Clopidogrel–Paclitaxel Drug–Drug Interaction: A Pharmacoepidemiologic Study

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Paclitaxel is mainly eliminated by CYP2C8 in the liver. CYP2C8 is strongly inhibited by the clopidogrel metabolite acyl-β-D-glucuronide. To determine if this interaction has clinical relevance, we identified 48 patients treated with clopidogrel and paclitaxel using databases and a prescription register. Peripheral sensory neuropathy was retrospectively evaluated from medical charts and compared to that of 88 age- and sex-matched controls treated with paclitaxel and low-dose aspirin. By a cumulative dose of 1,500 mg paclitaxel, 35% of the patients had developed severe neuropathy. The overall hazard ratio between clopidogrel use and severe paclitaxel neuropathy was 1.7 (95% confidence interval, 0.9–3.0). Among those receiving a high-dose paclitaxel regimen, the hazard ratio was 2.3 (95% confidence interval, 1.1–4.5). Our study indicates that clopidogrel is associated with a clinically relevant increased risk of neuropathy in patients treated with high-dose paclitaxel.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ *In vitro* evidence and case studies indicate that a drug–drug interaction might exist between paclitaxel and clopidogrel, mediated through inhibition of CYP2C8 by the metabolite clopidogrel acyl-β-D-glucuronide.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The study investigated whether concurrent clopidogrel and paclitaxel use is associated with increased risk of paclitaxel toxicity.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ This study demonstrates an ~2-fold increased risk of severe peripheral sensory neuropathy associated with concomitant use of clopidogrel in cancer patients treated with paclitaxel in doses of 135 mg/m^2 or greater.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ This interaction needs to be considered when planning paclitaxel chemotherapy in patients treated with clopidogrel.

Paclitaxel is a chemotherapeutic agent effective in the treatment of ovarian, breast, and lung cancer.[1–3] As with other chemotherapeutics, severe adverse reactions such as peripheral sensory neuropathy and neutropenia are frequent.[3–5] Paclitaxel area under the curve (AUC) and time above total concentrations of 0.05 μmol/L (T>0.05) have been associated with development of neutropenia and neuropathy.[6–9] Paclitaxel is typically administered every third week or weekly, in doses normalized to body surface area ranging from 80 up to 260 mg/m^2.[10] Despite the dose normalization, the interindividual variability in severity of paclitaxel toxicity is considerable.[11] This variability is generally attributed to a plethora of host, environmental, and genetic factors.[9,12,13] A host factor influencing paclitaxel toxicity was indirectly suggested recently by Tornio *et al*.,[14] who demonstrated that glucuronidation converts clopidogrel to a strong inhibitor of the metabolism of the antidiabetic agent repaglinide. Experiments *in vitro* showed that the perpetrator was clopidogrel acyl-β-D-glucuronide, which strongly inhibits the liver enzyme CYP2C8, which is the enzyme mainly responsible for repaglinide metabolism. In healthy volunteers, clopidogrel increased the repaglinide area under the concentration time curve (AUC) by up to 5 times. Tornio *et al*. also carried out *in silico* simulations that showed that clopidogrel acyl-β-D-glucuronide fits the active site of CYP2C8, thus further implying CYP2C8 involvement.[14] The principal route of paclitaxel elimination is 6α-hydroxylation catalyzed by CYP2C8.[15] Use of clopidogrel might thus increase paclitaxel AUC and thereby possibly also increase the risk and severity of paclitaxel toxicity. We recently published a case report on a 60-year-old woman with ovarian cancer who was

