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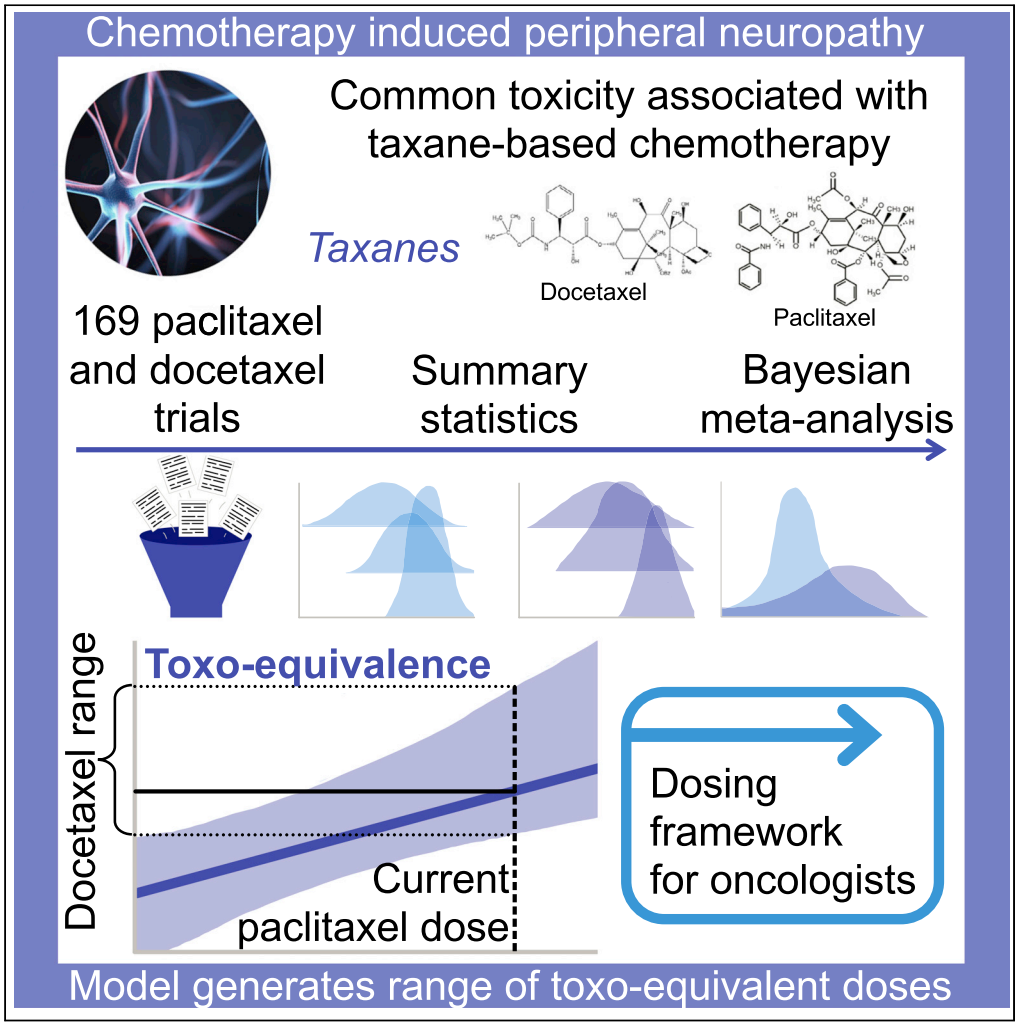

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Highlights

We created a dosing framework for oncologists using published clinical trials

Our approach leverages existing publicly available data via Bayesian meta-analysis

This framework uses a toxicity outcome rather than more common efficacy outcomes

The output range of equivalent doses provides guidance within one treatment cycle

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Development of a bayesian toxo-equivalence model between docetaxel and paclitaxel

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SUMMARY

Members of the taxane class of chemotherapies, staples of cancer treatment since the 1990s, can induce chemotherapy-induced peripheral neuropathy (CIPN), a potentially irreversible outcome related to cumulative exposure. Switching between taxanes is often clinically necessary; however, different taxanes have different efficacies, toxicities, and dosing strategies, necessitating an evidence-based schema focused on toxicity. We performed a systematic review and meta-analysis of the literature on docetaxel and paclitaxel, extracting cumulative dose, rates of CIPN, and subject demographics, thereby establishing their dose-toxo-equivalence relationship through a Bayesian meta-analysis model, calculating doses of the two drugs that are expected to have comparable rates of CIPN, along with credible intervals. Our final model, based on 169 studies, produces credible interval widths that provide guidance within one treatment cycle. In practice, this model provides a framework under which oncologists can make treatment switching and dosing decisions, hopefully reducing patient risk of CIPN.

INTRODUCTION

Over the past century, the evolution of cancer care including diagnosis, surgery, radiation, and chemotherapy has profoundly evolved (Lukong, 2017). Plant alkaloids are a categorization of anticancer therapies which include the taxanes that were first discovered in 1971 and initiated in clinical practice in the 1990s. Before their introduction, use of other cytotoxic agents were the mainstay, particularly the use of anthracycline-based regimens which emerged in the 1960s and continue to be a common component of various cancer treatment regimens as well as the role of hormonal therapies, such as the first approval of tamoxifen. Subsequently, drug development discoveries have continued to include the use of targeted agents and evaluation of novel biomarkers which may provide increasingly effective treatment strategies in the era of personalized medicine.

