64.7%)	129 (63.2%)
1 (No. of patients (%))	31 (13.2%)	32 (14.9%)	29 (14.2%)
2 (No. of patients (%))	24 (10.3%)	26 (12.1%)	19 (9.3%)
3 (No. of patients (%))	12 (5.1%)	8 (3.7%)	15 (7.4%)
4 (No. of patients (%))	17 (7.3%)	10 (4.7%)	12 (5.9%)

Table 2

Parameter estimates for the K-PD model

Parameter (units)	Estimate	%BSV [shrinkage]	Bootstrap Estimate Median (90% CI)	Bootstrap %BSV
K_{in} (unit/day)	0.0084	118% [53%]	0.00767 (0.0049, 0.0106)	113%
Baseline CIPN score (unit)	0.5	33% [36%]	0.493 (0.359, 0.592)	36.5%
Slope for paclitaxel (unit/mg/day)	0.882	34.2%[36%]	0.914 (0.690, 1.327)	30.2%
Slope for nab-paclitaxel (unit/mg/day)	0.826		0.847 (0.667, 1.201)	
Slope for ixabepilone (unit/mg/day)	9.74		10.08 (7.673, 14.538)	
KDE for paclitaxel (day^{-1})	0.0086	145%[36%]	0.0089 (0.0064, 0.0159)	146%
KDE for nab-paclitaxel (day^{-1})	0.0122		0.013 (0.0098, 0.0218)	
KDE for ixabepilone (day^{-1})	0.0047		0.0049 (0.0036, 0.0071)	
Covariance between baseline and slope		33.6%		31.5%
Additive residual error (unit)	1.90			1.90

BSV: between subject variability