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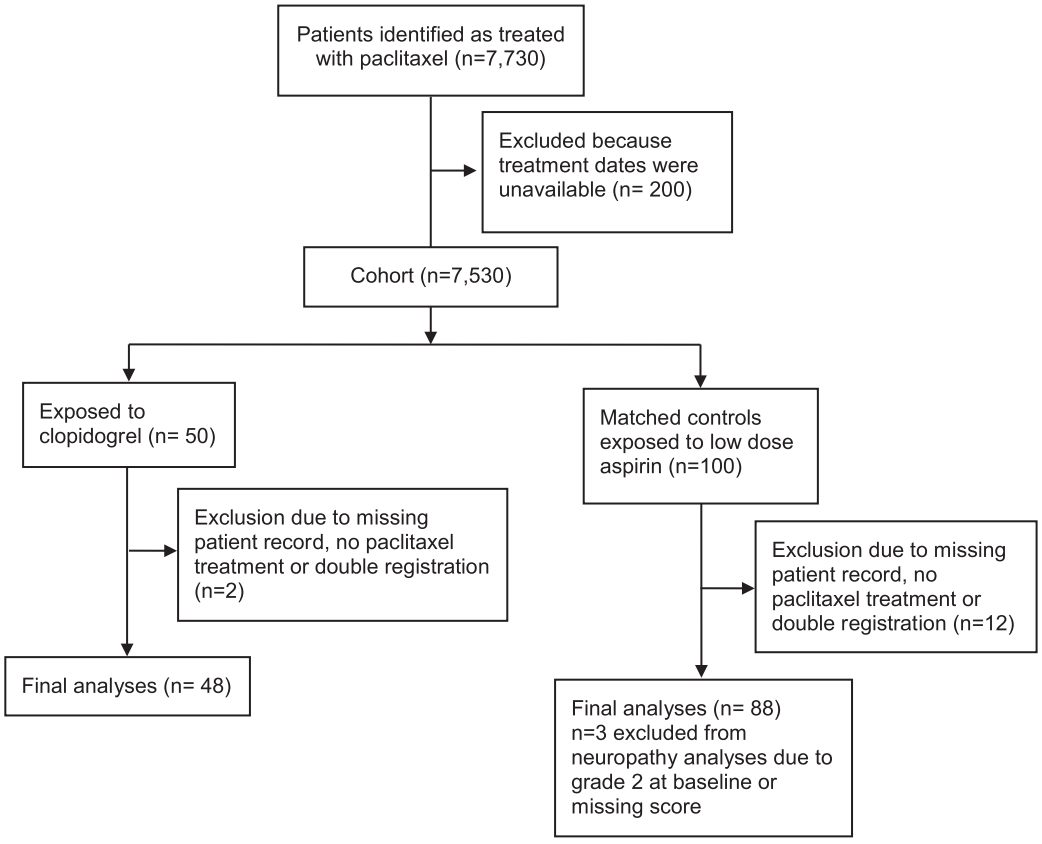

Figure 1 CONSORT diagram.

treated with both clopidogrel and paclitaxel. She was hospitalized three times during her paclitaxel treatment due to nausea and vomiting, and her treatment was discontinued after only four cycles because of severe neuropathy.[16] In addition, we reported the results of an *in vitro* experiment showing that clopidogrel acyl-β-D-glucuronide at clinically relevant concentrations inhibits the depletion rate of paclitaxel and the formation of 6α-hydroxylation of paclitaxel in human liver microsomes by 51% and 77%, respectively.[16]

The primary aim of this study was to investigate—in a controlled design—whether cotreatment with clopidogrel increases the risk of paclitaxel-induced peripheral sensory neuropathy. The secondary aim was to examine the occurrence of other paclitaxel-related toxicities, including neutrophil depression, nausea and vomiting, and paclitaxel compliance.

RESULTS

Patients

A total of 7,730 patients treated with paclitaxel were identified across seven hospitals. No patients from Herning Hospital were eligible for inclusion because treatment dates were not available for any of the 200 patients identified at the site. Of the 7,530 remaining patients, 50 patients (0.6%) were identified as having an active clopidogrel prescription at the time of the first course of paclitaxel. These 50 patients and 100 matched users of low-dose aspirin were included in the final stage with review of individual medical charts. In 14 cases the medical charts were unavailable, paclitaxel was discontinued before the first dose, or the patient was included twice due to treatment at different hospitals. The final population eligible for analysis thus included 48 patients exposed to clopidogrel and 88 matched patients using low-dose aspirin (**Figure 1**). Patient characteristics are shown in **Table 1**.

