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ORIGINAL COMMUNICATION

Taxane-induced peripheral neuropathy has good long-term prognosis: a 1- to 13-year evaluation

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Abstract Taxane-induced neuropathy is a frequent complication, in particular in women with breast cancer. The incidence can be variable and ranges from 11 to 87%, depending on the taxane used and identified risk factors, such as cumulative dose, additional neurotoxic chemotherapy agents and previous nerve fragility. However, little is known about long-term outcome and interference with daily life activities. The objective of this study was to assess clinical and electrophysiological neurological evaluation (ENMG) in a cohort of patients, 1–13 years (median 3 years) after the end of the last cure. Sixty-nine women were enrolled in the lymphology unit of Cognacq-Jay's Hospital. They were 58 ± 9 years old (mean age ± SD) and had been treated by docetexel ($n = 56$), paclitaxel ($n = 10$) or both ($n = 3$), 1–13 years before. Sensory neuropathy occurred in 64% and totally disappeared within months for only 14% after cessation of treatment. However, if symptoms were still present at the time of examination, they were considered as minor by almost all patients, with no interference with daily life activities (grade 2 CTCAE v.3.0). ENMG was accepted by 14 patients; it was normal in 7, and showed sensory axonal neuropathy in 5 and sensory-motor neuropathy in 2. The incidence of taxane-induced neuropathy is high, more frequent with paclitaxel than docetaxel, and is characterized by minor or moderate axonal sensory polyneuropathy. When persistent, it is extremely well tolerated by the patient. When clinical motor signs occur, the patient should be referred to a neurologist.

Keywords Chemotherapy · Taxanes · Docetexel · Paclitaxel · Peripheral neuropathy

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Introduction

A woman's chance of developing breast cancer in her lifetime is about one in eight. Taxanes, paclitaxel (Taxol™) and docetaxel (Taxotere™) are among the most active chemotherapy agents used in the management of breast cancer, particularly in the adjuvant and metastatic setting. These anticancer agents bind and stabilize microtubules, resulting in inhibition of cell division and finally cell death [1]. This mechanism explains why clinical success is also accompanied by significant side effects, among them peripheral neuropathy.

Taxane-induced polyneuropathy usually presents as paresthesias and dysesthesias located first in the toes, then spreading proximally and to the upper limbs, or concomitant quadridistal paresthesias, with a glove-and-stocking distribution [2, 3]. The prevalence has been variously reported from 59 to 87% for paclitaxel [4, 5] and from 11 to 64% for docetaxel [4, 6]. The wide range of neuropathy incidence may be explained by the chosen diagnostic criteria and the neurologist and/or electroneuromyographic contribution to the diagnosis. Few large studies have been published to date. Neurological symptoms have been

described at the acute phase only. They mainly consist of sensory polyneuropathy, sometimes painful or with associated motor deficits, which may affect daily life activities, alter quality of life, and result in dose modification or chemotherapy discontinuation [5].

The importance of predicting side effects and patient's adherence to the treatment is fundamental. As far as we know, only one study [5] has assessed taxane-induced neuropathy prognosis; this study included 46 patients with a mean 33-week follow-up. The aim of our study was to assess the long-term taxane-induced neuropathy outcome in patients examined 1–13 years after the last cure and followed in a post-cancer lymphoedema treatment center. We analyzed the prevalence of these neuropathies in this specific population, clinical and electrophysiological characteristics, risk factors, evolution, functional impact on daily activities and patients' perceptions of the residual neurological symptoms.

Patients and methods

Patients

Patients with a medical past of gynecological cancer treated with taxanes (docetaxel or paclitaxel) and consecutively admitted to the lymphology unit of Cognacq-Jay's Hospital between November 2009 and May 2010 were systematically examined, and clinical history and examination recorded by a neurologist. If the medical history or physical examination was congruent with a peripheral neuropathy, an electroneuromyographic (ENMG) examination was proposed secondarily in the Neurophysiological Unit of Lariboisière's Hospital (Paris, France). This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Oncological characteristics (treatment onset, chemotherapy regimen with total cumulative dose, treatment duration and associated chemotherapy) were collected during the review of hospital files.