Even with emergent therapies, taxanes (cabazitaxel, docetaxel, and paclitaxel in particular) remain an effective component of cancer treatment, a backbone of breast cancer therapy regimens; besides, taxanes have shown to benefit patients with a variety of primarily solid tumors and are thus in widespread use for cancer treatment in a variety of settings (Bonomi et al., 2000; Citron et al., 2003; Gatzemeier et al., 2000; Icon and Ago Collaborators, 2003; James et al., 2016; Jones et al., 2006; McGuire et al., 1996; Sledge et al., 2003; Sweeney et al., 2015; Tannock et al., 2004). Taxanes have a unique mechanism that induces microtubule stabilization (differing affinity for β tubulin (Mosca et al., 2021; Nabholtz and Gligorov, 2005)) and inhibits depolarization causing apoptosis. Although there are similarities in their mechanism of action, there are differences in the drug delivery system parameters including pharmacokinetic and pharmacodynamic characteristics (linear versus nonlinear), cell cycle specificity, drug interaction, and pharmacogenomic characteristics; therefore, these may result in differential efficacy and toxicity profiles of paclitaxel and docetaxel, the most commonly used taxanes in clinical practice.

A common dose-limiting toxicity of taxanes is chemotherapy-induced peripheral neuropathy (CIPN) (Hershman et al., 2014; Rivera et al., 2017). CIPN is most commonly a sensory neuropathy, although motor and/or autonomic dysfunction can also occur (Seretny et al., 2014). CIPN resulting from taxanes is a

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cumulative dose-dependent toxicity, which can cause persistent effects for years after cessation of therapy and may not resolve (Argyriou et al., 2012; von Hehn et al., 2012; Kerckhove et al., 2017). As such, CIPN commonly results in dose modification of taxanes in treatment plans or stopping taxane-based regimens entirely because of toxicity. CIPN etiology is multifactorial, likely depends on factors such as unit dose, schedule, and infusion time (Katsumata et al., 2009; Spriggs et al., 2007), as well as patient-level factors such as age, diabetes, baseline presence of peripheral neuropathy, genetic predisposition (Adjei et al., 2021; Chen et al., 2015; Ghetti et al., 1990), and other subjects not yet known (Bhatnagar et al., 2014; Park et al., 2013; Zajączkowska et al., 2019).

Medical oncologists commonly switch between taxanes for a variety of reasons, including hypersensitivity reactions, tolerability, treatment schedule, and resource availability. Taxanes contain a boxed warning for hypersensitivity reactions; these are common, tend to occur early in the treatment course (within the first few days) before evaluation of treatment response or accumulation of long-term toxicities that are contra-indications to further taxane therapy, such as CIPN (Boulanger et al., 2014; Lee et al., 2009; Panday et al., 1997). Despite the commonality of switching taxanes in clinical practice, developing a schema for doing so is challenging for a number of reasons. Although their mechanism of action is similar, differences in pharmacokinetic, pharmacodynamics. and pharmacogenomic characteristics may result in differential efficacy and toxicity profiles of paclitaxel and docetaxel (Baldwin et al., 2012; Gelderblom et al., 2001; Kudlowitz and Muggia, 2013; Sparreboom et al., 1998; Synold et al., 2001; van Zuylen et al., 2001). Prior studies have been inconclusive regarding CIPN rates between taxanes, which further complicates developing guidelines for switching between these agents (Bhatnagar et al., 2014; Jones et al., 2005; Karafiath et al., 2017; Kudlowitz and Muggia, 2013; Sparano et al., 2008).

The few studies that have compared docetaxel and paclitaxel head-to-head have focused on efficacy, not toxicity, and the studies that do include these drugs are interested in treatment effect estimates rather than dose-response estimation. Given the unmet need for an evidence-based schema for taxane switching, we aimed to conduct a systematic review and meta-analysis to develop a dose equivalence model between paclitaxel and docetaxel based around CIPN as a frequent dose-limiting toxicity, hereafter referred to as the dose-toxo-equivalence model, adjusting for common risk factors for CIPN.

RESULTS

In Table 1 we summarize the studies included in our final model. After applying all exclusion criteria, the resulting pool of studies included 99 in docetaxel and 70 in paclitaxel, representing 14,343 and 7,638 patients, respectively. The complete results of our article screening process are summarized in the PRISMA flow diagram found in Figure 1. In addition, our consideration of the PRISMA guidelines for conducting a meta-analysis can be found in Tables S1and S2. The number of individuals under study in individual trials was comparable across drugs, with a median of 63 in docetaxel and 60 in paclitaxel. Trials in docetaxel had a significantly higher median percentage of male samples (67%) than in paclitaxel (0%) and had a slightly higher median age (61 years versus 58), reflecting enrichment for prostate cancer (exclusively male and older) and non-small cell lung cancer (predominantly male and older). A smaller proportion of docetaxel trials (70%) allowed for previous chemotherapy exposure than paclitaxel (86%). The most common dose gap in dosing among docetaxel trials was 3 weeks, whereas in paclitaxel trials it was 1 week. The range of all-grade CIPN rates (from ~16% to ~60%) is reflective of the current body of literature on CIPN among patients treated with taxanes (Hershman et al., 2014; Song et al., 2017).

The final model fit as chosen by the penalized DIC is summarized in Table 2. The posterior parameter samples used in the calculation of toxo-equivalence ($\beta_1, \beta_2, \beta_3, \beta_4$) showed convergence in the sampling chains, with no indication of autocorrelation concerns. The effect of dose gap was significant in all model parameters except β_6, with credible intervals that did not contain 0.

