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Symptom Management and Supportive Care

Concomitant Medications and Risk of Chemotherapy-Induced Peripheral Neuropathy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Peripheral neuropathy • Paclitaxel • Risk factors • Concomitant medications • Comorbidities

Abstract

Background. Peripheral neuropathy is the dose-limiting toxicity of many oncology drugs, including paclitaxel. There is large interindividual variability in the neuropathy, and several risk factors have been proposed; however, many have not been replicated. Here we present a comprehensive study aimed at identifying treatment and physiopathology-related paclitaxel-induced neuropathy risk factors in a large cohort of well-characterized patients.

Patients and Methods. Analyses included 503 patients with breast or ovarian cancer who received paclitaxel treatment. Paclitaxel dose modifications caused by the neuropathy were extracted from medical records and patients self-reported neuropathy symptoms were collected. Multivariate logistic regression analyses were performed to identify concomitant medications and comorbidities associated with paclitaxel-induced neuropathy.

Results. Older patients had higher neuropathy: for each increase of 1 year of age, the risk of dose modifications and grade 3 neuropathy increased 4% and 5%, respectively. Cardiovascular drugs increased the risk of paclitaxel dose reductions (odds ratio [OR], 2.51; p = .006), with a stronger association for beta-adrenergic antagonists. The total number of concomitant medications also showed an association with dose modifications (OR, 1.25; p = .012 for each concomitant drug increase). A dose modification predictive model that included the new identified factors gave an area under the curve of 0.74 ($p = 1.07 \times 10^{-10}$). Preexisting nerve compression syndromes seemed to increase neuropathy risk.

Conclusion. Baseline characteristics of the patients, including age and concomitant medications, could be used to identify individuals at high risk of neuropathy, personalizing chemotherapy treatment and reducing the risk of severe neuropathy. ***The Oncologist*** 2019;24:e784–e792

Implications for Practice: Peripheral neuropathy is a common adverse effect of many cancer drugs, including chemotherapeutics, targeted therapies, and immune checkpoint inhibitors. About 40% of survivors of cancer have functional deficits caused by this toxicity, some of them irreversible. Currently, there are no effective treatments to prevent or treat this neuropathy. This study, performed in a large cohort of well-characterized patients homogenously treated with paclitaxel, identified concomitant medications, comorbidities, and demographic factors associated with peripheral neuropathy. These factors could serve to identify patients at high risk of severe neuropathy for whom alternative non-neurotoxic alternatives may be considered.

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Introduction

Chemotherapy-induced peripheral neuropathy is a dose-limiting toxicity for many anticancer drugs [1]. Approximately half of the patients treated with chemotherapy develop neuropathy, which can lead to dose reductions and early treatment discontinuations and can decrease the quality of life of the patients, in some cases in a long-term manner [2–6]. Paclitaxel, a taxane widely used for solid tumor treatment, causes peripheral neuropathy in most patients, with severe symptoms in about 25% of cases [7]. There are no effective therapies to treat or prevent the peripheral neuropathy; furthermore, recent studies suggest potential harms of commonly used supplements, such as acetyl-L-carnitine [8, 9]. Thus, the identification of risk factors for this toxicity could help to personalize treatments, reducing the risk of severe neuropathy.

The total cumulative dose of paclitaxel, drug schedule, and concurrent platinum treatment augment the risk of paclitaxel-induced peripheral neuropathy (PIPN) [10–12]. In addition, patients' characteristics, such as an older age, increased body mass index, race, and genetic background also influence PIPN risk [11, 13–16]. Comorbidities such as diabetes mellitus, Charcot–Marie–Tooth disease, alcoholism, liver diseases, and concurrent medications have also been suggested to predispose patients to drug-induced peripheral neuropathies [11, 12, 17–19]. However, many of these results have not been replicated or have contradictory results in the literature. Some limitations that could explain these discrepancies include that many studies are retrospective, have limited sample sizes, study heterogeneous series of patients with numerous tumor types and chemotherapy treatments, and use diverse neuropathy assessments, some of low accuracy. The scarcity of large and comprehensive studies, and the lack of agreement in the literature prevent incorporating these data into the clinic. Here, we performed a study to identify concomitant medications and physiopathologic factors associated with PIPN in a cohort of more than 500 paclitaxel-treated patients. Neuropathy severity was measured by two clinically relevant endpoints: paclitaxel dose modifications caused by the neuropathy, registered in the medical records, and neuropathy grade, evaluated according to symptoms self-reported by the patients.

Materials and Methods

Patients

A series of 503 patients with cancer, either breast (82%) or ovarian (18%) tumors, treated with paclitaxel, the majority (98%) in first line, and only a few with metastatic disease (7%), were recruited in five Spanish hospitals from 2011 to 2016 (Table 1).