Inclusion criteria

The clinical inclusion criteria were based on the symptoms and neurological findings indicative of a neuropathy. Symptoms were possibly attributed to taxanes if they developed after the introduction of treatment, during the cures or not after the next month after the end of the last cure. If symptoms were reduced or had disappeared after treatment was reduced or stopped, imputability was considered as highly probable; if symptoms remained unchanged, imputability was considered probable if no other possible cause could be identified.

Neurological examination

Patients were systematically asked about paresthesias, dysesthesias, loss of dexterity, and the location and progression of symptoms. Clinical examination systematically included light touch, pinprick sensation, vibration and position sensation, Romberg's maneuver, the Medical Research Council Scale for Muscle Strength (0/5 no movement to 5/5 normal muscle strength), trophicity and deep tendon reflexes. Polyneuropathy was defined by the presence of bilateral and symmetrical neurological symptoms predominating on the lower limbs. The evolution of the symptomatology over time and until the date of examination was examined as follows: symptom evolution (worse, identical, reduced, totally disappeared), topography (spreading, regressive, totally disappeared) and total duration (months). Moreover, any concomitant medical history that could have worsened or triggered the toxic neuropathy was collected: diabetes, alcohol abuse, dysthyroidism, hepatitis C, HIV infection, significant and fast (<1 month) loss of weight (>5 kg), associated neurological toxic medication and neurotoxic chemotherapy. Patients were also asked about concomitant or subsequent skin changes in order to take into account a possible hand-foot syndrome (HFS). We questioned the patients and also referred to their hospital files.

Symptomatic patients were asked what they had been told when symptoms occurred and how they considered their symptoms, if persistent, at the time of examination. We graded them according to the National Cancer Institute Common Toxicity Criteria version 3.0 (CTCAE v3.0): grade 1, asymptomatic, detected on examination/testing only; grade 2, symptomatic, interfering with function but not interfering with activities of daily living (ADL); grade 3, symptomatic, interfering with ADL; grade 4, life-threatening, disabling; grade 5, death. This scale was used rather than the Total Neuropathy Score to assess chemotherapy-induced peripheral neuropathy in order to compare our data with those in the previous literature, which preferentially reports the use of the CTC scale.

Electroneuromyography (ENMG) examination

The ENMG was performed by one of the neurophysiologists who had screened the patients for inclusion. Neurophysiological studies, using a Viking Select (Viasys, v10b, 2002), incorporated conventional motor and sensory nerve conduction studies: motor conduction velocities, F waves distal latencies, compound motor and sensory action potentials, and sensory conduction studies of the median, ulnar, peroneal, tibial and sural nerves. EMG exploration was performed with a concentric needle electrode in the bilateral distal muscles (extensor digitorum brevis, tibialis

anterior and gastrocnemius) and in the territory of the complaint of the patient; if the latter was considered "neurogenic," more proximal muscles were pricked as well as in the upper limbs, taking into account the tolerance of the patient.

The ENMG examination was classified as moderate or severe, sensory, motor or sensory-motor, and axonal or demyelinating polyneuropathy. Other diagnoses are otherwise specified.

Analysis

Patients were analyzed separately, according to the type of chemotherapy (docetaxel, paclitaxel or both). Results are expressed as mean ± standard deviation (SD), and in median, and 1st and 3rd interquartile ratios (Q1–Q3) when the mean was not representative of the population distribution.

Results

Patient characteristics (Tables 1, 2)

Sixty-nine patients were consecutively examined during a 7-month period, 1–13 years (mean: 3.9 ± 2.5 years, median: 3 years, Q1–Q3: 2–5 years) after the last taxane cure. They were exclusively women, and the mean age at the time of examination was 58 ± 9 years (36–80). Sixty-two had a medical history of breast cancer, one had a leiomyosarcoma, and six had ovarian cancer.

Fifty (72%) of the patients received associated anticancer drugs, and among them 41 (82%) received one or both of the following: 5-FU ($n = 35$) and platinum-based agents for all ovarian cancers ($n = 6$).