Clopidogrel–paclitaxel interaction

Peripheral sensory neuropathy Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or worse developed in 47 of 133 (35%) patients; data were missing for one patient and two patients had grade 2 at baseline, and were excluded from the dose-to-neuropathy analyses. Clopidogrel use was associated with an overall increased risk of neuropathy with a crude hazard ratio of 1.7 (95% confidence interval (CI), 0.9–3.0). This increased to 2.0 (95% CI, 1.0–3.9) for high-dose paclitaxel users and further to 2.3 (95% CI, 1.1–4.5) after additional stratification and adjustments (**Table 2**, **Figure 2**). Nausea/vomiting grade 3 was registered in 13 of 136 (10%) of all patients. The crude hazard ratio of developing nausea/vomiting was 1.5 (95% CI, 0.5–5.0) in clopidogrel-exposed patients. Noncompliance was registered in 79 of 136 patients (58%). The crude hazard ratio of noncompliance (composite endpoint) was 1.3 (95% CI, 0.8–2.0) in clopidogrel-exposed patients. Febrile neutropenia grade 3 was registered in 10 of 136 patients (7%). The crude hazard ratio of developing febrile neutropenia was 1.9 (95% CI, 0.5–6.4) in clopidogrel-exposed patients. Hazard ratios for developing other toxicities are shown in **Supplementary Table S1**. Median

Table 1 Cancer patients treated with paclitaxel

	Clopidogrel	Aspirin (controls)
Number of patients	48	88
Age (years, median interquartile range (IQR))	66 (61-74)	67 (60-73)
Male sex (*n*)	12 (25%)	20 (23%)
Body surface area (m^2, median IQR)	1.80 (1.70-1.94)	1.77 (1.65-1.88)
Performance status (Eastern Cooperative Oncology Group) (*n*)		
0	19 (40%)	31 (35%)
1	17 (35%)	35 (40%)
2+	12 (25%)	22 (25%)
Cancer diagnosis (*n*)		
Ovarian or peritoneal cancer	5 (10%)	15 (17.0%)
Breast cancer	17 (35%)	26 (30%)
Other malignancy	26 (54%)	47 (53%)
Cancer treatment (*n*)		
Previous chemotherapy	10 (21%)	21 (24%)
Concurrent chemotherapy	39 (81%)	72 (82%)
Miscellaneous conditions (*n*)		
Patients with alcohol consumption below 14 and 21 drinks per week for females and males, respectively (*n*)	31 (65%)	63 (72%)
Patients with a prescription within ATC group A10 (diabetes medication)	7 (15%)	17 (19%)

(10^{th};90^{th} percentile) absolute nadir counts were $3.3*10^9$/L (1.4;7.3) and $1.45*10^9$/L (0.25;5.5) for leukocytes and neutrophils, respectively. Nadirs of both leukocytes and neutrophils were statistically significantly lower in the clopidogrel group (Wilcoxon Rank sum test), but only for the paclitaxel low-dose patients (**Figure 3**).

DISCUSSION

This study is the first to demonstrate a clinically relevant drug–drug interaction between clopidogrel and paclitaxel. We specifically investigated whether or not the clopidogrel–paclitaxel drug–drug interaction recently shown *in vitro* and substantiated in a case report was detectable in a clinical setting and of clinical significance. Accrual of patients with active clopidogrel prescriptions was lower than expected, limiting the statistical precision; however, for patients treated with paclitaxel in doses of 135 mg/m^2 or greater the data indicate an ~2-fold increased risk of patients developing neuropathy grade 2 or higher when using clopidogrel. Importantly, with crude hazard ratios of neuropathy of 1.1 (95% CI, 0.3–4.1) and 2.0 (95% CI, 1.0–3.9) for low-dose and high-dose paclitaxel, respectively, paclitaxel dose appear to be important for manifesting the interaction.

