Support Care Cancer (2006) 14: 223–229
DOI 10.1007/s00520-005-0868-6

ORIGINAL ARTICLE

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Is advanced age associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy?

Received: 26 April 2005
Accepted: 29 June 2005
Published online: 15 July 2005

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Abstract *Purpose:* The current setting tested the hypothesis that advanced age would be strongly associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy (CIPN). *Patients and methods:* We prospectively studied 35 cancer patients treated with paclitaxel or cisplatin-based regimens for lung or breast cancer. All patients underwent a detailed clinical and electrophysiological evaluation for screening of CIPN at baseline, at the third, the sixth course of chemotherapy and up to 3 months after its cessation. Means of a modified Peripheral Neuropathy (PNP) score summarized the results of the clinical and electrophysiological study. *Results:* Patients were divided according to their age in two groups (mean age difference, p=0.000) to those younger than 65 years (group I, n=18) and those older or equal than 65 years (group II, n=17). According to the clinical, neurological and electrophysiological variables of each patient, the incidence and severity of CIPN was determined and then compared between groups. The incidence of neurotoxicity was similar (p=0.869) between group I (9/18 patients, 50%) and group II (8/17 patients, 52.9%). Likewise, according to the mean PNP scores, the severity of CIPN was similar between age groups (p=0.897). The between-age-groups comparison of electrophysiological data revealed no significant differences in any of the motor or sensory conduction parameters examined. *Conclusion:* Our study indicates that elderly cancer patients do not have greater risk of CIPN, whilst advanced age was not associated with worst severity of CIPN.

Keywords Chemotherapy · Elderly · Incidence · Severity · Neurotoxicity

Introduction

Lung and breast cancer are considered two of the most frequent types of non-hematological malignancies in the general population [23]. More than 50% of patients suffering from lung or breast cancer were diagnosed when they were older than 65 years, whilst more than 30% were diagnosed when they were over the age of 70 [11, 12, 23]. The risk of chemotherapy-induced adverse events increases with aging, being more frequent in cancer patients older than 65 years of age than in younger patients [10].

Mucositis, myelosupression, cardiomyopathy and peripheral neuropathy are most likely to complicate chemotherapy administration. Elderly patients with cancer are considered less capable of tolerating standard chemotherapy regimens than younger patients, mainly due to co-existing pathologies, reduction of organ function related to age and greater risk for toxicities that would also be more severe [9]. This belief leads to dose reductions of cytotoxic chemotherapy, a fact that certainly compromises the final outcome, adversely affecting their quality of life (QOL). On the other hand, several studies have shown

that, with appropriate supportive care, otherwise healthy elderly cancer patients can obtain similar benefits from the standard chemotherapy regimens as younger patients [15, 22].

Chemotherapy-induced peripheral neuropathy (CIPN) is a well-recognized adverse effect of efficient modern chemotherapy agents, including taxoid derivates and platinum compounds [21]. CIPN might lead to severe disability, adversely affecting the QOL of cancer patients, independent of age. To date, CIPN consists a major dose-limiting adverse effect of paclitaxel or cisplatin-based chemotherapy, occurring both in younger and older patients with cancer [21].

To our knowledge, there is a relative paucity of data concerning the establishment of a potential correlation between advanced age and occurrence of CIPN. Another issue of great interest is whether elderly cancer patients experience more severe CIPN than younger patients.

For the purposes of the current study, we have built the hypothesis that following treatment with paclitaxel or cisplatin-based chemotherapy, the study patients aged older than 65 would manifest increased rates of CIPN occurrence compared to younger patients, whilst the severity of CIPN would be worst in elderly cancer patients than in younger patients. The aim of the current study was to test the above hypothesis.

Patients and methods

This was a single-center, prospective, comparative study which was initiated following approval by the Institutional Review Board of Patras Medical School. Thirty-five adult patients with cancer, 23 males and 12 females, aged 62.5± 7.3 years, scheduled to be treated with six courses of paclitaxel or cisplatin-based regimens for breast or lung cancer, were prospectively studied in the current setting. According to standard oncology protocols, all participants received appropriate supportive care for managing of other toxicities than neurotoxicity, such as the use of myelopoietic growth factors and antiemetics. Eligible patients had to meet the following criteria: (a) satisfactory liver and renal function, (b) life expectancy ≥9 months and (c) WHO performance score of 0–1 and ability to understand medical advice. All patients gave informed written consent prior to study entry.