All patients were women of European origin except one from North Africa. Some have been previously described in genetic risk studies [16, 20, 21]. All patients were older than 18 years of age, had documented histologic breast or ovarian cancer neoplasia; a life expectancy of ≥12 weeks; Eastern Cooperative Oncology Group performance status

Table 1. Characteristics of patients (n = 503)

Characteristics	n (%)
Age, median (min–max), yr	52 (30–82)
Body surface area, median (min–max), m^2	1.69 (0.74–3.21)
Tumor type	
Breast	413 (82.1)
Ovary	90 (17.9)
Tumor stage	
I	122 (24.3)
II	200 (39.8)
III	97 (19.3)
IV	36 (7.2)
Unknown	48 (9.5)
Line of treatment	
First line	492 (97.8)
Second line[a]	11 (2.2)
Chemotherapy treatment[b]	
FEC+P	171 (34.0)
AC+P	114 (22.7)
P+FEC	71 (14.1)
P+AC	18 (3.6)
C+P	91 (18.1)
Others	38 (7.6)
Paclitaxel, median (IQR)	
Number of cycles	8 (8–12)
Total dose, mg	1,400 (1,262–1,620)
Paclitaxel dose modifications due to neuropathy[c]	
Dose reduction	38 (7.6)
Treatment suspension	45 (8.9)
Maximum sensory neuropathy grade[d]	
G0	63 (12.5)
G1	63 (12.5)
G2	131 (26.0)
G3	246 (48.9)

[a]Patients with second-line paclitaxel treatment and no previous cytotoxic drugs in first-line therapy.
[b]Some patients receiving chemotherapeutic drugs in combination with targeted therapy (bevacizumab, trastuzumab, or pertuzumab) are included in the table according to the chemotherapy agents received. Regimens were as follows: FEC+P, 5-fluorouracil 600 mg/m^2 1-hour infusion, epirubicin 90 mg/m^2 1-hour infusion, and cyclophosphamide 600 mg/m^2 1-hour infusion, every 21 days, followed by paclitaxel 80, 90, or 100 mg/m^2 1-hour infusion every 7 days; AC+P, doxorubicin 60 mg/m^2 1-hour infusion and cyclophosphamide 600 mg/m^2 1-hour infusion every 21 days, followed by paclitaxel 80, 90, or 100 mg/m^2 1-hour infusion every 7 days; P+FEC, paclitaxel 80, 90, or 100 mg/m^2 1-hour infusion every 7 days, followed by 5-fluorouracil 600 mg/m^2 1-hour infusion, epirubicin 90 mg/m^2 1-hour infusion, and cyclophosphamide 600 mg/m^2 1-hour infusion every 21 days; P+AC, paclitaxel 80, 90, or 100 mg/m^2 1-hour infusion every 7 days, followed by doxorubicin 60 mg/m^2 1-hour infusion and cyclophosphamide 600 mg/m^2 1-hour infusion every 21 days; C+P, carboplatin area under the curve 5–6 mg/mL × h 1-hour infusion followed by paclitaxel 175 mg/m^2 3-hour infusion every 21 days.
[c]When in the same patient paclitaxel dose was reduced and later on paclitaxel treatment was suspended, the patient is included in the table as "treatment suspension."
[d]Maximum sensory neuropathy grade by U.S. National Cancer Institute Common Terminology Criteria for Adverse Events version 4 scale. Abbreviations: AC, doxorubicin and cyclophosphamide; C, carboplatin; FEC, fluorouracil, epirubicin, and cyclophosphamide; IQR, interquartile range; P, paclitaxel.

Table 2. Paclitaxel-induced peripheral neuropathy characteristics of the 503 patients included in the study

	Paclitaxel-induced peripheral neuropathy			
	Grade 0	Grade 1	Grade 2	Grade 3
	(*n* = 63)	(*n* = 63)	(*n* = 131)	(*n* = 246)
Neuropathy items evaluated	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Sensory. Numbness, tingling or discomfort in hands or feet (FACT/GOG-Ntx questions 1–4)				
Patients with numbness, tingling or discomfort in hands or feet	0 (0)	58 (92)	127 (97)	245 (99.6)
Patients without numbness, tingling or discomfort in hands or feet	63 (100)	5 (8)	4 (3)	1 (0.4)
Myalgia. Joint pain or muscle cramps (FACT/GOG-Ntx question 5)				
Patients with joint pain or muscle cramps	0 (0)	6 (10)	22 (17)	102 (41)
Patients without joint pain or muscle cramps	63 (100)	57 (90)	109 (83)	144 (59)
Functional. Trouble buttoning buttons, feeling shape of objects, or trouble walking (FACT/GOG-Ntx questions 8, 9, and An6)				
Patients with trouble buttoning buttons, feeling shape objects or trouble walking	0 (0)	2[a] (3)	41[b] (31)	239 (97)
Patients without trouble buttoning buttons, feeling shape objects or trouble walking	63 (100)	61 (97)	90 (69)	7[c] (3)
Weakness in limbs or joint stiffness in hands or feet (additional questions included in our assessment)				
Patients with weakness in limbs or joint stiffness in hands or feet	0 (0)	6 (10)	43 (33)	209 (85)
Patients without weakness in limbs or joint stiffness in hands or feet	63 (100)	57 (90)	88 (67)	37 (15)

[a]Mild and intermittent symptoms that did not affect activities of daily living (ADL).
[b]Symptoms did not affect self-care ADL.
[c]Patients without trouble buttoning buttons, feeling the shape or objects, or trouble walking. However, five patients had weakness in limbs and two had weakness in limbs and joint stiffness, which were considered to limit self-care ADL.
Abbreviation: FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity.