The estimated equivalence relationship produced by this model is presented in Figure 2 with the candidate range of paclitaxel doses on the X axis and the estimated equivalent dose of docetaxel on the Y axis, both in mg/m^2. The center line represents the median-estimated relationship, whereas the upper and lower dotted lines mark the bounds of the 95% credible interval from the calculation across the posterior distributions of $\boldsymbol{\beta}$. Note that the lower bound of the credible interval is clipped at 0 mg/m^2, because dosage values must be nonnegative. The width of the resulting credible interval was roughly equal to one

Table 1. Summaries of study characteristics by taxane type. Categorical variables are presented as count (%) and compared using a Chi-square test and both discrete and continuous numerical variables are presented as median [Q1, Q3] and compared using a Kruskal-Wallis test

	Docetaxel	Paclitaxel	p
N	99	70	
Total patients represented	14,343	7,638	
Rate of all grade neuropathy (%) (median [Q1, Q3])	26.0 [15.8, 40.8]	44.1 [19.3, 59.3]	0.003
Number in the taxane arm (median [Q1, Q3])	63 [41, 188]	60 [42, 113]	0.57
Median age (median [Q1, Q3])	62 [55, 66]	59 [55, 62]	0.02
Percent male (%) (median [Q1, Q3])	67 [0, 86.5]	0 [0, 73.1]	<0.001
Year (median [Q1, Q3])	2008 [2002, 2013]	2005 [2002, 2014]	0.768
Prior taxane exposure (%)			
No	53 (63.9)	38 (65.5)	0.981
Yes	30 (36.1)	20 (34.5)	
Prior platinum exposure (%)			
No	42 (50.0)	28 (46.7)	0.822
Yes	42 (50.0)	32 (53.3)	
Prior chemotherapy exposure (%)			
No	28 (30.4)	10 (14.5)	0.03
Yes	64 (69.6)	59 (85.5)	
Disease (%)			
Breast cancer	26 (26.3)	26 (37.1)	<0.001
Cervical CA	1 (1.0)	0 (0.0)	
Endometrial	2 (2.0)	1 (1.4)	
Gastric cancer	0 (0.0)	2 (2.9)	
GEJ cancer	5 (5.1)	8 (11.4)	
Head and neck	2 (2.0)	3 (4.3)	
Melanoma	2 (2.0)	3 (4.3)	
NHL	0 (0.0)	1 (1.4)	
NSCLC	37 (37.4)	8 (11.4)	
Ovarian	4 (4.0)	14 (20.0)	
Penile	0 (0.0)	1 (1.4)	
Prostate cancer	18 (18.2)	0 (0.0)	
Sarcoma	0 (0.0)	2 (2.9)	
Urothelial cancer	2 (2.0)	1 (1.4)	
Trial phase (%)			
2	37 (38.5)	32 (45.7)	0.443
3	59 (61.5)	38 (54.3)	
Median followup duration (months) (median [Q1, Q3])	18.00 [11.7, 22.0]	16.05 [10.8, 34.0]	0.53
Unit dose (mg/m^2) (median [Q1, Q3])	75.00 [70.00 77.5]	95.00 [80.0, 175.0]	<0.001
Cycle length (months) (median [Q1, Q3])	0.75 [0, 0.75]	0.25 [0, 0.75]	0.557
Median number of cycles (median [Q1, Q3])	4 [3, 6]	6 [4, 8]	0.001
Median cumulative dose (mg/m^2) (median [Q1, Q3])	310.0 [228.5, 499.2]	919.7 [656.5, 1085.4]	<0.001
Dose gap (weeks) (%)			
1	15 (15.2)	38 (54.3)	<0.001
2	3 (3.0)	2 (2.9)	
3	77 (77.8)	30 (42.9)	
4	4 (4.0)	0 (0.0)	