The underlying mechanism for this drug–drug interaction seems to be based on the fact that ingested clopidogrel is converted to clopidogrel acyl-β-D-glucuronide, which directly interacts with the CYP2C8 enzyme in the liver and other tissues. This interaction transiently reduces the CYP2C8 hydroxylation of paclitaxel to 6α-hydroxypaclitaxel. The effect is likely to wane as the clopidogrel acyl-β-D-glucuronide is eliminated with time. The half-life of both clopidogrel and the acyl-β-D-glucuronide metabolite is ~3 h.[14] The half-life of paclitaxel is dose/infusion-time-dependent. For the common regimen of 175 mg/m^2 paclitaxel infused over 3 h, data indicate that concentrations after 12 h are expected to be below 5% of peak values.[12] At least for this regimen, the implication is that clopidogrel and paclitaxel administered within 1–3 h of each other will have the greatest impact, whereas 10–12 h separation, e.g., taking clopidogrel in the evening and having paclitaxel infusion before noon, would be expected to significantly attenuate the effect. In the present study we had no records of when patients ingested clopidogrel and had their paclitaxel infusion, but it seems reasonable to assume that for most of the patients both would be administered before noon, in an ambulant hospital stay, or taken with breakfast. Another limitation is the retrospective and unblinded design. Investigators were specifically asked not to seek out information about clopidogrel and aspirin status when filling in the case record forms and to declare for each case if they had prior or acquired knowledge about the patient's clopidogrel status. In 28 of 136 patients (21%), the investigator declared that he or she knew if the patient was exposed to clopidogrel or not. As expected, this knowledge was more frequent in the clopidogrel group. However, among these 28 patients neuropathy grade 2 or greater occurred more frequently in the control group (8 of 13, 67%) than in the clopidogrel group (4 of 15, 33%). As such, this does not seem to have biased our findings towards a positive association. The study involved all major oncology departments in Denmark. However, some of the participating centers could not identify all patients treated with paclitaxel from the entire study period. We are of the opinion that additional effort in including more patients would only have been feasible by extending the study to include other countries.

While this study is the first controlled study of the clopidogrel–paclitaxel drug–drug interaction in a clinical setting, the case report published in 2016 also prompted at least one other publication on the subject. Shinoda *et al.*[17] were able to retrospectively identify eight patients in which clopidogrel and paclitaxel were used in combination. They found that grade 3 neutropenia occurred in all cases (100%), febrile neutropenia in four cases (50%), and that paclitaxel discontinuation was required in four cases (50%). However, no control group was included. At this stage, all published observations, including *in vivo* and *in vitro* data, thus unequivocally point in the same direction. This fact and the relatively simple and plausible mechanism of interaction strongly suggest that the interaction is real. Formal *in vivo* pharmacokinetic data are lacking, but with the current results such studies would need to be designed very carefully to be considered ethical, e.g.,

Table 2 Cox regression hazard ratios (95% confidence intervals) of developing peripheral sensory neuropathy grade 2 or worse over accumulated paclitaxel dose[a]