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 naive or when clinical or electrophysiological evidence of peripheral neuropathy was disclosed at baseline. The stage of disease was not within inclusion/exclusion criteria. 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.

Clinical evaluation

The clinical evaluation of neuropathy was based on the Neurological Symptom Score (NSS) and Neurological Disability Score (NDS) proposed by Dyck and Thomas [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) [14].

Electrophysiological evaluation

Neurophysiological examination was carried out unilaterally (right side), employing standard methods by means of surface stimulation and recording [13]. 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), was 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 [13, 18]. The battery of the clinical and electrophysiological tests described above was repeated by the same neurologist after the third, the sixth course of chemotherapy and 3 months after its suspension. The findings of all electrophysiological evaluations, both pretreatment and post-treatment, were confirmed by an independent senior neurologist.

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. [7]. PNP scores graded neurotoxicity as mild (1–11), moderate (12–23) and severe (>24), corresponding to the WHO grading scales 1–3 for CIPN [17].

Enrolled patients were divided according to their age in two groups, namely, those younger than 65 years (group I) and those older or equal than 65 years (group II). According to the neurological, clinical and electrophysiological variables of each patient, the incidence and severity of CIPN was determined and then compared between groups (younger vs elderly patients).

Statistical analyses

Descriptive statistics were generated for all variables. The overall incidence of CIPN in younger patients vs elderly patients was compared using the two-sided chi-square test with Yate's correction; whilst according to the PNP scores, differences in the severity of CIPN between groups were estimated using the Wilcoxon-signed ranks test. The changes in mean electrophysiological scores were calculated by subtracting each patient's baseline value from her/his last value and were examined using independent sample *t* tests. All tests were two sided and significance was set at $p<0.05$. The SPSS for Windows (Release 10.0, SPSS Inc., Chicago, IL, USA) performed the statistics.

Results

Demographics and baseline clinical characteristics

Cisplatin or paclitaxel-based regimens were administered according to the specific tumour type as follows: 13 breast cancer and 6 lung [non-small cell lung carcinoma (NSCLC)] cancer patients were treated per each one of the six chemotherapy courses with paclitaxel 175 mg/m^2-based regimens every 3 weeks. Sixteen lung (SCLC) cancer patients were treated per each one of the six chemotherapy courses with cisplatin 60 mg/m^2-based regimens every 3 weeks. None of the patients enrolled received a combination regimen of paclitaxel plus cisplatin. Overall patients initially enrolled received the six-scheduled courses of treatment and were consequently assessable for analysis. Eighteen (51.4%) were included according to their age in group I (<65 years) and 17 (48.6%) were included in group II (≥65 years). With the exception of mean age in which a strong statistical difference ($p=0.000$) was noted, the rest of the demographics and baseline characteristics were generally well balanced between groups (Table 1).

Table 1 Baseline and clinical characteristics in patients of each age group

Variable	Group I (<65 years) *n*=18		Group II (≥65 years) *n*=17	
	N	%	*N*	%
Sex (males vs females)	12	66.7	11	64.7
Age (SD)	56.3±3.7		69.1±3.2	
Age (range)	50–64		65–77	
Tumour type				
Lung cancer				
SCLC	9	50	7	41.2
NSCLC	2	11.1	4	23.5
Breast cancer	7	38.9	6	35.3
Number of patients on specific drug treatment				
Cisplatin	8	44.4	8	47.1
Paclitaxel	10	55.6	9	52.9
Drug dose per each one of the six CMT courses (mg)				
DDP mean±SD dose	120.1±4.7		120.9±3.4	
Paclitaxel mean±SD dose	331.4±21.6		328.3±24.4	

DDP Cisplatin, *PCT* paclitaxel, *CMT* chemotherapy

Interpretation of data in each group of patients

Group I (<65 years) CIPN occurred in 9 out of the 18 patients (50%). According to the PNP score, the severity of CIPN was graded as mild in three of them (16.7%), moderate in four (22.2%) and severe in the remaining two (11.1%) patients. Predominantly distal numbness/paresthesia limited to fingers/toes (*n*=4) or in a stocking-and-glove (*n*=3) distribution were observed. In four patients, a reduction of malleolar vibratory and pin sensation up to wrist/ankle was revealed, whilst three patients had suppressed ankle reflexes. Two patients experienced severe neuropathy, manifested with distal numbness/paresthesia extended up to the knees/elbows, decreased pin and vibration sensation up to the knees/elbows, ankle reflexes absent and reduced reflexes elsewhere and mild to moderate toe extensor weakness. Complete absence of CIPN was observed in the remaining nine patients of this group. The overall group's mean PNP scores were 8.3±9.5 (range 0–28).