≤2; adequate bone marrow, renal, and hepatic functions; no previous history of neuropathy; and no previous paclitaxel or platinum drug treatment, and all patients had taken some form of contraception. Exclusion criteria included neuropathy grade 1 or higher (according to the U.S. National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], version 4) at paclitaxel treatment start. The recruitment of patients and collection of samples were approved by local internal ethical review committees, and all patients gave written informed consent to participate in the study.

Clinical Data

Demographic and clinical data, including information regarding tumor type, stage, histology, previous cancer history, paclitaxel treatment regimen, number of paclitaxel cycles, total paclitaxel administered dose, modifications to paclitaxel treatment (dose reductions and treatment suspensions) and their cause, were collected from the medical records of the patients in each hospital participating in the study (Table 1).

Concomitant drugs were recorded for 428 patients; comorbidities were recorded for all 503 patients in the study. Concomitant medications are defined as those drugs (taken at least 3 days per week) during placlitaxel treatment. The comorbidities incorporated in the analysis (including diabetes mellitus, hypothyroidism, arterial hypertension, dyslipidemia, nerve compression syndromes, arthrosis, liver disease, peripheral vascular, or autoimmune diseases) were those diagnosed before paclitaxel treatment start. Concomitant medications and comorbidity data were obtained after patients had completed paclitaxel treatment; data were collected from the medical records and confirmed through telephonic interview (Table 2). Autoimmune diseases studied included arthritis, Crohn's disease, ulcerative colitis, and Sjögren's syndrome. Nerve compression syndrome included carpal tunnel syndrome, vertebral disc prolapse, and spinal stenosis.

Paclitaxel-Induced Peripheral Neuropathy

Peripheral neuropathies causing functional impairment in patients usually lead to treatment modifications. Peripheral neuropathy is paclitaxel's dose-limiting toxicity, and it usually leads to dose modifications (i.e., dose reductions and early treatment discontinuations). Paclitaxel dose modifications caused by neuropathy were extracted from the medical records of the patients and were used as an indication of a clinically relevant neuropathy.

In addition, peripheral neuropathy symptoms were assessed in all patients in a systematic manner, and the maximum neuropathy experienced during paclitaxel treatment was classified in grades, according to the NCI CTCAE version 4 scale. Neuropathy symptoms were self-reported by the patients, following a structured interview performed by a qualified nurse (L.S.B.) trained by a neurologist (G.G. G.) [16]. The interview also covered possible symptoms before starting paclitaxel treatment; patients with baseline neuropathy were excluded. The interview covered the eight sensory, myalgia, and functional neuropathy items of the FACT/GOG-Ntx (Functional Assessment of Cancer

Therapy/Gynecologic Oncology Group-Neurotoxicity) questionnaire [22, 23], plus additional questions related to weakness and joint stiffness (supplemental online Table 1). We followed the NCI CTCAE version 4 scale, which defines grade 3 neuropathy as "severe symptoms; limiting self care ADL; assistive device indicated for motor neuropathy."

The interviews were performed with the 503 patients after they finished paclitaxel treatment (with a median of 10 months and interquartile range of 5–18 months). The order in which interviews were performed was independent of PIPN grade and was based on enrollment date. In some patients (n = 173), symptoms were followed up in time with additional interviews. In addition, for 136 patients, neuropathy data were also self-recorded during each paclitaxel cycle through a written questionnaire. Correlation between the maximum PIPN grades obtained through the telephone interview and from the written questionnaire was high (Spearman correlation coefficient of 0.76; $p = 2 \times 10^{-25}$). The maximum PIPN grade self-reported in the telephone interview was used for the analyses.

Statistical Analysis

Binary logistic regression analysis was used to evaluate the association between paclitaxel treatment modifications caused by neuropathy (i.e., dose reduction and treatment suspension) or maximum peripheral neuropathy of grade 3 with concomitant medications and comorbidities. Only comedications and comorbidities present in at least 20 patients were included in the analysis. Multivariate analysis adjusting for potential confounders (with forward selection) included age, body surface, tumor type, cancer stage, treatment schedule, and previous chemotherapy treatments. Paclitaxel infusion time was 1 hour for breast and 3 hours for ovarian cancer, in all patients except seven (0.1%). Predictive models were created using stepwise logistic regression analysis. In these, the discrimination power of the models was evaluated by computing receiver operating characteristic (ROC) curves and area under the curve (AUC). SPSS software version 19 (IBM Corporation, Armonk, NY) was used to perform the statistical analyses. Bilateral p values <.05 were considered statistically significant.

