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Age and the Risk of Paclitaxel-Induced Neuropathy in Women with Early-Stage Breast Cancer (Alliance A151411): Results from 1,881 Patients from Cancer and Leukemia Group B (CALGB) 40101

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

Key Words. Paclitaxel • Neuropathy • Older • Geriatric • Breast cancer

Abstract

Purpose. A few previous studies report a direct relationship between older age and chemotherapy-induced neuropathy. This study further evaluated this adverse event's age-based risk.

Methods. CALGB 40101 investigated adjuvant paclitaxel (80 mg/m^2 once per week or 175 mg/m^2 every 2 weeks) in patients with breast cancer and served as a platform for the current study that investigated age-based differences in neuropathy. Grade 2 or worse neuropathy, as per Common Terminology Criteria for Adverse Events version 4, was the primary endpoint; patients were assessed at baseline, every 6 months for 2 years, and then annually for 15 years.

Results. Among these 1,881 patients, 230 were 65 years of age or older, 556 were 55–64 years, and 1,095 were younger than 55; 1,226 neuropathy events (commonly grade 1 or 2) were reported in 65% of the cohort. The number of grade 2 or worse events was 63 (27%), 155 (28%), and 266 (24%) within respective age groups (p = .14). In univariate analysis, only motor neuropathy had a higher age-based incidence: 19 (8%), 43 (8%), and 60 (5%), respectively (p = .04); in multivariate analyses, this association was no longer statistically significant. Other endpoints, such as time to onset of neuropathy (time from trial enrollment to neuropathy development) and time to improvement (time from maximal grade sensory neuropathy to a one-category improvement), showed no statistically significant age-based differences. In contrast, obesity was associated with neuropathy, and every 2-week paclitaxel was associated with trends toward neuropathy.

Conclusion. Although paclitaxel-induced neuropathy is common, older age is not an independent risk factor. *Clinical trial identification number.* NCT00041119 (CALGB 40101). ***The Oncologist*** 2019;24:617–623

Implications for Practice: Age alone is not an independent risk factor for paclitaxel-induced neuropathy.

Introduction

Previous studies provide mixed results as to whether older patients with cancer are at greater risk for chemotherapy-induced neuropathy. In a 1,048-patient study in metastatic breast cancer, Lichtman and others reported that older

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patients manifest an increase in frequency and severity of paclitaxel-induced neuropathy [1]. Among patients ≥65 years of age, 55–64 years of age, and < 55 years of age, the percentage of patients with grade 3 or worse neurosensory neuropathy was 28%, 18%, and 17%, respectively (p < .0001), suggesting an increased risk for neuropathy with advancing age. A similar trend was observed for grade 3 or worse neuromotor neuropathy with rates of 14%, 8%, and 5%, respectively (p = .0002). Providing corroborative evidence of this direct relationship between advancing age and worse symptomatology, Hershman and others undertook a pooled analysis of 1,401 patients who had received a variety of neuropathy-inducing chemotherapy agents [2]. These investigators observed not only that paclitaxel-induced neuropathy was worse than that from docetaxel but also that older age was associated with higher rates of neuropathy; for each 1-year increase in age, the risk of chemotherapy-induced neuropathy increased by 4% (p = .006). The study from Hershman and others focused on older patients to the exclusion of a much younger cohort, thus perhaps narrowing the scope of its findings. Nonetheless, taken together, these two studies—which overall appear to show that more than one in four older patients can develop severe neuropathy—further heighten concerns about treating older patients with neurotoxic chemotherapy agents.

In contrast, a series of much smaller studies suggest that older patients with cancer, when compared with their younger counterparts, do not suffer higher neuropathy rates [3–5]. In aggregate these other studies support the conclusion that advancing age influences neither the prevalence nor the severity of chemotherapy-induced neuropathy. Importantly, this negative neutral conclusion underscores the need to address further the question of whether older patients who receive neurotoxic chemotherapy are predisposed to such toxicity by virtue of older age alone.