Twenty-five (36%) remained free of neurological symptoms at the date of inclusion, and 44 (64%) had complained or were still complaining of four distal paresthesias or of numbness and finger paresthesias, or of a loss of dexterity; 6 of the 44 symptomatic patients (14%) reported total symptom disappearance in "a few weeks" following the last cure (this last point could not be precisely described by our patients). Among these symptomatic patients, 17 (39%) had abnormal neurological examinations. However, they all considered their symptoms as minor and could be classified as having grade 2 (CTCAE v3.0) sensory neuropathy. Only three patients considered their symptoms as severe and were graded 3 (CTCAE v3.0) (two in the docetaxel group and one in the paclitaxel group). The first one improved within weeks, and her neuropathy was graded 2 at the time of inclusion. The other two presented asymmetrical sensory-motor neuropathy. No neurological examination description could be found in the final hospitalization files, except for the three patients who developed more severe symptoms (Table 1).

Table 1 Clinical characteristics of the cohort of patients treated by taxanes

	Total $n = 69$	Docetaxel $n = 56$	Paclitaxel $n = 10$	Both $n = 3$
Asymptomatic *n* (%)	25 (36)	22 (40)	3 (30)	0
Symptomatic *n* (%)	44 (64)	34 (60)	7 (70)	3 (100)
Four extremities paresthesia	37 (84)	28 (82)	7 (100)	2 (67)
Fingers paresthesia	4 (9)	4 (12)	0	0
Loss of dexterity	3 (7)	2 (6)	0	1 (33)
Onset of symptoms *n* (%)				
During the cure	30 (68)	23 (68)	5 (71)	2(67)
1 month after the last cure	14 (32)	11 (33)	2 (29)	1 (33)
Evolution *n* (%)				
Total and progressive disappearance of symptoms	6 (14)	5 (15)	1 (14)	0
Progressive reduction of symptoms	12 (27)	9 (26)	2 (29)	1 (33)
Persistence of unchanged symptoms	26 (59)	20 (59)	4 (57)	2 (67)
Abnormal clinical examination *n* (%)	17 (39)	11 (32)	5 (71)	1 (33)
Classification of *residual* symptom intensity by patients *n* (%)				
Minor	36 (95)	28 (97)	5 (83)	3 (100)
Moderate	0	0	0	0
Severe	2 (5)	1 (3)	1 (17)	0

Table 2 Characteristics of abnormal electroneuromyography (ENMG); 5-FU, 5-fluorouracil

Type of chemotherapy	Patient type of cancer	Taxane cumulative dose/associated drug	Physical examination	ENMG
Paclitaxel	1 Ovarian	900 mg/m^2 + carboplatin	Distal and proximal lower limb paresis and areflexia, pinprick hypoesthesia, loss of vibratory perception	Severe asymmetrical peripheral axonal sensory motor polyneuropathy
	2 Breast	600 mg/m^2 + 5FU	Lower limbs areflexia, toes hypoesthesia	Moderate peripheral axonal sensory polyneuropathy
	3 Ovarian	900 mg/m^2 + Cisplatin	Lower limbs areflexia, toes hypoesthesia	Moderate peripheral axonal sensory polyneuropathy
Docetaxel	4 Breast	300 mg/m^2	Toe and finger hypoesthesia	Moderate peripheral axonal sensory polyneuropathy
	5 Breast	350 mg/m^2 + 5FU	Toe and finger paresthesia	Moderate peripheral axonal sensory polyneuropathy
	6 Breast	525 mg/m^2	Loss of dexterity, fingers paresthesia	Bilateral carpal tunnel syndrome
	7 Breast	525 mg/m^2	Toe and finger paresthesia, deep tendon areflexia, lower limbs motor deficit	Severe asymmetrical peripheral axonal sensory motor polyneuropathy + left carpal tunnel syndrome

None of the patients could remember swelling, erythema or desquamation of the hands or feet that could have corresponded to hand-foot syndrome, and these were not related in the hospital files.

Fourteen out of the 44 (32%) symptomatic patients agreed to have an ENMG examination: 7 had normal results; the results of the other 7 are described in Tables 2 and 3.

Docetaxel group

Fifty-six patients were exposed to docetaxel [mean age 58 ± 9 years (36–80)]. The mean cumulative dose was 400 ± 205 mg/m^2 (75–100 mg/m^2 by cycle). The median cumulative dose was 350 mg (Q1–Q3: 262–525). The patients were examined 1–13 years after the last cure (mean: 4 ± 2.6 years, median: 3 years, Q1–Q3: 2–5 years). Thirty-four (60%) presented neurological symptoms that consisted of four distal paresthesias in 28 (82%), which were concomitant for the majority, finger paresthesias in 4 (12%) and loss of dexterity in 2 (6%). They occurred during the first cycles of chemotherapy in 23 patients (68%). 5-FU was added in 25 patients: 15 remained asymptomatic and 10 experienced peripheral neurological symptoms, which completely disappeared for 2.