Results

Study Population

The study included 503 eligible patients with cancer, 413 (82%) with breast and 90 (18%) with ovarian cancer, and paclitaxel was used in the first line in 492 (98%) of them. Paclitaxel dose modifications caused by the neuropathy occurred in 83 (17%) of the women, 38 (8%) had dose reductions, and 45 (9%) had early suspension of paclitaxel treatment (Table 1). Maximum peripheral neuropathy during paclitaxel treatment was systematically assessed; 63 (13%) patients had no signs of neuropathy (grade 0), whereas 440 (88%) exhibited neuropathy symptoms: 63 (13%) had grade 1, 131 (26%) grade 2, and 246 (49%) grade 3 (Table 2; full details in supplemental online Table 2).

The median age of the patients was 52 years, and the most frequent comorbid diseases were hypertension, hypothyroidism, dyslipidemia, nerve compression syndromes, and arthrosis (in 14%, 12%, 9%, 6%, and 4% of the patients, respectively; Table 3). Concomitant medications were taken by most of the patients (65% for all types of medications; 63% if vitamins and minerals supplements were excluded). The most common concomitant drugs were benzodiazepines, cardiovascular drugs, proton pump inhibitors, thyroid replacements, statins, and antidepressants (taken by 19% to 10% of patients; Table 3).

Regarding PIPN, both paclitaxel dose modifications caused by neuropathy and maximum neuropathy grade during treatment were analyzed. The Spearman's correlation coefficient between these variables (r = .23; p = .004) confirmed a positive but not perfect correlation between the two events. Dose modifications occurred in 29%, 8%, 3%, and 0% of patients with PIPN grades 3, 2, 1, and 0, respectively. This suggests that the two neuropathy outcome measurements analyzed, one dictated by the clinician and the other self-reported by the patient, are complementary assessments. Regarding the accumulated dose for paclitaxel treatment modifications, at 768 mg, 95% of patients did not have a dose modification caused by neuropathy; at 1,020 mg, 90% did not, and at 1328 mg, 85% did not.

Age Increases the Risk of Paclitaxel-Induced Neuropathy

Patients with an older age had higher risk of paclitaxel dose modifications caused by neuropathy and a higher risk of having grade 3 neuropathy ($p = 1.0 \times 10^{-3}$ and $p = 1.1 \times 10^{-5}$, respectively; multivariate analysis; Table 4). For each increase in age of 1 year, the risk of neuropathy increased by 4% and 5%, respectively.

The effect of age in the subgroup of patients who did not take any concomitant medication during paclitaxel treatment (150/428, 35%, with an age that varied from 32 to 73 years) showed a tendency toward increased risk of grade 3 PIPN (odds ratio [OR], 1.04; 95% confidence interval [CI], 0.99–1.09; p = .057), suggesting a direct effect of age on the neuropathy. The associations between body surface, tumor type, cancer stage, type of treatment, and previous chemotherapy and the PIPN are shown in Table 4.

Concomitant Medications, Comorbidities, and Paclitaxel-Induced Neuropathy Risk

The age of the patients correlated positively with the number of comorbidities and number of concomitant medications (Spearman's correlation coefficients, 0.42 and 0.40, respectively); thus, subsequent analyses were adjusted for age and other potential treatment- and tumor-related confounders.

The risk of paclitaxel dose modifications caused by neuropathy increased for patients taking cardiovascular drugs (OR, 2.51; p = .006, multivariate analysis; Fig. 1. OR, 2.9; p = .003 when accumulated paclitaxel dose was also added as covariate). Specifically, beta-adrenergic antagonist increased the risk of PIPN by fivefold (OR, 4.9; p = .013, multivariate analysis; OR, 6.2; p = .014 when accumulated paclitaxel dose was also added as covariate), whereas the effect