	Events in clopidogrel group	Events in aspirin group	Unadjusted	Full stratification and adjustment[b]	Test of interaction (*P*-value)
Overall	42% (20/48)	31% (27/86)	1.7 (0.9-3.0)	1.7 (0.9-3.2)	
Paclitaxel dose					
Low dose (<135 mg/m^2)	29% (4/14)	29% (6/21)	1.1 (0.3-4.1)	0.7 (0.2-2.9)	
High dose (≥135 mg/m^2)	47% (16/34)	32% (21/65)	2.0 (1.0-3.9)	2.3 (1.1-4.5)	$P = 0.19$
Sex					
Males	25% (3/12)	17% (3/18)	2.0 (0.3-11.7)	1.2 (0.1-11.4)	
Females	47% (17/36)	35% (24/68)	1.8 (1.0-3.4)	1.7 (0.9-3.4)	$P = 0.69$
Age					
<65	33% (7/21)	29% (9/31)	1.3 (0.5-3.4)	1.6 (0.5-4.7)	
≥65	48% (13/27)	33% (18/55)	2.1 (1.0-4.4)	1.8 (0.8-4.0)	$P = 0.59$
Performance status (Eastern Cooperative Oncology Group)					
0	53% (10/19)	39% (12/31)	2.2 (0.9-5.3)	2.8 (1.1-6.9)	
1	41% (7/17)	33% (11/33)	1.4 (0.5-3.6)	1.0 (0.3-3.2)	$P = 0.62$
2	25% (3/12)	18% (4/22)	1.4 (0.3-6.4)	2.6 (0.2-29.4)	$P = 0.74$
Concomitant chemo					
No	33% (3/9)	25% (4/16)	1.6 (0.3-7.3)	0.9 (0.2-5.3)	
Yes	44% (17/39)	33% (23/70)	1.8 (0.9-3.3)	1.9 (1.0-3.6)	$P = 0.50$
Previous chemotherapy					
1st line	41% (15/37)	34% (22/65)	1.7 (0.9-3.3)	2.0 (1.0-4.0)	
2nd line or greater	40% (4/10)	25% (5/20)	1.4 (0.4-5.1)	1.5 (0.4-6.1)	$P = 0.44$
Miscellaneous conditions					
Patients with alcohol consumption below recommended limit	35% (11/31)	29% (18/62)	1.4 (0.6-3.0)	1.8 (0.8-4.4)	
Patients with alcohol consumption above recommended limit	50% (3/6)	0% (0/1)	—	—	—
Patients without prescriptions within ATC group A10 (diabetes medication)	44% (18/41)	30% (21/70)	1.8 (1.0-3.5)	1.8 (0.9-3.5)	
Patients with prescription within ATC group A10 (diabetes medication)	29% (2/7)	38% (6/16)	0.9 (0.2-4.8)	1.2 (0.1-13.9)	$P = 0.63$

[a]Data were censored at 1,500 mg accumulated paclitaxel dose. [b]Stratified for paclitaxel dose, concurrent chemotherapy, sex, treatment line, and adjusted for performance status and cancer diagnosis.

only enrolling patients on low-dose paclitaxel using clopidogrel and only for a single paclitaxel cycle.

In conclusion, we provide additional evidence of a drug interaction between clopidogrel (through clopidogrel acyl-β-D-glucuronide) and paclitaxel, and that this interaction is of clinical significance.

METHODS

The study is a register-based cohort study with review of patient medical charts. Patient diagnoses, demographical characteristics, and chemotherapy toxicity data were collected on cancer patients treated with paclitaxel from January 1st 2004 to July 31st 2015. Data sources included the Danish National Database of Reimbursed Prescriptions (DNDRP),[18] and individual patient medical charts. The purpose was to compare development of paclitaxel toxicity in patients using clopidogrel (exposed) to those using low-dose aspirin (unexposed). The study was approved by the Danish Data Protection Agency, Region Syddanmark (J. no.: 2008-58-0035) and the Danish Health Authority (J. no.: 3-3013-1238/1/). Approval from the Scientific Ethical Committee was not required.

Data sources

DNDRP contains data on all prescription drugs dispensed to Danish citizens since 2004. The data include the type of drug, date of dispensing, and quantity. The dosing information and the indication for prescribing are not available. Drugs are categorized according to the Anatomic