The current study was therefore undertaken to provide clarity on whether a direct relationship exists between older age and the development of chemotherapy-induced neuropathy. This study's focus on paclitaxel-induced neuropathy is clinically germane not only because this chemotherapy agent causes relatively high rates of neuropathy but because paclitaxel is used to treat a variety of cancers commonly diagnosed in older patients [6, 7].

Subjects, Materials, and Methods

Overview

For the current study, CALGB 40101 served as a platform to assess comparative rates and severity of neuropathy based on patient age [8, 9]. CALGB 40101, referred to herein as the parent study, is a previously reported phase III trial that compared single-agent paclitaxel versus doxorubicin and cyclophosphamide as adjuvant therapy in patients with breast cancer with 0–3 tumor-positive lymph nodes; it demonstrated a lack of noninferiority, favored doxorubicin and cyclophosphamide with respect to relapse-free survival, and was amended over time for paclitaxel dosing but showed less toxicity with paclitaxel. Chemotherapy dose calculations had been based on actual body weight. The study reported here tested the hypothesis that paclitaxel-induced neuropathy is more prevalent and severe in older patients with cancer; it focused exclusively on patients who received postoperative single-agent paclitaxel in CALGB 40101 and who had available adverse event data. Using the parent study CALGB 40101 as a platform to test this hypothesis seemed particularly appealing because this parent trial captured all grades of adverse events in all enrolled patients as well as patient-reported outcomes in a planned subgroup.

The Mayo Clinic Institutional Review Board had approved a written protocol that outlined the current study's primary endpoint, other endpoints, and detailed analysis plans.

Definitions of Age-Based Patient Groups and Neuropathy Endpoints

The independent variable of interest was age at study registration and was categorized as follows: (a) 65 years of age or older, (b) 55–64 years of age, or (c) <55 years of age. These categories were formulated based on precedent as well as on the parent trial's age distribution that allowed for a reasonable sample size within each group [1].

Common Terminology Criteria for Adverse Events version 4 had been used to capture neuropathy adverse events prior to the initiation of each cycle of chemotherapy, every 6 months for 2 years after completion of chemotherapy, and then annually until 15 years after enrollment. In addition, a subgroup of patients had been asked to complete the validated, 11-item FACT/GOG-Ntx questionnaire, which enabled patients to report neuropathy symptoms with a 5-point scale [10]. This questionnaire was administered after completion of chemotherapy at the same time points as above.

Statistical Analysis

All grades of neuropathy had been recorded in the parent trial and are descriptively reported in this study; the primary study endpoint compared grade 2 or worse maximal neuropathy between age-based groups. The decision to focus on grade 2 or worse neuropathy was derived from precedent in the published literature, clinical relevance and meaning, and the fact that this cut point lent more power to the analyses [11–13]. Trends in neuropathy were assessed with a Cochran-Armitage linear trend test or a Jonckheere-Terpstra trend test, as appropriate. A multivariate logistic regression model was used to assess the impact of obesity, chemotherapy dosing (to be administered every 2 weeks vs. weekly), and performance score on neuropathy occurrence. Kaplan–Meier curves were constructed for each age group to estimate time to onset of neuropathy (defined as time from trial enrollment to neuropathy development) as well as time to improvement of neuropathy (defined as time from maximal grade of neuropathy to a one-category improvement in neuropathy); Cox regression models were used to make comparisons between groups. A deliberate decision was made not to incorporate total cumulative doses of paclitaxel into the model because neuropathy data from different time points were used. Similar