At the time of inclusion, 20 (59%) of the patients had unchanged and persistent symptoms, 9 (26%) observed symptom reduction, while only 5 (15%) had become asymptomatic in a few weeks.

The neurological examination was abnormal in 11 of the 34 (32%) patients who had initially presented neurological symptoms: weak or absent lower limb deep tendon reflexes (10), distal hypoesthesia (4) and mild ataxia (3), and one had proprioceptive abnormalities associated with a left lower limb monoparesis.

Eleven patients accepted the ENMG, and seven had normal results. In the patients who were still symptomatic (mild distal hypoesthesia with decreased deep tendon reflexes) we found: moderate axonal sensory neuropathy (2), isolated bilateral carpal tunnel syndrome (1) and 1 asymmetrical lower limb sensory-motor neuropathy with increased left F wave latencies and S1 neurogenic detection, suggesting additional root impairment with asymptomatic left carpal tunnel syndrome (Tables 2, 3, patient 7). For this last patient who had unilateral monoparesis, lumbar MRI showed spinal stenosis and left pluriradicular compression.

Six patients presented associated hypothyroidism and five diabetes mellitus. Among these patients, all but one experienced four distal paresthesias, which were persistent for three, improved for four and had totally regressed for two. No other risk factor for developing a neuropathy was identified (in particular alcoholism, nutritional deficiency or significant weight loss), except neurotoxic chemotherapy as described above.

Six patients presented clinical symptoms consistent with carpal tunnel syndrome. None of them was diabetic. Only for one did performing ENMG confirm the clinical diagnosis.

Paclitaxel group

Ten patients were exposed to paclitaxel, mean age 58 ± 8 years (43–74). The mean cumulative dose was 597 ± 296 mg/m^2 (150 mg/m^2 by cycle). The median

Table 3 Electroneuromyographical results of the patients in Table 2

Nerves	1 (Ovarian)	2 (Breast)	3 (Ovarian)	4 (Breast)	5 (Breast)	6 (Breast)	7 (Breast)
Motor conduction studies							
Peroneal							
DML, ms R/L	NR/5.5	2.6/2.9	3.6/2.9	4.6/4.4	4/3.6	4.1/4.5	5/11.1
MEP amplitude, mV R/L	NR/0.4	3.8/4.9	4.1/3.9	5/3.9	2.9/3.3	2.7/3.7	0.8/0.2
MCV, m/s R/L	NR/35	47/45	43/45	48/46	45/44	47/51	40/39
F latency, ms R/L	NR/NR	46/46	44/45	46/46	49/NO	–/–	46/NR
Tibial							
DML, ms R/L	5.0/4.8	4.3/3.4	3.8/4.1	4.9/5	–/5.0	3.9/4.9	4.4/4.8
MEP amplitude, mV R/L	0.5/0.5	6.6/5.7	7.8/6.6	5.5/6.3	–/11.1	4.2/5.7	4.3/4.2
MCV, m/s	35/35	41/40	41/44	–/–	–/50	42/48	38/39
F latency, ms	–/–	50/50	51/50	54/53	–/56	–/–	53/56
Median							
DML, ms R/L	–/3.4	–/2.9	–/3.1	–/3.4	–/3.6	3.9/3.3	3.6/7.1
MEP amplitude, mV R/L	–/5.8	–/4	–/4.3	–/7	–/5.6	5.8/6.8	4.6/2.7
MCV, m/s	–/54	–/58	–/47	–/50	–/53	45/48	46/37
F latency, ms	–/30	–/29	–/27	–/27	–/30	–/–	–/–
Ulnar							
DML, ms R/L	–/2.9	–/2.3	–/2.4	–/2.5	–/2.6	2.2/2.6	–/2.6
MEP amplitude, mV R/L	–/5.8	–/9.8	–/7.2	–/7.6	–/7.8	8.6/8.8	–/7.2
MCV, m/s	–/54	–/56	–/54	–/58	–/55	–/59	–/56
F latency, ms	–/31	–/30	–/30	–/29	–/30	–/–	–/25
Sensory conduction studies							
Sural							
SEP amplitude, μV R/L	5/6	8/8	6/7	7/7	7/9	10/10	34/15
SCV, m/s	36/38	42/40	39/40	40/39	34/34	41/40	40/38
Superficial peroneal							
SEP amplitude, μV R/L	NR/NR	4/3	5/4	5/3	–/4	9/9	2/3
SCV, m/s	NR/NR	39/36	38/40	–/38	–/35	40/41	36/38
Median							
SEP amplitude (palm), μV R/L	6/7	–/30	–/12	10/6	–/14	11/18	18/NR
SCV, m/s	34/37	–/42	–/41	42/44	–/40	33/39	43/NR
Ulnar							
SEP amplitude, μV R/L	1/3	–/6	–/6	5/3	3/4	10/11	–/9
SCV, m/s	–/36	–/49	–/44	40/42	35/40	44/45	–/43
Detection							
Extensor digitorum brevis, R/L	NR/NR	N/N	N/N	–/N	N/N	–/–	N/den
Tibialis anterior, R/L	NR/den	–/N	N/N	N/N	–/–	–/–	N/den
Gastrocnemius, R/L	–/–	–/–	–/–	–/–	–/–	–/–	–/den
Vastus medialis, R/L	Fib, PSW/–	–/–	–/N	–/–	–/–	–/–	–/N
FDM, R/L	–/N	–/N	–/–	N/N	–/–	–/–	–/N
ABD pollicis brevis, R/L	–/–				–/N	–/–	N/den