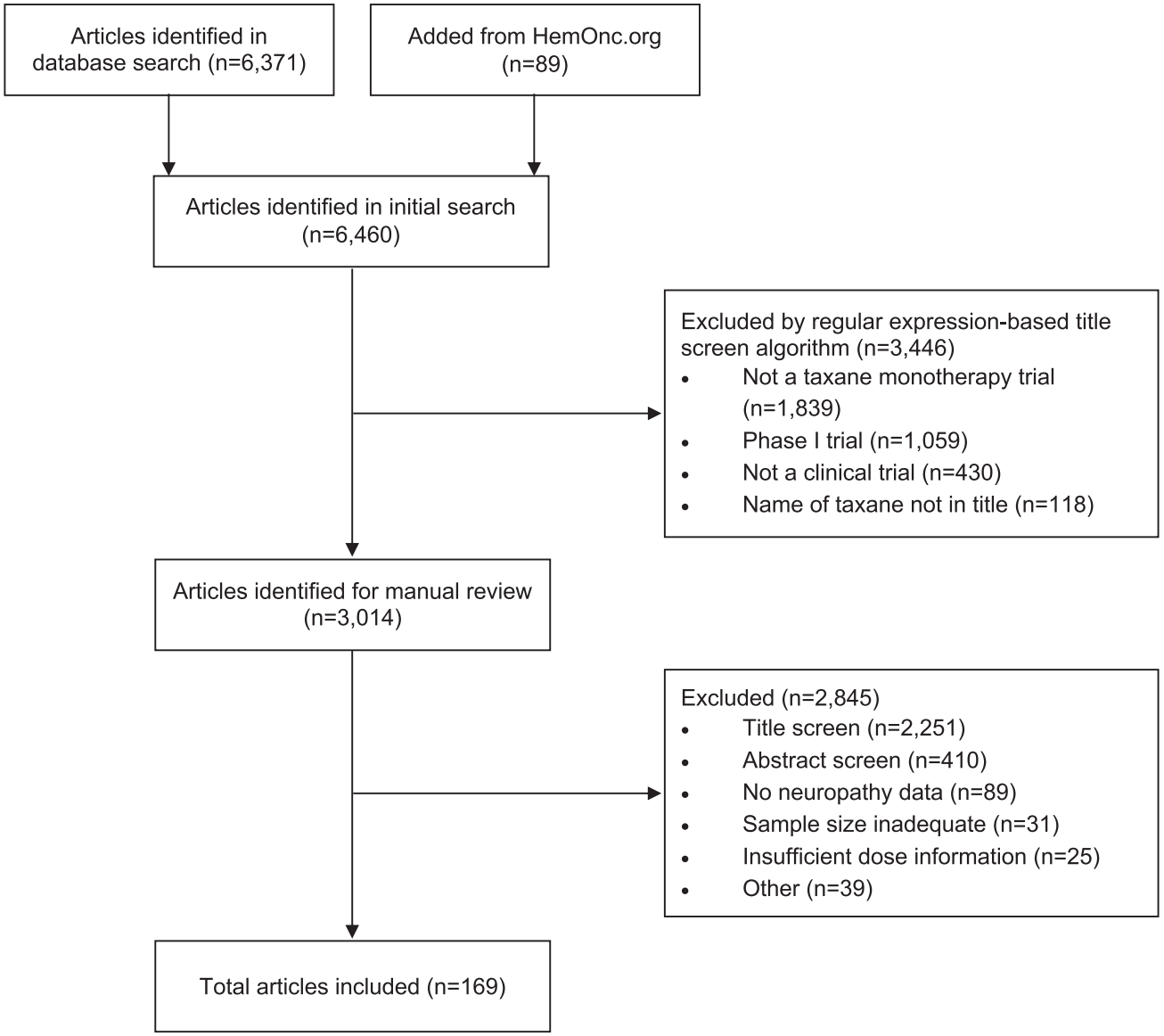

Figure 1. PRISMA flow diagram showing articles included for analysis. See also Tables S1 and S2 for the PRISMA checklists for abstracts and manuscripts

treatment cycle of docetaxel on either side of the median equivalent dose, resulting in guidance with an estimated error of only one cycle when choosing a treatment regimen. In Table 3 there are several examples of equivalent doses as estimated by the model, each chosen to reflect common treatment protocols that may be of interest.

Because of the gender imbalance between our docetaxel and paclitaxel trials, and given that we had equal numbers of studies in breast cancer for each drug (n = 26), comprising roughly 30% of our dataset, we also performed a subgroup analysis of breast cancer trials. We find that the dose-toxo-equivalence curve produced by this subset (seen in Figure 3, in green) is similar to that generated by the complete data (in maroon). The credible intervals are substantially wider because of the reduced sample size (52 total trials as opposed to 169); however, the estimated median equivalence curve is consistent with that produced by our complete dataset, suggesting that the imbalance in sex between the two drugs did not significantly impact the estimation of the toxo-equivalence curve.

Table 2. Mean, standard deviation, and quantile parameter estimates for the final model fit to the taxane data, along with the Gelman-Rubin (G-R) statistics and effective sample size (ESS) from the sampling chain of each parameter

	Mean	SD	2.5%	50%	97.5%	G-R	ESS
β_1	−0.76	0.21	−1.18	−0.76	−0.34	1	5756
β_2	−0.65	0.18	−1.01	−0.65	−0.29	1	12966
β_3	0.58	0.12	0.34	0.58	0.83	1	32211
β_4	0.38	0.10	0.18	0.38	0.58	1	27936
β_5	−0.18	0.08	−0.34	−0.18	−0.02	1	25895
β_6	0.61	0.38	−0.13	0.62	1.35	1	5010
$1/\tau^2$	1.12	0.14	0.86	1.11	1.43	1	40370

DISCUSSION

Taxanes remain among the most ubiquitous drugs used in the treatment of cancer, particularly solid tumors, forming the backbone of widely-used regimens for treating primarily solid tumors. Although often well-tolerated, there are a number of reasons why clinicians may decide to switch between the various taxanes. Breakthrough hypersensitivity reactions do occur; in the event of such a reaction, a clinician may elect to switch between different taxanes, although there is a significant cross-reactivity rate between paclitaxel and docetaxel hypersensitivity reactions (Dizon et al., 2005; Sánchez-Muñoz et al., 2011). Although similar, the toxicity profiles of the various taxanes are not identical; for instance, docetaxel causes higher rates of fluid retention, whereas paclitaxel is associated with higher rates of myalgia and cardiac arrhythmias (Chiu et al., 2017; Verweij et al., 1994). Taxane shortages or selective acquisition by healthcare systems are certainly possible; in either case, substituting one taxane for another may become logistically necessary. Although switching between taxanes is common, there are minimal data guiding clinicians on how to do so in a systematic manner which would result in roughly equivalent toxicity. Although it is conventional to focus on efficacy and effectiveness, toxicity is a primary driver of tolerability and treatment discontinuation because of toxic effects such as CIPN is distressingly frequent, especially for patients with advanced or metastatic disease, many of whom choose to focus on maximization of quality of life rather than necessarily extension of life (Ezendam et al., 2014; Mols et al., 2014).