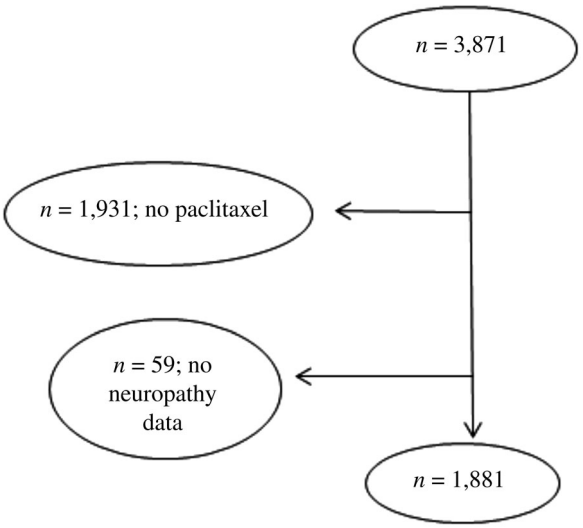

Figure 1. A total of 1,881 patients were included in this study, as derived from the original parent trial that included 3,871 patients.

analyses were used for patient-reported FACT/GOG-Ntx data. Odds ratios and hazard ratios along with 95% confidence intervals are reported. A p value of <.05 was considered statistically significant. All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Demographics

A total of 1,881 patients met this study's eligibility criteria and are included in this report (Fig. 1). Within this cohort, 230 patients were 65 years of age or older, 556 were 55–64 years of age, and 1,095 were younger than 55 years of age. Baseline demographics appear in Table 1.

Patients had been treated with the following, as per the parent study protocol: (a) paclitaxel 80 mg/m^2 intravenously once per week for 12 weeks (n = 138), (b) paclitaxel 80 mg/m^2 intravenously once per week for 18 weeks (n = 136), (c) paclitaxel 175 mg/m^2 intravenously every 2 weeks for 8 weeks (n = 981), and (d) paclitaxel 175 mg/m^2 intravenously every 2 weeks for 12 weeks (n = 626). Completion rates of assigned adjuvant chemotherapy were as follows: 86% for patients older than 65 years of age, 93% for patients between 55 and 64 years of age, and 89% for patients <55 years of age. Based on age, the average total dose (SD) of administered paclitaxel was as follows: 1,390 mg (454) for patients 65 years of age or older, 1,571 mg (496) for patients between 55 and 64 years of age, and 1,555 mg (506) for patients younger than 55 years of age.

Age-Based Neuropathy Events

The total number of neuropathy events of any grade was 1,226, with 65% of the cohort experiencing this adverse event (Table 2). Older patients manifested statistically higher rates of total neuropathy and motor neuropathy, although these findings lost their statistical significance in multivariate analyses that incorporated obesity, paclitaxel dosing (weekly vs. every 2 weeks), and performance score into the model. Importantly, rates of sensory neuropathy were not statistically different in comparisons between age groups.

Table 1. Baseline demographics

Characteristic	Age groups[a,b] ≥65 yr (n = 230), n (%)	55–64 yr (n = 556), n (%)	<55 yr (n = 1,095), n (%)
Median age (range), yr	68 (65–81)	59 (55–64)	47 (22–54)
Body mass index			
<30	132 (57)	292 (53)	628 (57)
≥30	93 (40)	260 (47)	457 (42)
Assigned paclitaxel dosing			
80 mg/m^2 weekly	26 (11)	78 (14)	170 (16)
175 mg/m^2 every 2 weeks	204 (89)	478 (86)	925 (84)
8-week duration	144 (63)	298 (54)	539 (49)
12-week duration	74 (32)	217 (39)	473 (43)
18-week duration	12 (5)	41 (7)	83 (8)
Performance score			
0	197 (86)	494 (89)	997 (91)
1	33 (14)	62 (11)	98 (9)

[a]Age groups are defined in years based on age at entry into the parent trial.
[b]Percentages do not always sum to 100% because of rounding.

Primary Endpoint of Grade 2 or Worse Neuropathy

The total number of grade 2 or worse neuropathy events was 484, with 26% of the cohort having had at least one such reported event—but with all grades of neuropathy appearing in Table 2. Within age groups, the numbers of grade 2 or worse total neuropathy events were 63 (27%), 155 (28%), and 266 (24%) in patients 65 years of age or older, 55–64 years of age, and younger than 55 years of age, respectively (p = .14; Table 2).