Group II (≥65 years) CIPN occurred in 9 out of the 17 patients (52.9%). According to the PNP scores, the severity of CIPN was graded as mild in four (23.5%), moderate in three (17.6%) and severe in two (11.8%) patients. Predominantly distal numbness/paresthesia limited to fingers/toes (*n*=4) and in a stocking-and-glove (*n*=3) distribution were observed. Patients with severe neuropathy (*n*=2) complained about distal numbness/paresthesia extended up to the knees/elbows and had decreased pin and vibration sensation up to the knees/elbows and ankle reflexes absent and reduced reflexes elsewhere. They also had mild to moderate toe extensor and finger abduction weakness. Complete absence of CIPN was observed in the remaining eight patients of this group. The overall group's mean PNP scores were 8.8±9.9 (range 0–30).

Table 2 Overall incidence and severity of neurotoxicity between age groups

	PN					
	Incidence of PN	No PN	Minor	Moderate	Severe	*p* Value[a]
Group I (<65 years) *n*=18	9/18 pts, 50%	9	3	4	2	0.869
Group II (≥65 years) *n*=17	8/17 pts, 52.9%	8	4	3	2	

Pts Patients, *PN* peripheral neuropathy
[a]Yate's corrected *p* value

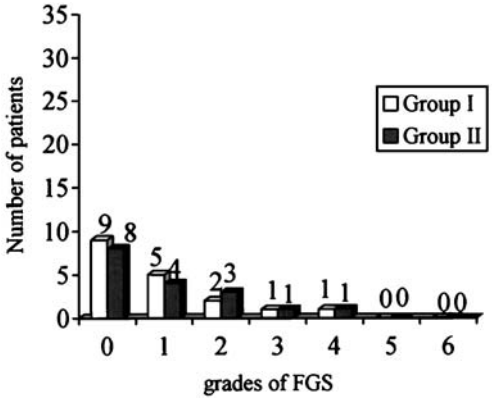

Fig. 1 Assessment of functional ability between age groups

Comparison of data between the age groups

The incidence of CIPN was similar (relative risk 1.06, 95% confidence intervals 0.54–2.11, Yate's corrected *p* value=0.869) between group I (9/18 patients, 50%) and group II (8/17 patients, 52.9%) (Table 2). Likewise, according to the mean PNP scores, the severity of CIPN was similar between age groups (Wilcoxon-signed ranks test, *p*=0.897).

Between-group comparison of the mean changes from baseline to subsequent scores 3 months after cessation of chemotherapy showed insignificant differences in all the motor and sensory conduction parameters examined. Table 3 describes the overall changes in mean electrophysiological scores from baseline to subsequent scores between groups.

As assessed by the FGS scores, the functional ability of elderly patients was similar to that of younger patients. CIPN influenced the functional ability of patients assigned to both age groups in similar rates, estimating it as grade 1 (minor symptoms, fully capable of manual work) in 5 and 4 for younger and elderly patients, respectively; grade 2 (able to walk >10 m unaided) in 2 and 3 for younger and elderly patients, respectively; grade 3 (able to walk >10 m with a walker or support) in 1 and 1 for younger and elderly patients, respectively; and grade 4 (bed- or chair-bound) in 1 and 1 for younger and elderly patients, respectively (Fig. 1).