Table 3. Comorbid diseases and concomitant medications

Comorbid diseases and concomitant medications[a]	All patients *n* (%)	Patients with dose-modifying neuropathy *n* (%)	Patients with grade 3 neuropathy *n* (%)
Comorbid diseases (*n* = 503)			
Hypertension	69 (14)	20 (29)	47 (68)
Hypothyroidism	61 (12)	11 (18)	26 (43)
Dyslipidemia	43 (9)	10 (23)	20 (46)
Nerve compression syndrome	29 (6)	10 (34)	20 (69)
Arthrosis	21 (4)	6 (29)	16 (76)
Diabetes mellitus	18 (4)	6 (33)	10 (56)
Liver disease	10 (2)	2 (20)	5 (50)
Peripheral vascular disease	8 (2)	3 (38)	5 (63)
Autoimmune disease	8 (2)	2 (25)	3 (38)
Concomitant medications (*n* = 428)			
Benzodiazepines	81 (19)	14 (17)	48 (59)
Cardiovascular	73[b] (17)	25 (34)	49 (67)
Renin-angiotensin aldosterone antagonists	56 (13)	18 (32)	39 (70)
Beta-adrenergic antagonist	13 (3)	6 (46)	10 (77)
Calcium channel antagonist	10 (2)	4 (40)	5 (50)
Gastrointestinal	74 (74)	16 (22)	36 (49)
Proton pump inhibitors	70 (16)	15 (21)	34 (49)
Endocrine	68 (16)	13 (19)	30 (44)
Thyroid replacement	58 (14)	10 (17)	24 (41)
Antidiabetic	14 (3)	4 (29)	7 (40)
Dyslipidemics	55 (55)	17 (31)	30 (55)
Statins	51 (12)	15 (29)	28 (55)
Neuropsychiatric	46 (11)	14 (30)	30 (65)
Antidepressants	43 (10)	11 (26)	27 (63)
Antipsychotic	4 (1)	2 (50)	3 (75)
Anticonvulsant	3 (1)	2 (67)	3 (100)
Vitamin/minerals supplements	42 (10)	8 (19)	21 (50)
Herbal supplements	42 (10)	9 (21)	19 (45)
Diuretics	31 (7)	7 (23)	20 (65)
Thiazide	25 (6)	5 (20)	16 (64)
Loop	5 (1)	1 (20)	4 (80)
Potassium-sparing	4 (1)	2 (50)	2 (50)
Analgesic	25 (6)	9 (36)	17 (68)
NSAID	19 (4)	7 (37)	12 (63)
Antiplatelet/ anticoagulant	7 (2)	1 (14)	4 (57)
Sedative hypnotic	4 (1)	1 (25)	3 (75)
Pulmonary	4 (1)	1 (25)	3 (75)
Glucocorticoid	3 (1)	0 (0)	2 (67)
Antirheumatic	3 (1)	1 (33)	2 (67)

[a]Concomitant medications and comorbid diseases present in at least 1% of the population studied.
[b]Some patients took two or more cardiovascular drugs simultaneously.
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

of calcium channel antagonists and renin-angiotensin aldosterone antagonists was more modest and not statistically significant. The effect of other types of drugs on PIPN was not significant, but the total number of drugs taken concomitantly with paclitaxel treatment was associated with dose modifications due to neuropathy (p = .012; Fig. 1). As shown in Figure 2, patients taking three or more drugs had a threefold higher risk of drug modifications compared with patients not taking concomitant medications (p = .008, with or without adding paclitaxel accumulated dose as covariate).

Table 4. Neuropathy rates according to characteristics of the patients and their treatments

	Paclitaxel dose modifications due to neuropathy				Grade 3 neuropathy			
Characteristic	**No, *n* (%)**	**Yes, *n* (%)**	**OR (95% CI)[a]**	***p* value[a]**	**No, *n* (%)**	**Yes, *n* (%)**	**OR (95% CI)[a]**	***p* value[a]**
Total	420 (83)	83 (17)			257 (51)	246 (49)		
Age,[b] median, yr	51.0	55.9	1.04 (1.02–1.07)	**1.0×10^{-3}**	49.5	53.8	1.05 (1.03–1.07)	**1.1×10^{-5}**
Body surface,[b] median, m^2	1.68	1.70	1.43 (0.50–4.13)	.51	1.66	1.70	2.02 (0.81–5.02)	.13
Tumor type								
Breast	349 (85)	64 (15)	Reference		199 (48)	214 (52)	Reference	
Ovarian	71 (79)	19 (21)	1.07 (0.39–2.95)	.89	58 (64)	32 (36)	0.17 (0.06–0.42)	**1.8×10^{-4}**
Cancer stage								
I–II	261 (81)	61 (19)	Reference		157 (49)	165 (51)	Reference	
III–IV	115 (86)	18 (14)	0.62 (0.33–1.16)	.13	71 (53)	62 (47)	0.88 (0.56–1.38)	.58
Treatment								
FEC+P or AC+P	233 (82)	52 (18)	Reference		135 (47)	150 (53)	Reference	
P+FEC or P+AC	86 (97)	3 (3)	0.20 (0.06–0.68)	**.010**	54 (61)	35 (39)	0.76 (0.44–1.29)	.30
C+P or others	101 (78)	28 (22)	0.99 (0.38–2.55)	.98	68 (53)	61 (47)	2.26 (0.94–5.43)	.070
Previous chemotherapy								
No	413 (84)	79 (16)	Reference		253 (51)	239 (49)	Reference	
Yes	7 (64)	4 (36)	2.35 (0.51–10.91)	.27	4 (36)	7 (64)	1.59 (0.32–8.02)	.57

[a]Adjusted by age, body surface, tumor type, stage, treatment and previous chemotherapy.
[b]The logistic regression analysis included age or body surface as a continuous variable.
Abbreviations: AC, doxorubicin and cyclophosphamide; C, carboplatin; CI, confidence interval; FEC, fluorouracil, epirubicin, and cyclophosphamide; OR, odds ratio; P, paclitaxel.