Grade 2 or worse sensory neuropathy was more frequently reported than motor neuropathy, with 437 events (23%) of the former. By age group, reports of grade 2 or worse sensory neuropathy occurred at the following frequencies: 55 (24%), 138 (25%), and 244 (22%), respectively, in patients 65 years old or older, 55–64 years old, and younger than 55 years (p = .35). A total of 122 grade 2 or worse motor neuropathy events (7%) were reported; however, motor neuropathy showed a trend to suggest a higher incidence based on age: 19 (8%), 43 (8%), and 60 (5%), respectively, per the above age categories (p = .04). Of note, grade 2 or worse sensory and grade 2 or worse motor neuropathy were strongly associated (p < .0001). Results from multivariate regression models, which incorporated obesity, paclitaxel dosing (weekly vs. every 2 weeks), and performance score in the model, did not change the above conclusions, with one exception: motor neuropathy lost its statistically significant association with age (Table 3).

Table 2. Maximum neuropathy grades (Common Terminology Criteria for Adverse Events, version 4)

Grades	Patient age at trial entry				*p* values[a,b]
	All ages (*n* = 1,881), n (%)	≥65 yr (*n* = 230), n (%)	55–64 yr (*n* = 556), n (%)	<55 yr (*n* = 1,095), n (%)	
All neuropathy grades					
0	655 (35)	79 (34)	174 (31)	402 (37)	.043[c]
1	742 (40)	88 (38)	227 (41)	427 (39)	
2	334 (18)	43 (19)	106 (19)	185 (17)	
3	145 (8)	19 (8)	48 (9)	78 (7)	
4	5 (0)	1 (0)	1 (0)	3 (0)	
Motor grades					
0	1,655 (88)	194 (84)	478 (86)	983 (90)	.004[c]
1	104 (6)	17 (7)	35 (6)	52 (5)	
2	72 (4)	10 (4)	25 (5)	37 (3)	
3	47 (3)	9 (4)	17 (3)	21 (2)	
4	3 (0)	0 (0)	1 (0)	2 (0)	
Sensory grades					
0	702 (37)	88 (38)	190 (34)	424 (39)	.204
1	742 (40)	87 (38)	228 (41)	427 (39)	
2	310 (17)	41 (18)	98 (18)	171 (16)	
3	123 (7)	13 (6)	39 (7)	71 (7)	
4	4 (0)	1 (0)	1 (0)	2 (0)	

Percentages do not always sum to 100% because of rounding.
[a]*p* values refer to age-based trends of neuropathy rates (Jonckheere-Terpstra test).
[b]Trends for only grade 2 or worse neuropathy showed no statistically significant differences between groups for all neuropathy ($p = .142$) or for sensory neuropathy ($p = .35$). However, univariate analyses showed that grade 2 or worse motor neuropathy increased with age ($p = .044$).
[c]Older patients manifested trends to indicate higher rates of total neuropathy and motor neuropathy; however, these findings lost their statistical significance in multivariate analyses adjusted for obesity, paclitaxel dosing (every 2 weeks vs. weekly), and performance score.

In univariate and multivariate analyses, obesity and paclitaxel dosing (every 2 weeks vs. weekly) were either statistically significant in their ability to predict the development of neuropathy and, in particular, sensory neuropathy or were indicative of a trend toward neuropathy development. For example, obesity was associated with a > 30% greater incidence of neuropathy development, and every 2-week paclitaxel was associated with a 40% greater incidence of sensory neuropathy development.

Time to Neuropathy

Similarly, for grade 2 or worse total, motor, and sensory neuropathy, time to neuropathy was not statistically significantly different based on age in either univariate or multivariate models (Table 4), although statistically significant associations were seen with obesity and every 2-week administration of paclitaxel.

In an exploratory manner, we also examined the 1,179 patients who developed at least grade 1 sensory neuropathy and reported on time to improvement. No statistically significant differences were observed between groups with hazard ratios (95% confidence interval [CI]) for improvement in sensory neuropathy from maximum score of patients older than 65 years of age versus 55–64 years of age versus younger than 55 years of age of 0.95 (95% CI, 0.62–1.45), 0.92 (95% CI, 0.62–1.37), and 0.97 (95% CI, 0.73–1.29).

