J Neurol (2005) 252 : 1459–1464
DOI 10.1007/s00415-005-0887-8

ORIGINAL COMMUNICATION

Andreas A. Argyriou
Panagiotis Polychronopoulos
Gregoris Iconomou
Angelos Koutras
Haralabos P. Kalofonos
Elisabeth Chroni

Paclitaxel plus carboplatin-induced peripheral neuropathy

A prospective clinical and electrophysiological study in patients suffering from solid malignancies

Abstract *Objective* The current study intended to determine the incidence, severity and reversibility of paclitaxel plus carboplatin (CP)-induced peripheral neuropathy (CPPN) and to describe its clinical and electrophysiological features. *Patients and methods* We prospectively studied 21 adult patients scheduled to be treated with 6 courses of cumulative carboplatin plus paclitaxel (CP) regimens for a non-myeloid malignancy. They were followed-up by neurological examination and electrophysiological study during chemotherapy and 3 months after its discontinuation. The severity of neurotoxicity was assessed by means of a modified peripheral neuropathy (PNP) score. *Results* Evidence of CPPN was recorded in 14 of the 21 patients (66.6 %). The sensory symptoms were present in the lower limbs first and then involved the upper limbs. No statistical significance, concerning the changes from baseline to subsequent mean scores in all motor conduction parameters examined, was revealed. By contrast, comparisons of the mean changes at baseline and each of the follow-up studies showed significant decrease in all sensory action potentials examined. The mean PNP scores for patients that manifested some grade of neurotoxicity were 17.9 ± 9.8. The follow-up data 3 months after the discontinuation of chemotherapy showed that the CP-induced neuropathy was at least partially reversed. *Conclusion* CP-induced neuropathy was symmetrical, distal and predominately sensory in character, though minor to moderate motor signs were only evident in severely affected patients. Reversibility of CP-induced neuropathy was partially observed after the suspension of chemotherapy.

Key words carboplatin plus paclitaxel · peripheral neuropathy · monitoring · incidence · severity

Received: 7 February 2005
Received in revised form: 22 March 2005
Accepted: 13 April 2005
Published online: 15 November 2005

A. A. Argyriou, MD (✉) ·
P. Polychronopoulos, MD ·
E. Chroni, MD, PhD
Dept. of Neurology, Laboratory of Clinical Neurophysiology
University of Patras Medical School
P. O. Box 1045
Rion, Patras, Greece
Tel./Fax: +30-2610/993-949
E-Mail: andargyriou@yahoo.gr

G. Iconomou, PhD · A. Koutras, MD, PhD ·
H. P. Kalofonos, MD, PhD
Dept. of Medicine, Division of Oncology
University of Patras Medical School
Rion-Patras, Greece

Introduction

Paclitaxel is a taxane-based cytotoxic agent that possesses a broad spectrum of activity against several solid malignancies [24]. Peripheral nerve damage due to paclitaxel administration occurs as a result of paclitaxel capacity to bind to tubulin, blocking its polymerization, thus resulting in dysfunctional microtubules [22]. Rowinsky et al. [23] have first described that cumulative doses of paclitaxel that exceed 1000 mg/m^2 are strongly associated with a distal, predominantly sensory axonopathy, commonly resulting in changes in the treatment plan and in alterations in the quality of life (QOL) of patients with cancer.

Several phase I and II studies have shown that combination therapy with carboplatin plus paclitaxel (CP) is an active and reasonably well-tolerated regimen as first-line treatment of patients with metastatic breast, advanced non-small-cell lung and ovarian malignancies [9, 11, 14]. Despite the fact that the hematological toxicities encountered by the combined administration of CP are relatively limited, neurotoxicity remains an important dose-limiting adverse event. Previous studies,

which have compared the safety profile of the high neurotoxic regimen of cisplatin plus paclitaxel that of CP, have reported relative similarities concerning to the incidence and severity of neurotoxicity between those regimens [7, 18]. However, there is still a relative paucity of data concerning the clinical and electrophysiological profile of CP-induced peripheral neuropathy (CPPN). Another question which remains to be answered is whether carboplatin acts synergistically to paclitaxel, which is a well known neurotoxic drug.

The current study intended to address a threefold objective. First, to evaluate the incidence and severity of CPPN, second to determine its clinical and electrophysiological features and third to describe its natural history by following-up examination during chemotherapy and after the discontinuation of CP.