This association remained statistically significant (p = .028) when beta-adrenergic antagonists were added as a covariate in the analysis. A similar trend for patients taking three or more drugs was obtained for grade 3 neuropathy (Fig. 2B).

Regarding comorbidities, preexisting nerve compression syndromes (diagnosed previously to paclitaxel treatment) were shown to increase the risk of PIPN (OR, 2.6; p = .031, and OR, 2.1; p = .10, for dose modifications and grade 3 neuropathy, respectively; Fig. 1). Adding accumulated paclitaxel dose as covariate in the analysis did not substantially change the association results (i.e., OR, 2.5; p = .050 and OR, 2.1; p = .11, respectively). Hypertension and arthrosis showed higher rates of dose modifications and of grade 3 neuropathy, but differences were not statistically significant. Hypothyroidism and dyslipidemia did not show significant differences in PIPN.

Predictive Model to Predict Paclitaxel Dose Modifications Caused by Neuropathy

We included cardiovascular drugs, the number of concomitant medications, and nerve compression syndrome to construct a dose modification risk predictive model. The risk scores of the model were 3.22, 2.36, and 1.18 for cardiovascular drugs, number of concomitant medications, and compression syndrome, respectively (calculated as [0.86 × cardiovascular drugs] + [0.16 × number of drugs] + [1.17 × nerve compression] − 2.15). We assessed the accuracy of the classifier with ROC analysis, obtaining an AUC of 0.68 (95% CI, 0.57–0.70; $p = 2.2 \times 10^{-6}$). The AUC of the predictive model including the covariates used in the multivariate analysis (age, body surface, tumor type, cancer stage, treatment schedule, and previous chemotherapy treatments) was of 0.69 (95% CI, 0.62–0.75). Adding the newly identified risk factors (cardiovascular drugs, number of concomitant medications, and compression syndrome) to the model increased the predictive value (AUC of 0.74; 95% CI, 0.68–0.81; $p = 1.07 \times 10^{-10}$; supplemental online Fig. 1).

Discussion

The identification of chemotherapy-induced neuropathy risk factors could help to personalize cancer treatments, reducing the number of severe and long-term disabling neuropathies. However, few risk factors have been definitely identified, and many proposed have not been replicated. In the present study, we carried out a comprehensive analysis on a large series of well-characterized paclitaxel-treated patients to identify treatment-related and physiopathologic risk factors of PIPN. In agreement with previous studies, we found that age was associated with an increased risk of neuropathy [11, 14, 24–26]. The basis for this association remains undetermined, as it might reflect a higher number of comedications and comorbidities, which augment with the age of the patients and which could affect the neuropathy risk (e.g., through drug–drug interactions). In our study, older patients had more PINP, even when taking into account the number of concomitant medications, thus supporting a direct effect of age and suggesting age-related diminishment of body functions as a causative mechanism. However, this study also supports the idea that the number of comedications taken during paclitaxel treatment and some pathologies have a direct effect on PIPN (higher age-adjusted risk of PIPN; Figs. 1 and 2).

Polypharmacy has been shown to be common in patients with cancer undergoing chemotherapy [27]. In a