Patient-Reported Neuropathy Outcomes

Patient-reported outcome data were available for only 116 patients (data not shown). Eighty-one patients (70%) reported at least a 3-point change in score over time, indicative of neuropathy. Within age groups, patient-reported neuropathy occurred in 10 of 16 patients (63%) who were 65 years of age or older, in 28 of 37 (76%) patients 55–64 years of age, and in 43 of 63 (68%) patients younger than 55 years of age ($p = .96$).

Discussion

This large, age-based comparative study of neuropathy shows that age is not an independent predictor of this paclitaxel-induced adverse event. This absence of an age-based association is derived from an extensive set of analyses, which included evaluations of grade 2 and worse neuropathy, all grades of neuropathy, sensory neuropathy, motor neuropathy, health care provider- and patient-reported neuropathy, and time to neuropathy—all of which reached the same conclusion, namely, that older age does not appear independently to contribute to paclitaxel-induced neuropathy risk.

Table 3. Univariate and multivariate analyses for grade 2 or worse neuropathy

Variables	Univariate		Multivariate[a]	
	Odds ratio (95% confidence interval)	*p* value	Odds ratio (95% confidence interval)	*p* value
All neuropathy				
Obese vs. not	1.35 (1.09–1.66)	.005	1.34 (1.09–1.65)	.006
Every 2 weeks vs. weekly	1.34 (0.99–1.83)	.06	1.39 (1.01–1.92)	.045
Performance score (1 vs. 0)	1.01 (0.72–1.42)	.95	0.99 (0.7–1.40)	.96
Age, yr				
≥65 vs. <55	1.18 (0.85–1.62)	.32	1.12 (0.81–1.55)	.50
55–64 vs. <55	1.21 (0.96–1.52)	.11	1.18 (0.94–1.49)	.16
Motor neuropathy				
Obese vs. not	1.42 (0.98–2.07)	.065	1.40 (0.97–2.04)	.08
Every 2 weeks vs. weekly	0.92 (0.55–1.53)	.74	1.02 (0.59–1.75)	.96
Performance score (1 vs. 0)	1.05 (0.58–1.90)	.88	1.04 (0.57–1.89)	.90
Age, yr				
≥65 vs. <55	1.55 (0.91–2.66)	.11	1.33 (0.75–2.37)	.33
55–64 vs. <55	1.45 (0.96–2.17)	.08	1.44 (0.96–2.17)	.08
Sensory neuropathy				
Obese vs. not	1.35 (1.09–1.67)	.07	1.35 (1.09–1.67)	.007
Every 2 weeks vs. weekly	1.46 (1.05–2.03)	.02	1.47 (1.04–2.06)	.028
Performance score (1 vs. 0)	1.01 (0.71–1.43)	.98	0.98 (0.68–1.40)	.93
Age, yr				
≥65 vs. <55	1.10 (0.78–1.53)	.59	1.09 (0.77–1.53)	.63
55–64 vs. <55	1.15 (0.91–1.46)	.25	1.13 (0.89–1.44)	.33

[a]Multivariate analyses included in the models only the variables listed above.

Interestingly, and consistent with prior observations, the current study found that obesity is associated and that every 2-week paclitaxel administration trends toward an association with neuropathy in both univariate and multivariate models [2]. Because paclitaxel dosing was based on actual weight in the parent study, the association between obesity and neuropathy can perhaps be explained by greater nerve exposure to chemotherapy. The association between every 2-week paclitaxel administration and the development of neuropathy is more difficult to explain but is perhaps related to paclitaxel pharmacokinetics and, as a result, to perhaps greater nerve exposure to peak doses of drug. These previously reported, non-age-based associations serve to validate the lack of age-related findings reported here [14, 15].