Patients and methods

Study design

This was a single-center, prospective, evaluation study which was conducted in accordance with the principles of the Declaration of Helsinki. After approval by the Institutional Review Board of Patras Medical School, we only included patients who gave written informed consent prior to study entry.

Patients' selection

Adult patients with cancer scheduled to be treated with 6 courses of cumulative CP regimens for a non-myeloid malignancy were enrolled in the current study. Patients were recruited from the Division of Oncology at the University Hospital of Patras, Greece, whilst the clinical and electrophysiological evaluations were performed at the Neurology Department of the same institution.

Patients were only enrolled if they had satisfactory liver and renal function, life expectancy of at least 9 months, WHO performance score of 0–1 and ability to understand medical advice. Patients having history of peripheral neuropathy (i. e., hereditary, associated with nutritional agents and paraneoplastic causes) as well as patients with systemic diseases (i. e. diabetes mellitus, SLE, HIV, alcohol abuse) were drawn out from the study cohort. Patients were also excluded if they were not chemotherapy naïve, or when clinical or electrophysiological evidence of peripheral neuropathy was disclosed at baseline. The stage of disease was not within inclusion/exclusion criteria, as the study cohort aimed to represent the wide range of patients treated with CP in community based medical oncology practices. To eliminate the possibility of pre-existing neuropathy, all patients enrolled were evaluated at baseline by the same neurologist who performed both clinical and electrophysiological evaluation. The findings of all electrophysiological evaluations both pre- and post treatment were confirmed by an independent senior neurologist.

Clinical evaluation

The clinical evaluation of neuropathy was based on a modified Neurological Symptom Score (NSS) and Neurological Disability Score (NDS) proposed by Dyck et al. [8]. NSS selected symptoms such as weakness, numbness or pain, scoring as present [1] or absent (0). Clinical signs (i. e., cranial nerves function; joint position, pinprick and vibration sensation; muscle strength and deep tendon reflexes) were assessed using a modified version of NDS, ranging from 0 (no deficit) to 4 (absence of function/severest deficit). Hughes' Functional Grading Scale (FGS) assessed the functional ability, particularly mobility, ranging from 0 (healthy) to 5 (requiring artificial ventilation for at least part of the day) [13].

Electrophysiological evaluation

Neurophysiological examination was carried out unilaterally (right side), employing standard methods by means of surface stimulation and recording [12]. Electrophysiological study included motor conduction of ulnar and peroneal nerves with measurements of peak to baseline amplitude of compound muscle action potential (a-CMAP), distal motor latency (DML), motor conduction velocity (MCV) and F-wave minimum latency estimated from measurements of 20 F-waves. Sensory conduction of ulnar (orthodromic technique), sural and superficial peroneal nerves (antidromic technique and proximal segment) with measurements of peak-to-peak amplitude of sensory action potentials (a-SAP) and sensory conduction velocities (SCV), were also recorded. For longitudinal comparison of neurophysiological parameters we adopted the widely accepted criteria of identification of abnormalities, based on serial measurements on healthy human subjects [12, 19]. The battery of the clinical and electrophysiological tests described above was repeated by the same neurologist after the 3rd and 6th course of chemotherapy. To determine the course of neuropathy and identify a potential reversibility of peripheral nerve function, all patients were followed-up for 3 months after the suspension of chemotherapy and the results between the 6th chemotherapy course were compared to those of the follow-up evaluation.

Overall evaluation of neurotoxicity

The results of the clinical and electrophysiological study were summarized by means of a modified Peripheral Neuropathy (PNP) score, previously described by Chaudhry et al. [4]. PNP scores graded neurotoxicity as mild [1–11], moderate [12–23] and severe (> 24) corresponding to the WHO grading scales 1–3 for chemotherapy-induced peripheral neuropathy [17].

Statistical analyses

Descriptive statistics were generated for all variables. The changes in mean clinical and electrophysiological scores both during chemotherapy as well as between the 6th course of chemotherapy and 3 months after its cessation were examined using paired samples *t*-tests. All tests were two-sided and significance was set at the $P < 0.05$ level. The SPSS for Windows (release 10.0; SPSS Inc., Chicago, IL) performed the statistics.

Results

Demographics and baseline clinical characteristics

Six courses of carboplatin at an area under the curve (AUC) of 6 given over a 30 minutes infusion and paclitaxel at a dose of 175 mg/m^2 given over a 3 hour infusion were administered on day 1 to twenty-one patients with various cancer diagnoses. The demographics and baseline clinical characteristics of overall patients are given in Table 1.