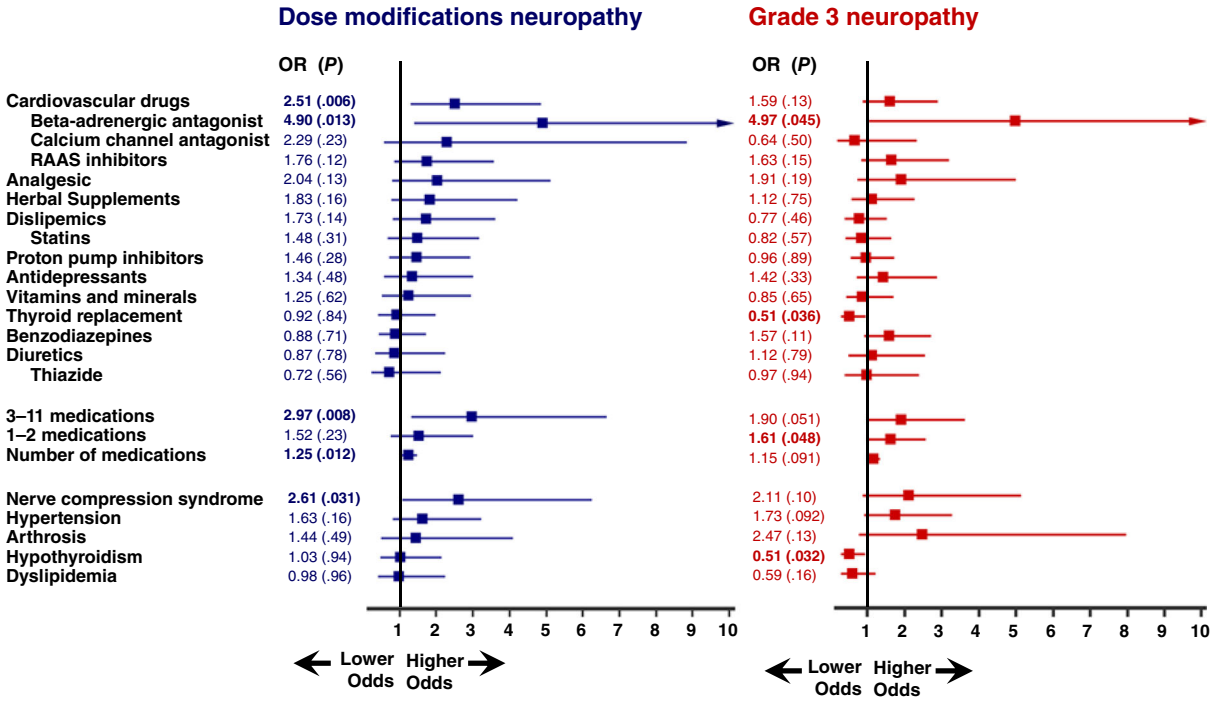

Figure 1. Association of dose modifications due to neuropathy and neuropathy grade 3 with comorbid conditions and concomitant medications. Multivariate logistic regression analyses were adjusted for age, body surface, tumor type, cancer stage, treatment schedule, and previous chemotherapy treatments. The analysis of concomitant medications did not take into account vitamin and mineral supplements. The number of drugs was analyzed as a continuous variable (Number of medications) and as a categorical variable with patients taking three or more drugs (3–11 medications) and those taking one or two drugs (1–2 medications), grouped together and compared with patients who did not take concomitant drugs during paclitaxel treatment. Each square represents an odds ratio, and each horizontal line is the 95% confidence interval. The vertical line is the line of equal odds.
Abbreviations: OR, odds ratio; RAAS, renin-angiotensin aldosterone antagonists.

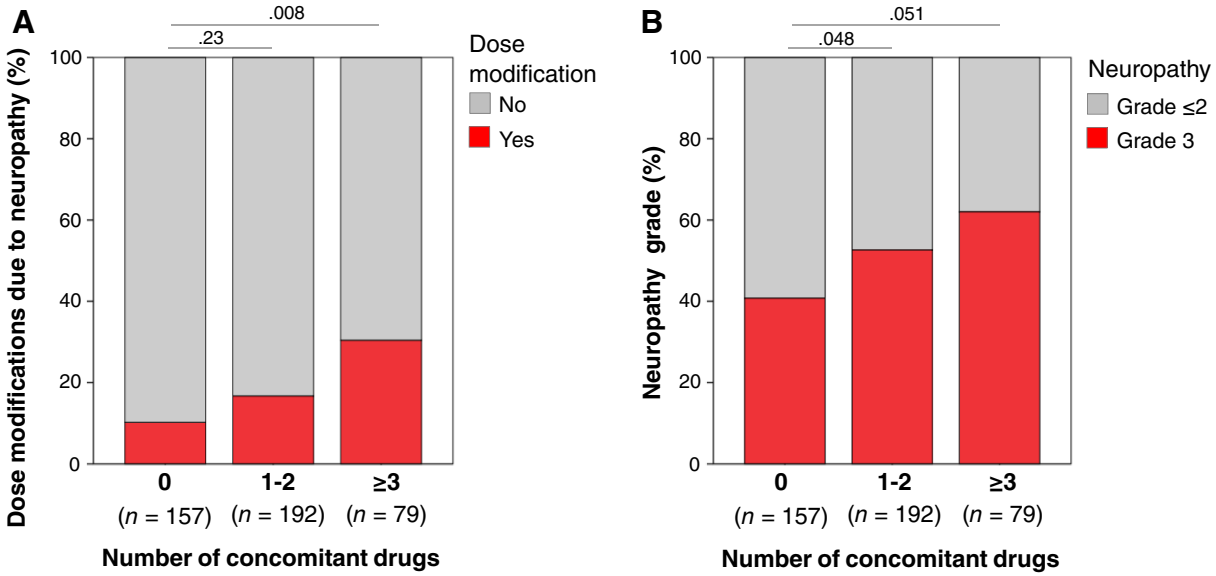

Figure 2. Effect of concomitant medications on paclitaxel-induced peripheral neuropathy. Paclitaxel dose modifications due to neuropathy (dose reduction and treatment suspension) **(A)** and grade 3 neuropathy **(B)** were compared among patients taking different number of concomitant drugs. There were 157 patients not taking concomitant drugs, 192 taking one or two drugs, and 79 taking three or more different drugs. The *p* values correspond to multivariate binary logistic regression analysis.