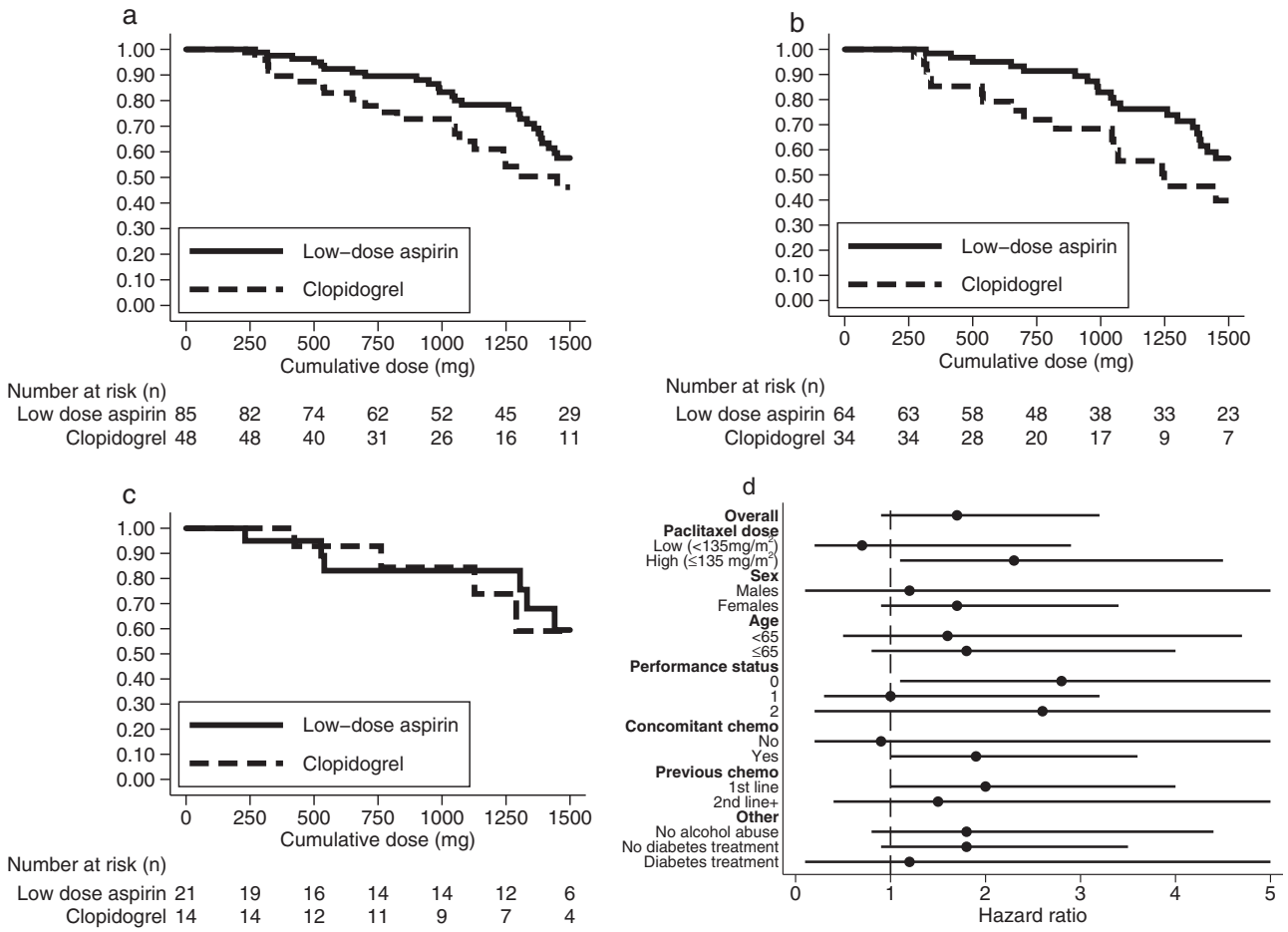

Figure 2 Kaplan–Meier and forest plot of developing peripheral sensory neuropathy grade 2 or worse over accumulated paclitaxel dose with data censored at 1,500 mg. The hazard ratios were 1.7 (0.9–3.0) (crude) and 1.7 (0.9–3.2) (adjusted and stratified) for the overall analysis (**a**). The hazard ratios were 2.0 (1.0–3.9) (crude) and 2.3 (1.1–4.5) (adjusted and stratified) for the high-dose paclitaxel (≥135 mg/m^2) group (**b**). The hazard ratios were 1.1 (0.3–4.1) (crude) and 0.7 (0.2–2.9) (adjusted and stratified) for the low-dose paclitaxel (<135 mg/m^2) group (**c**). The forest plot shows the point estimates and confidence intervals of the adjusted and stratified analysis (**d**).