Normal values are in brackets

Incomplete data are related to bad tolerance by the patient or fear of having the "lymphoedema arm" examined

DML Distal motor latency (<5 ms for lower limbs, <3.6 ms for median, <3 ms for ulnar); *MEP* motor-evoked potential amplitude (>2 mV for peroneal, >4 mV for tibial, >4 mV for median and >5 mV for ulnar); *MCV* motor conduction velocity (>42 m/s for peroneal, >40 m/s for tibial, >45 m/s for upper limbs); F waves (<50–55 ms for lower limbs and <28–30 ms for upper limbs); *SEP* sensory-evoked potential amplitude (>8 μV for lower limbs, >15 μV for median, >10 μV for ulnar); *SCV* sensory conduction velocity (>40 m/s for lower and upper limbs); *den* denervated muscle; *fib* fibrillation potential; *PSW* positive sharp waves; *R* right; *L* left; *NR* no response

cumulative dose was 525 mg (Q1–Q3: 350–780). The patients were examined 1–6 years (mean 2.9 ± 1.5 years, median 2.9 years, Q1–Q3: 2–3 years) after the last cure. Associated chemotherapy was given as follows: six patients had additional 5-FU (two in association with platinum-based agents), and four had associated platinum-based agents only.

Seven (70%) had presented neurological symptoms. All of them reported four distal concomitant paresthesias that began during the first cycles of chemotherapy for five. For the three patients who remained free of symptoms, one had received platinum-based agents, one had 5-FU-associated chemotherapy, and paclitaxel was given only for the last one.

Four (57%) had persistent symptoms and three a reduction of initial symptoms. Neurological examination was abnormal for five (71%): isolated absent ankle deep tendon reflexes (2), and lower limb areflexia and distal lower limb hypoesthesia associated with distal hypopallesthesia (3). All patients but one (Tables 2, 3, patient 1) considered their symptoms as minor. This patient initially had bilateral and symmetrical mild distal hypoesthesia, and toe motor deficit (MRC 4/5) appeared during the cures. Chemotherapy was not stopped, and the motor deficit spread more proximally within months until it affected the right ilopsoas and vastus medialis muscles.

Three who accepted the ENMG showed a moderate axonal sensory polyneuropathy in two, and in the third one (patient 1) treated for a metastatic ovarian cancer, severe asymmetrical sensory motor neuropathy. Pelvic gadolinium-injected magnetic resonance imaging (MRI) showed a peritoneal carcinosis and neoplasic infiltration of the lumbar plexus and nerves.

The classical pain syndrome attributed to paclitaxel (myalgia, arthralgia, aches and cramps) was very often experienced, but disappeared at the end of each cure and is not considered here.