Table 1 Patients' baseline and clinical characteristics

Variable	Study sample n = 21	
	N	%
Sex (females vs males)	13	81.3
Age ± SD	57.2 ± 11.5	
Tumor type		
Lung cancer (NSCLC)	5	23.8
Breast cancer	9	42.9
Ovarian cancer	7	33.3
Drug doses/course of CMT (mg)		
Carboplatin mean ± SD dose	fixed AUC 6	
Paclitaxel mean ± SD dose (range)	324.1 ± 29.5 (270–360)	

Incidence and severity of peripheral neuropathy

Evidence of CPPN was recorded in 14 of the 21 patients (66.6 %). The mean PNP scores for patients who manifested some grade of neurotoxicity were 17.9 ± 9.8 (range 6–32). According to the PNP scores, the severity of neurotoxicity was graded as mild in four (28.6 %), moderate in seven (50 %), severe in three (21.4 %), whilst the remaining 7 out of the overall 21 patients remained free of CPPN symptoms.

Clinical features of peripheral neuropathy

The sensory symptoms were initially manifested in the lower limbs first and then involved the upper limbs. The main clinical complaints were numbness/paresthesia in the distal extremities and more specifically limited to fingers/toes (n = 4) or in a stocking-and-glove distribution (n = 6). Cranial nerves were spared. There were graded proprioceptive sensory disturbances mainly in a stocking-and-glove distribution with vibration sensation being more affected. Ankle hyporeflexia was also observed (n = 7). In case of severely affected patients (n = 3) the distal numbness/paresthesia extended up to the knees/elbows, whilst all of them had decreased pin and vibration sensation up to the knees/elbows, ankle areflexia and hyporeflexia elsewhere. Mild weakness (n = 2), mainly involving the toe extension and finger abduction muscles was also evident (4/5 on the MRC scale). However, needle electromyography (EMG) performed only in those patients, revealed normal configuration of the motor units without active denervation potentials.

As assessed by the FGS scores, the functional ability of patients with evidence of CPPN was relatively influenced, estimating it as grade 1 (minor symptoms, fully capable of manual work) in 4, grade 2 (able to walk > 10m unaided) in 6 and grade 3 (able to walk > 10m with a walker or support) in four of them, whilst evidence of grade 4 functional ability (bed or chair-bound) was not observed.

Electrophysiological features of peripheral neuropathy

No statistical significance concerning the changes from baseline to subsequent mean scores in all motor conduction parameters was revealed (Table 2). By contrast, comparisons of the mean changes at baseline and each of the follow-up studies showed significant decrease in all a-SAPs examined, whilst the same comparisons for sensory conduction velocities failed to reach significance (Table 3). In case of severely affected patients (n = 3), the sensory conduction study revealed complete absence of a-SAPs in all nerves examined after the 3rd course of chemotherapy, whilst in all three patients, even those with mild weakness (n = 2), the ulnar and peroneal CMAPs did not change over time.

Course and prognosis of peripheral neuropathy

The follow-up data, 3 months after the discontinuation of chemotherapy, showed that the CP-induced neuropa-

Table 2 Motor conduction studies

	Baseline	3rd CMT	6th CMT	P value
Ulnar nerve				
DML (ms)	2.7 ± 0.6	2.5 ± 0.4	2.6 ± 0.4	0.564
a-CMAP (mV)	6.1 ± 1.7	6.5 ± 1.7	6.3 ± 1.8	0.745
MCV (m/s)	56.6 ± 6.0	56.3 ± 7.2	56.1 ± 7.4	0.711
F-wave min. lat. (ms)	25.5 ± 2.1	25.7 ± 2.8	25.4 ± 3.5	0.732
Peroneal nerve				
DML (ms)	3.7 ± 0.8	3.8 ± 1.1	4.0 ± 0.9	0.176
a-CMAP (mV)	3.6 ± 1.8	3.8 ± 1.7	3.4 ± 1.8	0.479
MCV (m/s)	51.3 ± 6.4	50.1 ± 5.7	52.1 ± 5.5	0.518
F-wave min. lat. (ms)	46.6 ± 3.0	45.5 ± 4.5	46.1 ± 4.3	0.663