Therapeutic Chemical (ATC) index, and the quantity dispensed for each prescription is expressed by the number of defined daily doses (DDD).[18]

Patient characteristics

Patient characteristics were recorded from medical charts by regional investigators at each site. Characteristics included ECOG performance status (Eastern Cooperative Oncology Group), age, height, and weight before index date, alcohol and smoking habits, and cancer diagnosis. In addition, paclitaxel course characteristics were recorded from the medical charts, including scheduled paclitaxel dose (mg/m^2) and dose frequency, combination therapy, line of chemotherapy, and prior radiotherapy. The following cancer-specific variables were also recorded: HER-2 status (human epidermal growth factor receptor 2), estrogen receptor status, tumor size, dissemination to lymph nodes, FIGO-stage (Fédération Internationale de Gynécologie et d'Obstétrique), and type of surgery.

Cohort and exposure definition

Patients prescribed at least one course of paclitaxel between January 2004 and July 2015 were identified from oncology departments at seven hospitals in Denmark: Odense University Hospital, Vejle Hospital, Aalborg University Hospital South, Aarhus University Hospital, Herlev

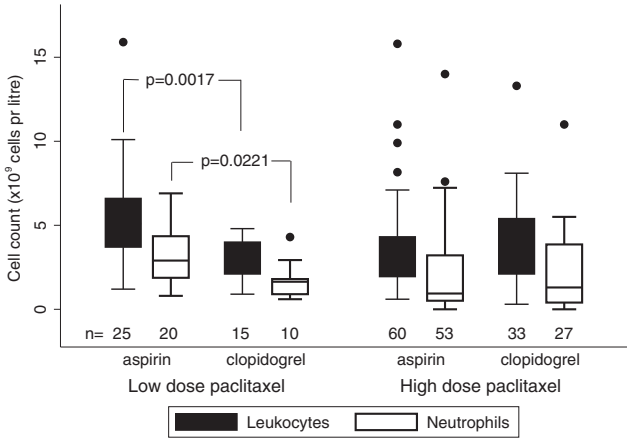

Figure 3 Neutrophil and leukocyte nadir of patients treated with low-dose (left) and high-dose paclitaxel (right). Boxes delimit upper and lower quartile and median, outliers are greater than 1.5 times the interquartile range from the upper quartile. Whiskers mark the extreme values that are not outliers.

Hospital, Rigshospitalet, and Herning Hospital. The index date was defined as the date of first paclitaxel infusion. At Rigshospitalet and Herlev Hospital, patients were identified using data from an electronic system for prescription of chemotherapy. Similarly, at Aarhus University Hospital, patients were identified in a register of chemotherapy prescription, which was established in 2007, thereby effectively excluding patients treated before 2007 from this site. At Vejle Hospital, patients were identified based on treatment regimens known to include paclitaxel from a department-specific patient index at the hospital pharmacy. The index was discontinued after January 2014, and a new production system did not provide complete treatment information, effectively excluding patients treated after this date from this site. At Herning Hospital, patients were identified from the patient medical chart from June 2011 onwards, and from a department-specific index before this date. At Odense University Hospital, patients were identified from a department-specific booking system for scheduling chemotherapy based on diagnoses known to be treated with paclitaxel. A list of all redeemed reimbursed prescriptions was retrieved from the DNDRP for each of the identified patients. The patients were then categorized as either exposed or nonexposed to clopidogrel. Each exposed patient was age- and sex-matched (within site) to two controls exposed to low-dose aspirin from the unexposed group. We chose aspirin users as our comparator group in order to minimize the possible confounding effect of factors related to the indication for using clopidogrel, as we assumed that both clopidogrel and aspirin would be used by patients with atherosclerotic disposition and that aspirin had no impact on paclitaxel pharmacokinetics. Clopidogrel and low-dose aspirin exposure was defined by having redeemed a prescription prior to the paclitaxel index date, of which the tablet supply overlapped with the paclitaxel treatment by at least 3 weeks. A package of 100 tablets was assumed to last (100+25%) 125 days, accounting for noncompliance or emptying of a previous package before using the new package.