Paclitaxel and docetaxel group

Three patients [mean age 68 ± 8 years (59–74)] received both drugs. The mean cumulative dose was 530 ± 319 mg/m^2 for docetaxel and 962 ± 437 mg/m^2 for paclitaxel. The patients were examined 1–4 years after the last cure. The three patients had presented four distal paresthesias that began after the first cures for three and involved loss of dexterity for one within the month she had stopped the treatment. One received associated platinum-based agents; two had persistent symptoms at the time of examination, and one experienced progressive symptom reduction.

The neurological examination was abnormal for one of them and showed general areflexia. All three patients refused ENMG examination.

Discussion

Taxane-induced peripheral neuropathy is a frequent clinical problem, but little is known about the neurological sequellae. Although very frequent in our series (60% in the docetaxel group and 70% in the paclitaxel group), the long-term neurological prognosis was very good, and residual neurological symptoms did not affect daily life activities.

Our patients were included in a consecutive way, but anamnestic data were collected in a retrospective way, with an obvious bias linked to the inaccurate recall of memories. Indeed, although patients' hospital files were helpful concerning the oncological data, there was no mention of neurological examinations except in three of them. However, the present study allows describing the long-term prognosis (median follow-up, 3 years) of taxane-induced neuropathy in a large cohort of patients for the first time. Most importantly, patients were examined by a neurologist, and criteria for neuropathy and chemotherapy imputability (paresthesias or loss of dexterity appeared after the onset of the taxane chemotherapy and not after the month following the last cure of the chemotherapy regimen) were carefully examined.

Docetaxel-induced neuropathy incidence has been reported variably in the literature at 11 [6], 49 [7] and 64% [4]. In contrast, the incidence of paclitaxel-induced neuropathy is regularly higher at 59 [4], 69 [8], 71 [3] and 87%. [5] Taxane-induced neurotoxicity studies have been carried out using a variety of doses, schedules and combined regimens of other neurotoxic chemotherapies, and the relation of the current dose to neurotoxicity is therefore difficult to determine.

The lowest dose triggering neuropathy could not be determined in our series, since neurological symptoms were almost never mentioned in the hospital files. However, loss of dexterity and finger paresthesias could be seen in docetaxel-treated patients at a cumulative dose of 100 mg/m^2 and four distal concomitant paresthesias at 225 mg/m^2. Information in the literature is controversial, and the dose ranges from 50 [6], to 200 [2, 7] to 371 mg/m^2 in a large study published by Jones et al. [4]. Severity, defined as interfering with daily life activities, could also be dependant on the total cumulative dose. Hilkens et al. [7] reported, in 15 patients treated by a cumulative dose of docetaxel >600 mg/m^2, only one severe sensory neuropathy and three moderate polyneuropathies. In our study, five of our patients had a cumulative dose >600 mg/m^2 (mean 880 mg/m^2), and all of them developed a mild sensory polyneuropathy that was still persistent at the time of our examination, except in one (Tables 2, 3, patient 7). For paclitaxel, Jones et al. [4] reported a cumulative dose of 715 mg/m^2 for onset of severe grade neuropathy. Although paclitaxel-induced neuropathy was very frequent in our

study, within this cumulative dose range, only one severe neuropathy was found, but later it could be attributed to pelvic nerve neoplasic infiltration.

The range of symptom severity within individuals at a similar dose level suggests that there are other factors precipitating neurotoxicity. Diabetes and associated platinum-based treatments were identified as risk factors for paclitaxel- [9–11] or for docetaxel-induced neuropathy [12]. In our series, five patients were diabetic in the docetaxel group, and all have developed four distal paresthesias that totally regressed for one. Previous nerve fragility is also an important risk factor. As reported by Martino et al. [13], a patient with Charcot-Marie-Tooth disease, an inherited genetic disorder of the peripheral nervous system, first treated by paclitaxel/carboplatin for ovarian cancer had such a worsening of her neuropathy, which impacted daily life activities, that paclitaxel was switched for docetaxel/carboplatin, resulting in the patient's dramatic improvement within 3 months. This also indicates that paclitaxel is probably more neurotoxic than docetaxel, as also suggested by the increased incidence of induced neuropathy with this latter drug. Chaudhry et al. [10] reported a 95% neuropathy incidence for an association of paclitaxel >350 mg/m^2 and cisplatin ($n = 8$), and Sarosy et al. [5] an 87% incidence ($n = 62$), while in our series, 7 (100%) of the paclitaxel symptomatic patients were treated with a combination of 5-FU or carboplatin/cisplatin. Platinum-based agents' role in the severity of neuropathy is difficult to assess since, as shown in previous studies, paclitaxel discontinuation generated a reduction of neurological symptoms, although platinum-based agents were continued. In contrast, 5-FU could not be proven to have a synergistic effect in our study, since 40% of patients receiving docetaxel and 5-FU developed a neuropathy, while 60% remained asymptomatic.