Table 3 Sensory conduction studies

	Baseline	3rd CMT	6th CMT	P value
Ulnar nerve				
a-SAP (μV)	11.2 ± 5.6	9.3 ± 5.1	8.1 ± 4.1	0.014
SCV (m/s)	51.7 ± 5.6	51.3 ± 4.7	52.6 ± 5.1	0.783
Sup. Peroneal nerve				
a-SAP (μV)	11.7 ± 5.3	9.2 ± 6.1	7.8 ± 4.7	0.006
SCV (m/s)	52.3 ± 7.1	46.1 ± 9.1	48.4 ± 4.8	0.249
Sural nerve				
a-SAP (μV)	14.5 ± 9.0	10.1 ± 7.3	9.7 ± 7.1	0.002
SCV (m/s)	54.6 ± 7.7	47.3 ± 9.3	46.3 ± 8.8	0.09

thy is at least partially remitted. All patients with evidence of mild or moderate CPPN have showed a gradual improvement in their clinical and electrophysiological profile (Table 4, Fig. 1). According to the PNP scores on the post treatment examination as compared to those at the 6th course of chemotherapy, no clinical or electrophysiological evidence of further CPPN worsening was disclosed. In case of severely affected patients (n = 3), the sensory conduction study performed at the last follow-up revealed that the sural a-SAP reappeared with low amplitude (2.1 mV) in one of them, so did the superficial peroneal a-SAP (1.8 mV) in another one. However, the severity of their clinical symptoms and signs remained nearly unchanged.

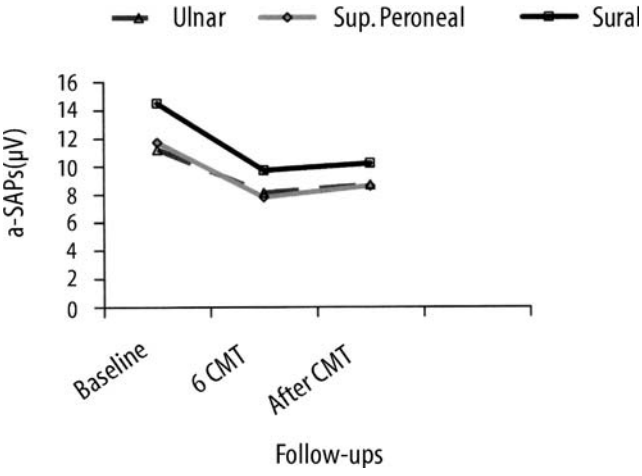

Fig. 1 Changes in electrophysiological scores (a-SAPs) during chemotherapy and three months after its suspension

Discussion

Neurotoxicity and its impact on the patients' quality of life is a well recognized limitation of a number of chemotherapeutic regimes, including CP. The main finding of the current study was that 14 of the 21 patients (66.6 %) treated with carboplatin (AUC 6) plus paclitaxel (175 mg/m^2 over 3 h) manifested a clinically overt peripheral neuropathy, whilst its severity was mild to moderate in the majority of patients.

The incidence of neuropathy observed in our series (66.6 %) corresponds to that previously published by du Bois et al. [7]. These authors reported incidence rates of neurotoxicity in 79 % of their patients treated with CP, a percentage which is approximately in line with our results. In contrast to these results, a significantly lower rate of 25 % and 28 % respectively, was reported from two other recent studies [15, 18].

Differences in the nature of studies and the methodology could account for the discrepancies. Ozols et al. [18] and du Bois et al. [7] evaluated the general tolerability and safety profile of CP as opposed to that of cisplatin and paclitaxel regimen, being not solely focused on assessing the direct effect of CP administration on the peripheral nerves. On the other hand, Markman et al. [15] have exclusively addressed the neurotoxicity profile of CP administration, but as authors recognized there were several important limitations in their study design, mainly concerning the retrospective analysis of the sample size and the lack of objective electrophysiological monitoring.

The current study has been focused on the neurological monitoring of CPPN, based on symptoms, clinical signs and electrophysiological findings, which were summarized by means of a modified PNP score, previously applied in studies referred to toxic neuropathies [1–4]. Specifically, the electrophysiological features of CPPN were defined by a detailed sensory and motor conduction study, including F-waves study performed in chemotherapy naïve patients during and 3 months after the cessation of chemotherapy. Thus, our conclusions were based on objective neurometric tests, ensuring the best possible interpretation of results. A potential limitation is that needle EMG was not included in the study protocol in order to avoid patients' discomfort. This was based on our determination to employ a simple, painless and non-invasive screening for the evidence of CPPN, which is required in terminally-ill patients. However, when performed in two cases with clinical weakness no abnormalities were disclosed. Although the lack of needle EMG could be considered as a possible limitation, the analysis of ulnar and peroneal CMAPs, as demonstrated in Table 2, is considered sufficient for purposes of follow-up studies. The mild muscle weakness observed in two cases, despite the unchanged ulnar and peroneal CMAPs, should be attributed to de-afferentation.