Table 3 Changes in mean electrophysiological scores from baseline to subsequent scores between age groups

	Baseline	Third CMT	Sixth CMT	3 months after CMT cessation	*p* Value
Ulnar a-SAP (μV)					
Group I	8.7±5.1	7.5±3.8	7.3±3.2	6.9±3.7	0.191
Group II	7.1±4.7	6.8±3.5	6.5±2	6.3±3.8	
S.Per/al a-SAP (μV)					
Group I	9.4±4.2	8±4.6	7±3.7	6.3±3.5	0.629
Group II	8.7±3.8	7.1±4	6.5±3.1	6.2±3.2	
Sural a-SAP (μV)					
Group I	11.7±8.1	9.6±6.4	9.1±7.1	8.4±6.9	0.776
Group II	9±4.1	6.7±4.1	6.5±3.7	6.1±3.5	
Ulnar a-CMAP (mV)					
Group I	5.9±1.2	6±1.5	6±1.9	6±1.8	0.321
Group II	4.8±1.3	5.3±1.7	5±1.6	5.4±1.3	
Ulnar MCV (m/s)					
Group I	54.7±5.4	54.7±5.3	55.6±6.3	55.6±5.4	0.313
Group II	52.9±3.8	54.5±6.1	54.1±7.9	55.9±7.2	
Per/al a-CMAP (mV)					
Group I	3.7±2.1	3.4±1.7	3.3±1.7	3.4±1.8	0.903
Group II	2.9±1.1	2.9±1.6	2.3±1	2.6±1.3	
Per/al MCV (m/s)					
Group I	49.4±5.8	48.9±6.1	50.3±6.7	50.8±6.9	0.452
Group II	47.7±4.7	46.8±5.5	48.3±5.4	48.3±4.9	

p Value (independent sample *t* test) refers to between groups' changes in mean electrophysiological scores from baseline to subsequent scores 3 months after cessation of chemotherapy *a-SAP* Amplitude of sensory action potential, *a-CMAP* amplitude of compound muscle action potential, *MCV* motor conduction velocity, *S.Per/al* superficial peroneal, *CMT* chemotherapy

The maximum severity of CIPN occurred in the time interval between chemotherapy courses 4 and 6. A correlation analysis performed in selected patients of both age groups revealed an advancement in the severity of neurotoxicity with increasing cumulative drug doses. Indicatively, a strongly significant correlation was revealed between the number of cycles and suppression of deep tendon reflexes (linear regression analysis, r=0.73). The latter documented a direct dose effect on the occurrence of CIPN that should be attributed to the drug doses accumulation, because it is established that at high cumulative doses of cisplatin and paclitaxel, the incidence of CIPN is expected to be 85% or even higher [1, 16].

Discussion

The existing literature on the experience with cisplatin or paclitaxel-based regimens at full dose intensities in the elderly is limited. To our knowledge, the current study is the first that has intended to prospectively ascertain whether advanced age is associated with increased incidence and severity of neurotoxicity, following administration of paclitaxel or cisplatin-based chemotherapy regimens at full-dose intensities.

Given that cancer affects more predominately the elderly than younger patients, whilst elderly patients have greater risks of chemotherapy toxicities, we have conducted this study to confirm the hypothesis that elderly patients with cancer would have greater risk of CIPN concerning its occurrence and severity. Our main finding was that both younger and elderly cancer patients manifested similar incidence rates of CIPN (50 vs 52.9%, respectively); even more, both age groups experienced similar CIPN severities. Hence, advanced age was not associated with increased occurrence and severity of CIPN in our series. Our results are in line with the incidence of neurotoxicity previously reported for these two agents at the cumulative doses that the patients received [16, 21]. An age-independent incidence of CIPN was also observed by Perez et al. [19], who screened the general toxicities in a mixed age sample, following weekly paclitaxel administration.

Inasmuch as it is a highly individualized term, the definition of "elderly" is controversially addressed. In this study, we used the typical age cut-off for definition of elderly (65 years), previously applied in the epidemiological literature. In clinical trials, however, the age over 70 years is considered as the age cut-off point for patients' selection, whilst the age of 75 is less commonly used. Nevertheless, our study sample was representative of cancer patients' populations, ranging in age from 50–77 years. However, a potential limitation in the study design may be that the mean age difference between groups was not wide enough to disclose age-related changes in nerve conduction velocities. A larger age gap might have shown some differences, but the target group of breast and lung cancer is usually consisted of patients aged between 50 and 80 years [11, 12, 23], corresponding to the age range (50–77 years) of patients studied in the current setting. Another possible limitation that should be mentioned is the relative small sample size, which has prevented us from the formation of subgroups according to tumour types and chemotherapeutic agents.