At the time of inclusion, four (12%) and two (6%) of the symptomatic patients treated by docetaxel reported having had isolated bilateral finger paresthesias and loss of dexterity. Only one accepted ENMG, and bilateral carpal tunnel syndrome was evidenced (Tables 2, 3, patient 6), without a history of diabetes mellitus or hypothyroidism. All of these patients had ispilateral lymphoedema, but could not remember its time of onset. Whether these symptoms can be attributed to taxanes or lymphoedema cannot be solved here. Interestingly, Vignes et al. [14] described a peculiar aspect of docetaxel-associated lymphoedema, a "scleroderma-like" lesion characterized by histiocytic and macrophagic infiltration and lymphangiectasia, without signs of vascularitis. It is reasonable to think that it could promote nerve entrapment, such as the median nerve, but this deserves a dedicated study.

Only 15% of patients observed a total disappearance of symptoms within months after the last cure. However, despite the persistence of symptoms for all the others (Table 1), they considered that symptoms were minor or moderate and did not interfere with daily life activities, as already reported [3, 15]. Indeed, only patients 1 and 7 reported pain, severe ataxia or motor deficits (Table 2). These two patients, treated respectively by a cumulative dose of 900 mg/m^2 paclitaxel associated with cisplatin and 525 mg/m^2 docetaxel, presented a sensory-motor polyneuropathy. The motor deficit was first distal and symmetrical. As taxanes were not discontinued, the evolution of the motor deficit was first attributed to taxane toxicity. Worsening to asymmetrical motor proximal deficit led to gadolinium-injected pelvis and lumbar spinal MRI, which evidenced diffuse peritoneal carcinomatosis with nerve infiltration (patient 1) and lumbar spinal stenosis with root involvement (patient 7). Although worsening of neuropathy can occur up to 4 months after the discontinuation of chemotherapy [6, 16], this particular evolution in our patients and the proximal involvement of lower limbs prompts us to seek another cause. In the same way, Chaudhry et al. [10] described one case of paclitaxel-induced sensory polyneuropathy complicated by unilateral foot drop, assessed on ENMG as a peroneal palsy at the fibular head. Moreover, motor neuropathies are rarely reported, whatever the taxane used [4, 6], and should be an additional alarm for the practitioner.

In 14 ENMGs, with all patients being symptomatic, seven had normal results, suggesting that small fibers were preferentially affected in those patients; four had classical axonal sensory polyneuropathy according to the electrophysiological data (symmetrical, length dependent and predominating in lower limbs), although the patients experienced four concomitant distal paresthesias; three had additional nerve and root entrapments (patients 1, 6 and 7; Tables 2, 3). Others usually found this classical electrophysiological pattern for paclitaxel [3, 10] and docetaxel [6, 12, 16]. The critical dose for abnormal ENMG was variable between studies and can only be addressed when ENMG is performed before and during the patient's follow-up at regular time points, which was not possible in our study. Park et al. [3], in 28 paclitaxel-treated patients, stressed early sensory dysfunction on ENMG that predated symptom onset. However, determining toxic chemotherapy thresholds is interesting in case of rapid, disabling, severe neurotoxicity, but this does not seem to be the case for taxane-treated patients.

Despite persistent sensory complaints, these were not considered sufficient to stop taxane chemotherapy, and no patient saw a neurologist. Given the absence of worsening in these patients and underlying disease, this attitude seems reasonable. Three of our patients were found to have hand-foot syndrome, which refers in fact to dysesthesias (tingling sensation) of the palms and soles progressing within a

few days to a burning sensation, swelling and erythema, affecting the hands more commonly than the feet, possibly developing into desquamation, which usually resolves with the drug discontinuation. However, no description of the clinical examination was found in the hospital medical records, and none of these three patients could remember a skin change, which is the hallmark of the disease.