We applied a Bayesian meta-analytic approach to generate a toxo-equivalence model between paclitaxel and docetaxel using observed rates of CIPN on systematically identified trials of paclitaxel and docetaxel monotherapy. This novel approach differs from standard meta-analytical approaches because of the nature of the outcome of interest, rate of CIPN, which is a summary measure of a single arm as opposed to an odds ratio or risk difference between two groups within the same trial. This distinction precluded the use of standard assessment of bias tools, which are designed for use with treatment effect estimates. Future

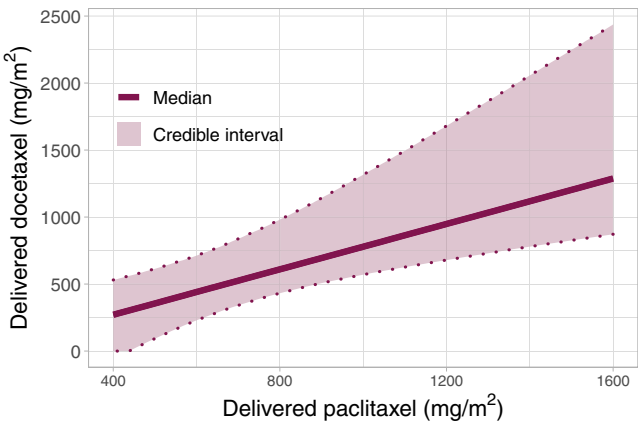

Figure 2. Estimated median dose equivalence relationship and 95% credible intervals for paclitaxel and docetaxel

Table 3. Sample dose-toxo-equivalences for different common clinical scenarios

Clinical scenario	Initial taxane cumulative dose	Median toxo-equivalent alternate taxane dose	LB toxo-equivalent alternate taxane dose	UB toxo-equivalent alternate taxane dose
Adjuvant breast cancer	Paclitaxel 960 mg/m^2	Docetaxel 743 mg/m^2	Docetaxel 543 mg/m^2	Docetaxel 1222 mg/m^2
Metastatic castrate-resistant prostate cancer	Docetaxel 750 mg/m^2	Paclitaxel 968 mg/m^2	Paclitaxel 642 mg/m^2	Paclitaxel 1345 mg/m^2

methodological work could be undertaken to assess the possible impacts of publication or other types of bias on the robustness of this approach. The posterior parameter samples from our Bayesian hierarchical fit are used to produce median and 95% credible intervals around the toxo-equivalent doses across a range of potential cumulative taxane exposures. With the resulting equivalence curve for a given dose of paclitaxel, a median estimate and credible range can be obtained for the toxo-equivalent dose of docetaxel and vice versa. This model can be applied in the case of switching between different taxane agents to identify a range of potentially equivalent exposures. For example, a typical adjuvant regimen for breast cancer includes a phase of paclitaxel monotherapy at 80 mg/m^2 administered in 12 weekly doses, amounting to a cumulative paclitaxel exposure of 960 mg/m^2. The lower bound on the dose-equivalence for docetaxel is 543 mg/m^2; this corresponds to roughly 7 cycles of docetaxel at a typical dose of 75 mg/m^2 every 21 days. Therefore, one can be reasonably confident that substituting paclitaxel with docetaxel in such a scenario would be unlikely to result in an increased risk of CIPN compared to the original regimen. However, it is important to consider the relative efficacy of a dose guided by this 95% credible interval as compared to the original dose of paclitaxel and to balance desired efficacy with the resultant risk of CIPN.

The meta-analytic component of this study contradicts some previously reported findings. The rate of peripheral neuropathy is often assumed by practicing clinicians to be higher with docetaxel compared to paclitaxel on the basis of a randomized trial comparing paclitaxel 175 mg/m^2 every 21 days to docetaxel 100 mg/m^2 every 21 days in the treatment of metastatic breast cancer (Jones et al., 2005). In this trial, the rates of grade 3 or higher CIPN and treatment discontinuation because of CIPN and motor neuropathy were higher on the docetaxel arm than the paclitaxel arm (Jones et al., 2005). By contrast, this study demonstrates that relatively higher levels of docetaxel exposure results in toxo-equivalent rates of CIPN when compared to paclitaxel. As an example, a typical adjuvant dose of docetaxel in the adjuvant therapy of breast cancer is cumulatively 300 mg/m^2 (75 mg/m^2 every 21 days for four cycles). Although the range of

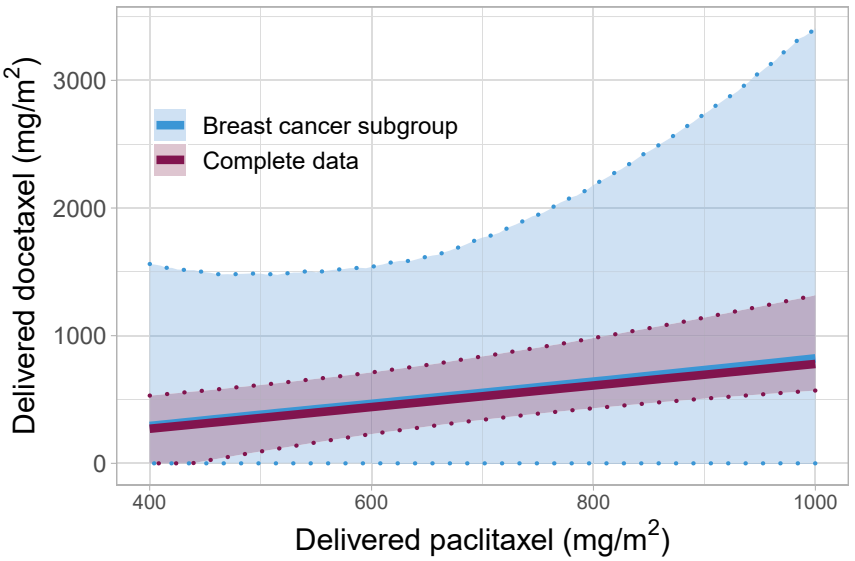

Figure 3. Estimated median dose equivalence relationship and 95% credible intervals for paclitaxel and docetaxel, comparing the results from a breast cancer subgroup study to those obtained using all 169 included trials