Myelosupression and mucositis are reported to be more frequent in elderly patients with cancer [4, 5, 20]. Our patients were given appropriate supportive care and myelopoietic growth factors, thereby allowing administration of chemotherapy at full dose intensity. They were also free of serious co-morbidities such as history of peripheral neuropathy, systemic diseases and history of chemotherapy administration, conditions that could compromise their general and neurological outcome. Based on the speculation that aging combined with the aforementioned co-morbidities could make a patient with cancer more prone to CIPN, one can suggest that the relative high selection criteria applied may represent a potential limitation in the study design. In view of the latter speculation, it should be mentioned that this strict inclusion criteria was set on an intention to clearly differentiate that the neuropathy resulted from the direct toxic effect of chemotherapy and not from other co-morbidities, such as diabetes mellitus, that similarly induce peripheral nerve damage. Moreover, patients with serious co-morbidities were excluded similarly from both study arms; hence, high selection criteria were applied both in younger and elderly patients. Thus, our results support the view that regarding neurotoxicity in particular, otherwise healthy elderly patients with cancer have no significantly enhanced risk of CIPN occurrence.

A dying back process starting for distal nerve endings followed by neuronal body changes is the most widely accepted type of paclitaxel neurotoxicity [21], whilst cisplatin administration induces peripheral neurotoxicity by damaging primarily the sensory neurones in the dorsal root ganglia [1]. In the current setting, the clinical and electrophysiological examinations in both age groups supported the diagnosis of a symmetrical, axonal, predominately distal sensory neuropathy, being in agreement with that previously described in case of cisplatin or paclitaxel-induced peripheral neuropathy [1, 21].

Several studies reported structural and biochemical changes of peripheral nervous system associated with aging. In consequence, functional deficit is clearly demonstrated by the decline of normal values in neurophysiological measurements in elderly patients [24]. Indeed, in our series, minor, not statistically significant reduction of velocities and amplitudes were evident at baseline between group I and group II measurements. Hence, based on clinical and experimental investigations regarding the influence of age on the peripheral nerve function [24], one might expect that the toxic effect of chemotherapy may have a greater impact on nerves of aged as compared to younger individuals. This possibility was not proven in the current se-

ries where nerve vulnerability showed to be unrelated to age. Perhaps, compensatory mechanisms, such as reduced energy requirements, terminal sprouting and expansion of target territory or enhanced neuronal excitability, might be sufficient to overcome neuronal tissue aging process [24]. Moreover, the gradual changes of peripheral nerve function may reach a significant level of functional deficit at a more advanced age than that of our patients, i.e. over 80 years.

A matter of great interest concerns the repair and regeneration process of nerve fibers in patients who developed CIPN. The issue of possible delayed or incomplete recovery associated with advanced age is the subject of our further research.

The prospective approach such as this used in the current study, based on methods involving clinical scales previously applied and validated in studies referred to toxic neuropathies [3, 6, 7] and on detailed electrophysiological follow-up evaluations performed by experienced neurophysiologists, offered the optimal setting for interpretation of results. To our opinion, detailed clinical and electrophysiological follow-up evaluations with emphasis on electrophysiological tests should be performed in cancer patients, independently of their age during chemotherapy administration. Needle electromyogram (EMG) might have yielded potentially additional electrophysiological data. Such an examination was not employed to avoid patients' discomfort, because such examinations may be painful and it is ethically difficult to perform them for purely scientific reasons. Although the lack of needle EMG could be considered as a possible limitation in the study design, it should be mentioned that the analysis of ulnar and peroneal CMAPs is considered sufficient for purposes of follow-up studies, particularly in case of a sensory neuropathy such as this disclosed in the current setting.

Except from improvement of growth factor support by development of more effective and safe myelopoietic agents, further trials of efficient neuroprotective agents are warranted to manage the neurotoxicity associated with chemotherapy. Vitamin E may be the answer, because in a recently published randomized controlled trial conducted by our group, it was shown that vitamin E supplementation significantly protects peripheral nerves from the toxic effect of paclitaxel and cisplatin-based chemotherapy [2].

Conclusion

The results of the current setting indicate that elderly cancer patients do not have greater risk of CIPN, whilst advanced age was not associated with worst severity of CIPN. The proper use of supportive care would make adverse the relative misconception about prognosis and treatment expectations, leading to treatment delays and dose reductions, obviously influencing the final outcome and QOL of elderly patients with cancer.

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