In conclusion, our series shows that the incidence of taxane-induced neuropathy is high (64%), more frequent with paclitaxel than docetaxel (70 vs. 60%), and is characterized by minor or moderate axonal sensory polyneuropathy. This peripheral neurological complication can occur with a low dose of chemotherapy (100 mg/m^2), as in our study, and is extremely well tolerated when persistent, 1–13 years after the end of the last cure, by the patient and by the practitioner. When clinical motor signs occur, the patient should be referred to a neurologist to investigate other causes.

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Roglio I, Bianchi R, Camozzi F, Carozzi V, Cervellini I, Crippa D, Lauria G, Cavaletti G, Melcangi RC (2009) Docetaxel-induced peripheral neuropathy: protective effects of dihydroprogesterone and progesterone in an experimental model. J Periph Nerv Syst 14:36–44
2. Lipton RB, Apfel SC, Dutcher JP, Rosenberg R, Kaplan J, Berger A, Einzig AI, Wiernik P, Schaumburg HHl (1989) Taxol produces a predominantly sensory neuropathy. Neurology 39:368–373
3. Park SB, Lin CS, Krishnan AV, Kiernan MC, Friedlander ML, Lewis CR, Kiernan MC (2011) Early, progressive, and sustained dysfunction of sensory axons underlies paclitaxel-induced neuropathy. Muscle Nerve 43:367–374
4. Jones SE, Erban J, Overmoyer B, Budd GT, Hutchins L, Lower E, Laufman L, Sundaram S, Urba WJ, Pritchard KI, Mennel R, Richards D, Olsen S, Meyers ML, Ravdin PM (2005) Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 22:5542–5551
5. Sarosy AG, Hussain MM, Seiden MV, Fuller AF, Nikrui N, Goodman A, Minasian L, Reed E, Steinberg SM, Kohn EC (2010) Ten-year follow-up of a phase 2 study of dose-intense paclitaxel with cisplatin and cyclophosphamide as initial therapy for poor-Prognosis, advanced-stage epithelial ovarian cancer. Cancer 116:1476–1484
6. New PZ, Jackson CE, Rinaldi D, Burris H, Barohn RJ (1996) Peripheral neuropathy secondary to docetaxel (Taxotere). Neurology 46:108–111
7. Hilkens PH, Verweij J, Stoter G, Vecht CJ, Van Putten WL, Van den Bent MJ (1996) Peripheral neurotoxicity induced by docetaxel. Neurology 46:104–108
8. Argyriou AA, Polychronopoulos P, Koutras A, Xiros N, Petsas T, Argyriou K, Kalofonos HP, Chroni E (2007) Clinical and electrophysiological features of peripheral neuropathy induced by administration of cisplatin plus paclitaxel. Eur J Cancer Care 16:231–237
9. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC (1993) Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol 20:1–15
10. Chaudhry V, Rowinsky EK, Sartorius SE, Donehower RC, Cornblath DR (1994) Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies. Ann Neurol 35:304–311
11. Lee JJ, Swain SM (2006) Peripheral Neuropathy Induced by Microtubule-Stabilizing Agents. J Clin Oncol 24:1633–1642
12. Hilkens PH, Pronk LC, Verweij J, Vecht CJ, van Putten WL, van den Bent MJ (1997) Peripheral neuropathy induced by combination chemotherapy of docetaxel and cisplatin. Br J Cancer 75:417–422
13. Martino MA, Miller E, Grendys EC Jr (2005) The administration of chemotherapy in a patient with Charcot-Marie-Tooth and ovarian cancer. Gynecol Oncol 97:710–712
14. Vignes S, Lebrun-Vignes B (2007) Sclerodermiform aspect of arm lymphoedema after treatment with docetaxel for breast cancer. J Eur Acad Dermatol Venereol 21:1131–1133
15. Nahleh Z, Pruemer J, Lafollette J, Sweany S (2010) Melatonin, a promising role in taxane-related neuropathy. Clinical Medicine Insights: Oncology 4:35–41
16. Hilkens PH, Verweij J, Vecht CJ, Stoter G, Van den Bent MJ (1997) Clinical characteristics of severe peripheral neuropathy induced by docetaxel (Taxotere). Ann Oncol 8:187–190