possible toxo-equivalences is wide between 2 and 3 cycles of the typical adjuvant dose, the median toxo-equivalent dose to this is 450 mg/m^2 of paclitaxel. This suggests that paclitaxel may be associated with higher rates of all-grade peripheral neuropathy than docetaxel, although additional data would be needed to confirm this. In addition, a strong correlation between various schedules of taxane (identified by the "dose gap") was not identified. This contradicts the results of some prospective trials, which demonstrate relatively lower rates of CIPN with weekly taxane schedules (Green et al., 2005). This suggests that it is possible that greater taxane exposure associated with regimens involving taxane administration every 21 days, as opposed to the schedule, is the cause of increased CIPN rates seen with those regimens.

The model applied here represents a systematic framework for switching between paclitaxel and docetaxel, which could potentially be used in a variety of clinical scenarios, including not only medication switching in clinical practice but also in the design of clinical trials where drug substitutions may need to be considered for various reasons during the study. Although this approach was developed with simulated individual patient-level data in the full methods work, an extension of this work with real-world individual patient-level data is needed for further validation and examination of efficacy.

Limitations of the study

This study has a number of limitations. Severe CIPN (CTCAE grade 3 or higher) often leads to chemotherapy discontinuation and is more clinically relevant than all-grade CIPN. Because of relatively lower rates of severe CIPN on virtually all of the included trials, it was not feasible to fit a model based on the more clinically relevant outcome; real-world data might clarify whether this is because of underreporting (Song et al., 2017). Because of much lower rates of hypersensitivity reactions with nab-paclitaxel, switching between either paclitaxel or docetaxel and this agent is often desirable and constructing a toxo-equivalence model with nab-paclitaxel would be very clinically relevant. Unfortunately, there are few trials of nab-paclitaxel monotherapy suitable for inclusion in this analysis to develop such a model. Although informative at the margins, there is a relatively wide confidence interval on the potential toxo-equivalent doses of paclitaxel and docetaxel, meaning that the potential range of toxo-equivalent doses of one taxane with respect to another is very wide. As the primary focus of this study was developing a toxo-equivalence model, it was appropriate to include trials evaluating taxanes in patients with a number of different cancer subtypes; this did limit our ability to develop such a companion model designed around efficacy, which would be clinically relevant. Because of the heterogeneity of data reporting in the included studies, adjusting for relevant patient-level characteristics known to be risk factors for CIPN, such as diabetes, was not feasible, and it may be that significant amounts of variation in CIPN seen on various trials relates to comorbidities and not the doses of taxanes used in and of themselves. Finally, taxanes are often used in combination in clinical practice (e.g., as a component of a platinum doublet as described above in the ovarian cancer example, or in the TCHP regimen for HER2+ breast cancer). Rates of CIPN may be different in these circumstances, especially when other regimen components are known to cause CIPN as well. Some modification of our approach may be needed in this case, particularly with respect to potential interactions between components of the regimen.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- RESOURCE AVAILABILITY
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  - Materials availability
  - Data and code availability
- METHOD DETAILS
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  - Data extraction and quality assessment
- QUANTIFICATION AND STATISTICAL ANALYSIS
  - Statistical methods

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2022.104045.

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AUTHOR CONTRIBUTIONS

Conceptualization, S.M.R. and J.L.W.; Methodology, S.M.R., P.D.W., J.L.W., Q.C., and E.A.S.; Validation, D.R.R.; Formal Analysis, E.A.S. and Q.C.; Investigation, S.M.R., P.D.W., and J.L.W.; Data Curation, S.M.R. and S.C.; Writing – Original Draft, E.A.S. and S.M.R.; Writing – Review & Editing, E.A.S., S.M.R., S.C., D.R.R., P.D.W., Q.C., and J.L.W.; Visualization, E.A.S.; Supervision, J.L.W. and Q.C.

DECLARATION OF INTERESTS

S.M.R. reports acting in an advisory role for Roche, Sanofi, EUSA pharma, and Janssen. J.L.W. reports funding from AACR; consulting fees from Roche, Westat, MelaxTech, and Flatiron Health; other from HemOnc.org LLC (ownership), outside the submitted work. All remaining authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Trial identifiers, raw extracted data, and calculated values	This manuscript; Harvard Dataverse	https://doi.org/10.7910/DVN/6BNWHE
Software and algorithms		
R software	R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.	R version 4.0.5; RRID: SCR_001905
R Analysis script	This manuscript; Harvard Dataverse	https://doi.org/10.7910/DVN/6BNWHE
R2jags software package	Su and Yajima, (2020). R2jags: Using R to Run 'JAGS'. R package version 0.6-1. https://CRAN.R-project.org/package=R2jags	R package version 0.6-1