Why do these results on age and neuropathy differ from some of the earlier-cited reports? One reason may hinge upon differing patient populations. The study reported here included only patients who were chemotherapy-naive prior to enrollment to the parent trial. In contrast, Lichtman and others and Hershman and others focused on metastatic cancer patients, many of whom had received prior chemotherapy. These investigators' ability to assess paclitaxel-induced neuropathy over time could have been confounded by earlier-administered cancer treatment. Indeed, neuropathy symptoms often persist over time; such earlier chemotherapy may have contributed to symptomatology that would otherwise have clearly been attributable to paclitaxel [16]. A second reason for these divergent findings may center on the fact that the current study undertook detailed multivariate analyses. Although we detected increased age-related rates of motor neuropathy in univariate analyses, the statistical significance of such findings was not maintained in multivariate analyses, leading us to conclude that the development of paclitaxel-induced neuropathy is not independently associated with advancing age.

Interestingly, one could perhaps argue that the findings of the current study are logically in concordance with observations from earlier investigations. Lichtman and others evaluated paclitaxel pharmacology in age-defined patient cohorts [17]. Although paclitaxel total-body clearance decreased with age, the resulting increase in exposure to this chemotherapy agent did not translate into clinically relevant adverse events. These findings of age-based variability in drug clearance coupled with the clinical ambiguity of their relevance have been confirmed by other investigators [18, 19]. The conclusions from these previous studies add plausibility to the absence of an independent association with age, as reported here.

The current study has limitations. First, although this study's focus on neuropathy is of great importance, the downstream ramifications of this chemotherapy-induced adverse event—limited functionality, sleep disturbance, loss of independence, risk of dangerous falls—remain unknown. Such morbidity is important for older patients with cancer but also for younger patients as they grow old over time. Furthermore, the parent study provided no

Table 4. Time to grade 2 or worse neuropathy

Variables	Univariate		Multivariate	
	Hazard ratio (95% confidence interval)	*p* value	Hazard ratio (95% confidence interval)	*p* value
All neuropathy				
Obese vs. not	1.28 (1.07–1.54)	.007	1.29 (1.08–1.54)	.006
Every 2 weeks vs. weekly	1.70 (1.29–2.24)	.001	1.76 (1.32–2.36)	<.001
Performance score (1 vs. 0)	0.99 (0.74–1.33)	.96	0.98 (0.73–1.31)	.87
Age, yr				
≥65 vs. <55	1.18 (0.90–1.56)	.229	1.13 (0.85–1.49)	.41
55–64 vs. <55	1.18 (0.97–1.43)	.108	1.17 (0.96–1.42)	.13
Motor neuropathy				
Obese vs. not	1.37 (0.96–1.97)	.085	1.36 (0.95–1.95)	.10
Every 2 weeks vs. weekly	1.08 (0.66–1.76)	.77	1.19 (0.70–2.03)	.52
Performance score (1 vs. 0)	1.03 (0.58–1.83)	.92	1.03 (0.58–0.83)	.93
Age, yr				
≥65 vs. <55	1.61 (0.96–2.70)	.07	1.38 (0.79–2.40)	.26
55–64 vs. <55	1.43 (0.97–2.12)	.07	1.43 (0.97–2.13)	.07
Sensory neuropathy				
Obese vs. not	1.28 (1.06–1.55)	.01	1.28 (1.06–1.55)	.01
Every 2 weeks vs. weekly	1.83 (1.35–2.47)	<.001	1.84 (1.35–2.51)	<.001
Performance score (1 vs. 0)	0.95 (0.73–1.35)	.95	0.97 (0.72–1.33)	.87
Age, yr				
≥65 vs. <55	1.11 (0.83–1.49)	.49	1.09 (0.81–1.46)	.57
55–64 vs. <55	1.13 (0.91–1.39)	.27	1.11 (0.90–1.37)	.32

A Cox proportional hazards model was used in these analyses and included only the variables listed above.