Another possible limitation in the study design is that the follow-up evaluation of 3 months after the suspension of chemotherapy might be not long enough, as in other types of neuropathy the recovery may take several months. However, given that the paclitaxel-induced neuropathy usually recovers shortly after the treatment is completed [27], the duration of 3 months after the

Table 4 Course of neuropathy according to changes in electrophysiological scores (a-SAPs) during chemotherapy and three months after its suspension

	Baseline	6th CMT	After CMT
Ulnar nerve			
a-SAP(μV)	11.2±5.6	8.1±4.1	8.7±4.7
Sup. Peroneal nerve			
a-SAP(μV)	11.7±5.3	7.8±4.7	8.6±4.9
Sural nerve			
a-SAP(μV)	14.5±9.0	9.7±7.1	10.2±8.9

chemotherapy suspension to perform the last follow-up was considered adequate.

The onset of symptoms in the lower extremities in addition to distal sensory loss and suppressed or absent ankle reflexes point towards a dysfunction of sensory nerves, corresponding to the profile of a toxic distal neuropathy [25]. Electrophysiological abnormalities, mainly involving the decrease or abolishment of a-SAPs, confirmed the predominance of sensory fibres involvement. Slowing of motor conduction velocities or F-waves latency delay that would suggest demyelination indirectly implying axonal rather than myelin-Schwann cell damage, were not disclosed.

Unlike the Markman et al. study [15], we have not found any clinical or electrophysiological evidence of further CPPN worsening after cessation of treatment. On the contrary, partial reversibility of neuropathy after the discontinuation of chemotherapy, as particularly demonstrated by the reappearance of sural a-SAP in 2 of 3 severely affected patients, was evident. This early recovery is difficult to explain on a structural basis and functional abnormalities should be considered. One could postulate that sensory axons were temporally disabled, perhaps due to the interruption of axoplasmatic outflow by cytotoxic drugs accumulation [24]. The suspension of chemotherapy allowed the partial recovery of neural function.

It has been shown that the taxanes family, which includes paclitaxel and docetaxel, produce a symmetric, axonal predominantly-sensory neuropathy with less prominent motor involvement, mainly affecting the distal extremities in a length dependent manner [3, 4]. Unlike those studies [3, 4] no significant changes of motor conduction parameters from baseline to subsequent scores was revealed in our study, whilst neurological examination disclosed mild distal muscle weakness in only two patients who also demonstrated severe neurotoxicity according to the PNP score.

There are relatively limited data available concerning the carboplatin impact on peripheral nerve function. Carboplatin does not seem to share the same toxic effect of cisplatin, which is a well-defined neurotoxic drug, despite the fact that they both are platinum-compounds. In a previously published trial, which compared the safety profile of carboplatin administration for treatment of ovarian cancer at an AUC 6 vs AUC 12, it was shown that both regimens are not associated with occurrence of grade 3–4 neurotoxicity [10]. Indeed, data from previously published studies suggest that a single-agent therapy with carboplatin at an AUC dose of less or equal than 6 is safe and almost unrelated to the occurrence of peripheral neuropathy [16, 26]. Given that in the current study we administered carboplatin at an AUC dose of 6, it is suggested that the occurrence of CPPN should be attributed to paclitaxel administration. This view was supported by the relatively similar to ours incidence rates of neuropathy reported in previous trials evaluating the safety of paclitaxel as single-agent, first-line treatment [5].

Paclitaxel-induced neuropathy has a vaguely defined pathophysiology. Although the neurotoxicity resulting from aggregation of intracellular neurotubules has repeatedly been reported [6], the primary target of paclitaxel toxicity is in a addressed conflicting way [20]. However, the predominant occurrence of distal loss of sensation in the large fibers would assume that a "dying back" process starting for distal nerve endings followed by neuronal body or axonal transport changes is the most widely accepted mechanism of paclitaxel neurotoxicity [21, 24].