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Jeremy Warner (jeremy.warner@vumc.org).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Trial identifiers, raw extracted data, and calculated values pertaining to our analysis have been deposited at Harvard Dataverse: https://doi.org/10.7910/DVN/6BNWHE and are publicly available as of the date of publication. The DOI is also listed in the key resources table.
- All original code has been deposited at Harvard Dataverse: https://doi.org/10.7910/DVN/6BNWHE and is publicly available as of the date of publication. The DOI is also listed in the key resources table.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

METHOD DETAILS

Study selection

In order to reduce potential confounding from concomitant chemotherapeutics, we restricted our analysis to studies of single-agent docetaxel or single-agent paclitaxel, including sequential administration (monotherapy). Online biomedical literature databases were searched by using a combination of keywords and subject headings. A pilot search string was created in PubMed. Initial results were discussed by a biomedical librarian (PW) and primary investigators (JW, SR). The revised search strategy was performed in Medline (PubMed) and EMBASE (Ovid SP) in May 2019. The following terms and their respective subject headings were combined when searching each database: neoplasms, cancer, tumors, tumours, malignant neoplasms, docetaxel, paclitaxel, monotherapy, single agent. A separate search was performed within the HemOnc ontology, which is derived from the HemOnc.org wiki of chemotherapy regimens (Warner et al., 2015, 2019). Search results were filtered to published manuscripts on monotherapy studies or a monotherapy compared to combination therapy. Results were further limited to clinical trial, controlled clinical trial, randomized controlled trial, prospective studies, multicenter study, phase 2 clinical trials, phase 3 clinical trials, and English language. Conference abstracts/proceedings and retrospective studies were excluded. The bibliographies of selected articles were further screened for potential studies.

Following the initial search, the abstracts and titles were manually reviewed to identify trials appropriate for inclusion in the study. Randomized or non-randomized clinical trials enrolling cancer patients aged ≥18 years taking paclitaxel or docetaxel monotherapy that reported sufficient data to compute the median cumulative dose of taxane exposure and all-grade rate of CIPN graded per the National Cancer Institute Common Terminology and Criteria for Adverse Event (CTCAE) schema were included. Of note, some clinical trials report by alternate methodologies, necessitating a procedure for remapping neuropathy grading. In general, the Eastern Cooperative Oncology Group (ECOG) and World Health Organization (WHO) systems have a lower threshold to classify CIPN as higher grade than the CTCAE system. ECOG neuropathy scale grades absent deep tendon reflexes as grade 2 CIPN, whereas the CTCAE system grades absent deep tendon reflexes as grade 1 CIPN. Both ECOG and WHO neuropathy grading systems classify severe paresthesias as grade 2 CIPN, whereas the CTCAE system grades "paresthesias interfering with activities of daily living as grade 3 CIPN". As such, grade 2 CIPN according to the ECOG and WHO scales was remapped to grade 3 CIPN.

Exclusion criteria included trials in HIV patients or central nervous system tumors (which are commonly associated with neurologic dysfunction and therefore for which neuropathy due to disease may be difficult to distinguish from CIPN), phase 1 trials, trials enrolling fewer than 30 participants, and trials other than primary clinical trials. These exclusion criteria were implemented to reduce the potential for bias in the included results, particularly since the outcome of interest in this study, rate of all-grade neuropathy, does not fit the definition of standard risk of bias assessment tools, which are intended for treatment effect estimates.

Data extraction and quality assessment

Once the candidate trials were identified, data was extracted in duplicate by two independent reviewers (SC and SR) using a standard protocol and data collection form. Disagreements were resolved by discussion with a third investigator (JW). Summary data extracted from the taxane arm(s) of each eligible trial included median age, sex proportions, drug name, phase of clinical trial, publication year, cancer type, overall occurrence of all grade peripheral neuropathy, and measures of chemotherapy exposure such as median cumulative taxane dose, median or relative dose intensity, number of cycles, cycle length, time gap between two consecutive doses of a chemotherapy cycle, unit dose and dose per cycle. For trials not directly reporting the median cumulative taxane dose, we calculated median delivered taxane by multiplying the unit dose, the number of doses per cycle, the median doses per cycle, and the median percentage of planned dose intensity received. Where the percentage of planned intensity received was not provided, the median for each particular taxane was used instead. No individual patient-level data was obtained for this study.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical methods

Summaries of metadata from all eligible trials were generated, stratified by taxane type. Continuous variables, including publication year, median cumulative taxane dose, number in the taxane arm, time gap between consecutive doses, rates of all-grade neuropathy, and median age were summarized as median and interquartile range and compared using the Kruskal-Wallis test. Categorical variables, including sex, cancer type, and phase of clinical trial were summarized as frequencies and counts.

To approximate the dose-equivalence relationship, a new approach had to be developed due to an unmet methodological need in the field of dose-equivalence studies. This approach leverages readily available information from published clinical trials to fit a Bayesian hierarchical model of neuropathy rate by trial as a function of drug type, cumulative dose, and potential other trial-level characteristics. Bayesian hierarchical models are a set of general methods for estimating the parameters of a posterior distribution while accounting for uncertainty at multiple levels of the observed data (Gelman et al., 2013; Lesaffre and Lawson, 2012). Working within this Bayesian framework provides a straightforward way of quantifying the uncertainty of the estimated dose toxo-equivalence relationship by leveraging the estimated posterior sample distributions; additionally, the hierarchical structure of the model accounts for both within- and between-study variability. Further details on the development and evaluation of this method can be found in our related methods paper (Sigworth, Rubinstein, Warner, Chen, and Chen, 2022, submitted manuscript), but here we describe the modeling steps undertaken in this specific application.