Toxicity assessment

Medical charts of exposed and nonexposed patients were reviewed by an investigator (clinical oncologist) at each hospital. Toxicity was retrospectively graded by the Common Terminology Criteria of Adverse Events (CTCAE) v. 4.03 using information in the medical charts.[19] The oncologists were asked specifically not to look up the patient's clopidogrel status before filling in the case report forms, and to declare afterwards if they inadvertently already had acquired this knowledge. Data collection was carried out using an electronic web-based Case Report Form (RedCap: https://projectredcap.org/). The recorded toxicities were peripheral sensory neuropathy (main endpoint), nausea/vomiting, compliance, febrile neutropenia, and nadir neutrophil/leukocyte counts. Nausea/vomiting was dichotomized according to whether or not a patient had at least one recorded occurrence of grade 3 nausea or vomiting at any time during treatment. Paclitaxel dose reductions, delays, and premature discontinuation were registered and used for the composite endpoint. Dose reduction was defined as at least one episode of dosing less than 90% of initial dose. Dose delay was defined as at least one episode of at least 2 days' treatment delay, but only if explicitly related to toxicity. Premature discontinuation was defined as a situation where paclitaxel was stopped prior to scheduled course termination and not resumed at a later point. If combination chemotherapy was given, any reductions, delays, and discontinuation concerned only paclitaxel. Compliance was finally graded as compliant or noncompliant, with the latter being any event of either paclitaxel dose delay, reduction, or premature discontinuation. Nadir counts of neutrophils and leukocytes were defined as the lowest observed value, at any time after a course of paclitaxel, but before the next course.

Statistical analyses

The preplanned main analysis was Cox regression analysis of the risk of developing peripheral sensory neuropathy CTCAE grade 2+ over accumulating paclitaxel dose between clopidogrel-exposed and nonexposed (i.e., those exposed to low-dose aspirin). Similarly, planned exploratory analyses included analyses of febrile neutropenia grade 3+, nausea and/or vomiting grade 3+, and compliance. The main analysis was amended *post hoc* by censoring data beyond 1,500 mg accumulated paclitaxel. This was done because the proportional hazards assumption was strongly violated beyond 1,500 mg, when visually assessed by log-log and Schoenfeld residuals plots and by formal testing (data not shown). The large majority of events occurred before 1,500 mg, and the risk of late neuropathy in patients without neuropathy by 1,500 mg appeared to approach zero with increasing accumulated doses beyond 1,500 mg. We therefore decided to use 1,500 mg as the censoring point for all time-to-event analyses. Analyses were adjusted for paclitaxel dose level with a cut-off at $\geq$135 mg/m^2, sex, age, performance status, concomitant chemotherapy (any vs. none), and line of chemotherapy (1st line vs. 2nd line or greater). Patients were classified as diabetics if they had redeemed any prescription within ATC group A10 prior to the index date. Additionally, we analyzed severity (nadir) of leukocytopenia and neutropenia (continuous variables) using a Wilcoxon rank sum test. All analyses were performed using Stata Release 14.2 (StataCorp, College Station, TX).

Additional Supporting Information may be found in the online version of this article.

CONFLICT OF INTEREST/DISCLOSURE

TLJ has declared travel and accommodation paid by SOBI. REH has declared honoraria, research funding, and travel paid by Roche. KDS has declared honoraria paid by AstraZeneca, teaching healthcare professionals, travel, and accommodation paid by SOBI and Roche, and a consulting and advisory role paid for by Abbvie. MLHM has declared travel and accommodation paid for by Roche. MMS has declared research funding, travel, and accommodation paid for by Roche. KA, TBS, JWP, SHP, AP, JH, KB, and TKB declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

T.K.B., K.A., M.M-S., T.B.S., T.L.J., R.E.H., K.D.S., J.W.V.P., M.L.H.M., S.H.P., A.P., J.H., and K.B. wrote the article; T.K.B., K.A., T.B.S., J.H., and K.B. designed the research; T.K.B., K.A., M.M-S., T.L.J., R.E.H., K.D.S., J.W.V.P., M.L.H.M., and S.H.P. performed the research; T.K.B., K.A., T.B.S., A.P., and J.H. analyzed the data.

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