To summarize, the current clinical and electrophysiological study in patients with solid malignancies treated with a CP regimen, showed a relatively high incidence rate of CPPN that was symmetrical, distal, axonal and predominately sensory in character. The follow-up data 3 months after the discontinuation of chemotherapy showed that the CP-induced neuropathy is at least partially remitted.

References

1. Argyriou AA, Chroni E, Koutras A, et al. (2005) Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. Neurology 64(1):26–31
2. Argyriou AA, Polychronopoulos P, Koutras A, et al. (2005) Peripheral neuropathy induced by administration of cisplatin and paclitaxel-based chemotherapy. Could it be predicted? Support Care Cancer 13(8):647–651
3. Berger T, Malayeri R, Doppelbauer G, et al. (1997) Neurological monitoring of neurotoxicity induced by paclitaxel/cisplatin chemotherapy. Eur J Cancer 33(9):1393–1399
4. Chaudhry V, Rowinsky EK, Sartorius SE, et al. (1994) Peripheral neuropathy from taxol and cisplatin combination chemotherapy: Clinical and electrophysiological studies. Ann Neurol 35: 304–311
5. Davidson NG (1996) Single-agent paclitaxel as first-line treatment of metastatic breast cancer: the British experience. Semin Oncol 23(suppl 11): 6–10
6. Dustin P (1980) Microtubules. Sci Am 243:66–76
7. du Bois A, Luck HJ, Meier W, et al. (2003) Arbeitsgemeinschaft Gynakologische Onkologie Ovarian Cancer Study Group. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 95(17):1320–1329
8. Dyck PJ, Thomas PK (1993) (eds): Peripheral Neuropathy (ed 3). Vol 2. Philadelphia, PA,WB Saunders, pp 1310–1317

9. Fountzilas G, Kalofonos HP, Dafni U, et al. (2004) Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol 15(10):1517–1526
10. Gore M, Mainwaring P, A'Hern R, et al. (1998) Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. J Clin Oncol 16(7):2426–2434
11. Huizing MT, van Warmerdam LJ, Rosing H, et al. (1997) Phase I and pharmacologic study of the combination paclitaxel and carboplatin as first-line chemotherapy in stage III and IV ovarian cancer. J Clin Oncol 15(5): 1953–1964
12. Kimura J (2001) Electrodiagnosis in diseases of nerve and muscle, principles and practice (ed 3). Oxford University press, pp 91–166
13. Kleyweg RP, Van der Meché FGA, Schmitz PIM (1991) Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. Muscle Nerve 14:1103–1109
14. Lilenbaum RC, Chen CS, Chidiac T, et al. (2005) Phase II randomized trial of vinorelbine and gemcitabine versus carboplatin and paclitaxel in advanced non-small-cell lung cancer. Ann Oncol 16(1):97–101
15. Markman M, Kennedy A, Webster K, et al. (2001) Neurotoxicity associated with a regimen of carboplatin (AUC 5–6) and paclitaxel (175 mg/m^2 over 3 h) employed in the treatment of gynecologic malignancies. J Cancer Res Clin Oncol 127(1):55–58
16. McGuire WP (1997) How many more nails to seal the coffin of dose intensity? Ann Oncol 8(4):311–313
17. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
18. Ozols RF, Bundy BN, Greer BE, et al. (2003) Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 21(17):3194–3200
19. Panayiotopoulos CP, Chroni E (1996) F-waves in clinical neurophysiology: a review. Methodological issues and overall value in peripheral neuropathies. Electroencephalogr Clin Neurophysiol 101:365–374
20. Peltier AC, Russell JW (2002) Recent advances in drug-induced neuropathies. Curr Opin Neurol 15(5): 633–638
21. Quasthoff S, Hartung HP (2002) Chemotherapy-induced peripheral neuropathy. J Neurol 249(1):9–17
22. Rowinsky EK, Cazenave LA, Donehower RC (1990) Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 82:1247–1259
23. Rowinsky EK, Eisenhauer EA, Chaudhry V, et al. (1993) Clinical toxicities encountered by paclitaxel (Taxol). Semin Oncol 20:1–15
24. Rowinsky EK, Donehower RC (1995) Paclitaxel (Taxol). NEJM 332: 1004–1014
25. Schaumburg HH, Spencer PS (1979) Toxic neuropathies. Neurology 29: 429–431
26. Thigpen JT (1997) Dose-intensity in ovarian carcinoma: hold, enough? J Clin Oncol 15(4):1291–1293
27. Windebank AJ (1999) Chemotherapeutic neuropathy. Curr Opin Neurol 12: 565–571