The outcome of interest in the Bayesian hierarchical model is the rate of all-grade neuropathy observed in trial i, denoted Π_i, which is converted to $Y_i = logit(\Pi_i)$. The necessary independent variables needed for the model fit are drug type, coded as indicators $X_{iD} = I(drug_i = docetaxel)$ and $X_{iP} = I(drug_i = paclitaxel)$, and normalized median cumulative dose d_i. The continuous variable of median age, age_i, is normalized to mean 0 and standard deviation 1 to improve model performance, and dose gap dg_i, coded in fractions of four weeks, is left untransformed. Median age was selected for inclusion due to advanced age being associated with worse CIPN outcomes (Adjei et al., 2021), while dose gap was included based on a previous study that found weekly dosing was associated with higher rates of neuropathy among paclitaxel patients (Sparano et al., 2008). Due to their clinical relevance, we believe it is possible these variables can explain heterogenicity in neuropathy outcomes beyond the association with cumulative dose.

Several transformations of median cumulative dose prior to normalization, D_i, were considered, specifically $\sqrt{D_i}$, $\ln(D_i)$, and a Box-Cox transformation with $\lambda = 0.22$ (chosen to maximize the objective function). Additionally, multiple model specifications were considered: with and without the inclusion of dg_i and age_i, and the inclusion of a random slope allowing the dose-response relationship to vary by trial (considered in models both with and without additional covariates). These model specifications were compared by first fitting each candidate model with a burn-in of 15,000 samples and then drawing 500,000 samples with a thinning interval of 50, across four independent chains. The penalized deviance information criterion (DIC) of each candidate model was then calculated and used to select the final model specification.

All candidate models had similar penalized DIC values, between 206 and 208, but the lowest overall was the fit with additional covariates, no random slope, and no transformation of dose D_i prior to normalization. Thus, median cumulative dose was normalized to mean 0 and standard deviation 1, with the resulting normalized doses of paclitaxel and docetaxel denoted d_{iP} and d_{iD} respectively.

The final model fit to the collected trial meta-data was $Y_i|\mu_i, \boldsymbol{\beta}, \mathbf{X_i} \sim \mathbf{N}(\psi_i, S_i^2)$, where $\mathbf{X_i}$ represents the data for trial i, S_i^2 is the variance of the logit, Y_i, and

$$\psi_i = \mu_i + \beta_1 + \beta_2 X_{iD} + \beta_3 X_{iP} d_{iP} + \beta_4 X_{iD} d_{iD} + \beta_5 age_i + \beta_6 dg_i. \quad \text{(Equation 1)}$$

A noninformative prior of $\mu_i|\tau^2 \sim N(0, \tau^2)$ was set for the random intercept μ_i, where τ^2 represents the level of between-trial variance with $\tau \sim InvGamma(0.001, 0.001)$. For the remaining $\boldsymbol{\beta}$ parameters, a noninformative prior of $\boldsymbol{\beta} \sim MVN(0, 10^6 diag(1))$ was set.

In interpreting this model, β_1 and β_2 are measures of the baseline effect of drug type on rate the log-odds of neuropathy. The slope terms of β_3 and β_4 represent the dose effect of 1 normalized unit of paclitaxel and docetaxel, respectively. The additional parameters β_5 and β_6 estimate the effect of one unit increases in normalized median age or dose gap (representing a 4 weeks increase in gap between doses). Finally, the random intercept μ_i measures the contribution to the log-odds of neuropathy from natural variation between trials.

Model fit and convergence was assessed based on the Gelman-Rubin statistic, autocorrelation plots, and effective sample sizes. Parameters were summarized as means and standard deviations as well as by quantiles of the posterior distributions. The posterior samples for $\boldsymbol{\beta}$ from these chains were used to estimate the equivalence relationship based on the calculation detailed in our related methods paper. In this case, the equivalence relationship for a given dose D_P of paclitaxel to D_D of docetaxel, in mg/m^2, is

$$D_D = \frac{\beta_3\left(\frac{D_P - \overline{D_P}}{sd_P}\right) - \beta_2 + \beta_4 \frac{\overline{D_D}}{sd_D}}{\beta_4 / sd_D} \quad \text{(Equation 2)}$$

where $\overline{D_P}$ is the mean cumulative dose of paclitaxel, $\overline{D_D}$ is the mean cumulative dose of docetaxel, and sd_P and sd_D are the scaling values for paclitaxel and docetaxel respectively. This equivalence is calculated for all posterior samples of $\boldsymbol{\beta}$ and a range of candidate median cumulative dose values of paclitaxel $D_P \in (400, 1600)$ in mg/m^2. Across the range of D_P doses, equivalent D_D doses are summarized into median and 95% credible intervals, which are then plotted.

Due to the sex imbalance between our included docetaxel and paclitaxel trials (with a median 67% male in docetaxel and 0% male in paclitaxel), we performed a subgroup analysis of breast cancer trials, which are all 0% male and are equally represented within our data for the two drugs of interest (n = 26 trials in each). Our subgroup model was fit with the same specifications as our full analysis, and equivalence was calculated as in Equation (2) but with the subgroup specific estimated coefficients. The results of this subgroup analysis were reported in the form of an additional equivalence curve and compared against the curve generated by our full analysis.

All analyses were performed using R version 4.0.5 (R Core Team, 2021), with model sampling performed using the R2jags package version 0.6–1 (Su and Yajima, 2020).