patient population aged 65 or more years, the mean number of daily medications was five, and 29% of the patients took at least one inappropriate medication [28]. The study by Maggiore et al., with a very heterogeneous population in terms of cancer types and chemotherapy treatments, found no association between the number of concomitant drugs and toxicity or hospitalization, only a tendency toward higher risk of adverse events for anticoagulants and

antiarrhythmics. Recent studies found an interaction between paclitaxel and the anticoagulant clopidogrel, a CYP2C8 inhibitor, with a clinically relevant increased risk of neuropathy in patients taking both drugs [29, 30]. In our study, only one patient received clopidogrel. The most common medications were benzodiazepines, cardiovascular drugs, and proton pump inhibitors. Cardiovascular drugs, especially beta-adrenergic antagonists, were found associated with an age-adjusted increased risk of PIPN (Fig. 1). Most of these drugs are not CYP2C8 or CYP3A4 inhibitors; thus, a direct interaction with paclitaxel metabolism is not expected. One could postulate that microvascular complications associated with the cardiovascular disease could increase PIPN. Beta-adrenergic antagonists included atenolol, bisoprolol, carvedilol, and nebivolol, and most of the patients treated with these drugs (69%) had arterial hypertension. Adverse effects of beta-adrenergic antagonists include cold extremities, Raynaud phenomenon, or peripheral ischemia, suggesting that, in addition to microvascular complications, these side effects in extremities may also contribute to the neuropathy symptoms caused by the chemotherapy. In regard to the number of drugs taken concomitantly with paclitaxel treatment, they were found to increase neuropathy risk (Fig. 2). Some of these drugs are related to peripheral neuropathy, such as statins [31] or proton pump inhibitors, which are associated with vitamin B12 deficiency [32], a peripheral neuropathy risk factor. The number of concomitant medications could also be an indirect measurement of the general health status of the patients, which in cisplatin-treated patients was found strongly associated with the neuropathy (OR, 0.59; $p < .0001$) [26].

Patients with nerve compression syndromes, including common conditions such as carpal tunnel syndrome and radiculopathies, showed an increased PIPN risk. However, it could be speculated that although patients did not have neuropathy symptoms when paclitaxel treatment started, the entrapment of nerves and chronic compression mononeuropathies related to these conditions might have occurred during treatment and may have led to a misattribution of symptoms, making it difficult to differentiate between tingling and numbness due to compression and due to paclitaxel. Further studies should address this issue. Diabetes mellitus and hypothyroidism cause peripheral neuropathy, and they have been suggested as risk factors for chemotherapy-induced neuropathy in patients with or without preexisting neuropathy symptoms [11, 17]. In our study, only 19 patients had diabetes mellitus, indicating reduced statistical power. Regarding hypothyroidism, the lack of association with PIPN, in agreement with previous studies, probably reflects efficient hormone replacement that prevents nerve damage [11]. Patients with hypertension showed a tendency toward increased neuropathy risk, but a previous study with taxanes did not support this [11].

Limitations to the study include a reduced number of patients with some comorbidities, reflecting the relatively young population studied (median age of 52 years). This led to important differences in the incidence of comorbidities with previous studies in elderly patients (e.g., diabetes mellitus in 26% vs. 4% of the patients for Hershman et al. [11] and this study, respectively) but better reflects the risk factors of a middle-aged population of patients with cancer. The lack of a validation series in this study indicates that associations should be confirmed in additional cohorts. In addition, some variables previously suggested as risk factors were not available for the analysis (e.g., baseline body mass index) [13]. Regarding PIPN evaluation, although it was performed in a systematic manner, patients were retrospectively recalling the symptoms experienced during paclitaxel treatment at different time points after treatment, which could have influenced the results. We incorporated paclitaxel dose modifications caused by the neuropathy as an independent clinically relevant neuropathy endpoint related to severe PIPN and clearly registered in the medical records. The correlation between dose modifications and the grade 3 neuropathy supports accuracy in PIPN grade estimation. In addition, unlike most previous studies on physiopathologic and clinical factors, most of our patients had nonmetastatic breast and ovarian cancer and were homogenously treated with paclitaxel.

Conclusion

We identified concomitant medications, especially beta-adrenergic antagonists, as novel PIPN risk factors. The results confirmed age as a causative factor increasing neuropathy risk and suggested nerve compression syndromes as a potential risk factor. Our study builds upon prior work by analyzing comedications in a middle-aged population homogenously treated with paclitaxel and by incorporating paclitaxel dose modifications caused by the neuropathy as a robust clinically relevant endpoint. Altogether, baseline personal characteristics could serve to identify patients at high PIPN risk, for whom alternative non-neurotoxic alternatives may be considered. Future studies should prospectively evaluate the effect of the identified risk factors to build prediction models for treatment personalization.

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Disclosures

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