assessment of specific reasons for chemotherapy discontinuation; as a result, we are unable to answer the important question of whether neuropathy resulted in a comparatively greater percentage of older patients stopping chemotherapy prematurely. Future studies should consider capturing such data when neuropathy-inducing chemotherapy agents are prescribed. Second, patient-reported outcomes have gained increased attention. Interestingly, the current study detected slightly higher rates of neuropathy with patient-reported outcomes. Such higher rates in reporting have been previously described and speak again to the value of patient-reported outcomes [20]. The current study might have been more informative had a larger portion of the cohort been asked to provide patient-reported outcomes, as patient-reported outcomes appear to be more sensitive in detecting neuropathy [21]. Nonetheless, the findings reported in this study clearly show that neuropathy is a problem for paclitaxel-treated patients. Third, only a small subset of patients in this study (12%) were 65 years of age or older, and it unknown how representative these patients were of older patients with cancer who are not treated on clinical trials. Although CALGB 40101 served as an opportunistic platform for the current study, it remains unknown how generalizable these findings are to a more general population of patients with cancer. In view of shifting demographics with a growing number of older patients' developing cancer, it will be important to seek more robust, age-based analyses of adverse events in the future. Finally, the parent study did not include a geriatric assessment, understandably because it did not specifically focus on age. However, future studies that administer neurotoxic chemotherapy agents to older patients with cancer might consider a baseline geriatric assessment—in conjunction with an assessment of morbidity, such as diabetes, that might worsen neuropathy—to gain a better sense of whether subgroups of older patients with cancer might be at greater risk for this adverse event; such data might also provide insight as to whether certain subgroups of older patients with cancer are at greater risk for neuropathy-induced morbidity.

Conclusion

In summary, the current study found that most patients who receive paclitaxel develop neuropathy—although often mild neuropathy—but that rates of this adverse event do not appear to differ notably between older and younger patients. All patients, regardless of age, should be closely monitored for neuropathy during paclitaxel administration, and future studies should focus on reducing the incidence of this common adverse event.

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Disclosures

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References

1. Lichtman SM, Hurria A, Cirrincione CT et al. Paclitaxel efficacy and toxicity in older women with metastatic breast cancer: Combined analysis of CALGB 9342 and 9840. Ann Oncol 2012; 23:632–638.

2. Hershman DL, Till C, Wright JD et al. Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in Southwest Oncology Group clinical trials. J Clin Oncol 2016;34:3014–3022.

3. Argyriou AA, Polytchronopoulos P, Koutras A et al. Is advanced age associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy? Support Care Cancer 2006;14:223–229.

4. Hensing TA, Peterman AH et al. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. Cancer 2003;98: 779–788.

5. Jatoi A, Allred JB, Suman VJ et al. Is age ≥ 70 years an important predictor of adverse events among patients enrolled in metastastic melanoma trials? Findings from pooled analyses of therapeutic trials. J Geriatric Oncol 2012;3: 307–311.

6. Gridelli C, Balducci L, Ciardiello F et al. Treatment of elderly patients with non-small cell lung cancer: Results of an international expert panel meeting of the Italian Association of Thoracic Oncology. Clin Lung Cancer 2015;16:325–333.

7. Teo MY, Power DG, Tew WP et al. Doublet chemotherapy in the elderly patient with ovarian cancer. ***The Oncologist*** 2012;17:1450–1460.

8. Shulman LN, Berry DA, Cirrincione CT et al. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0-3 positive lymph nodes: CALGB 40101 (Alliance). J Clin Oncol 2014;32:2311–2317.

9. Shulman LN, Cirrincione CT, Berry DA et al. Six cycles of doxorubicin and cyclophosphamide or paclitaxel are not superior to four cycles of adjuvant chemotherapy for breast cancer in women with zero to three positive axillary nodes: Cancer and Leukemia Group B 40101. J Clin Oncol 2012;30:4071–4076.

10. Huang HQ, Brady MF, Cella D et al. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: A Gynecological Oncology Group study. Int J Gynecol Cancer 2007;17:387–393.

11. Castellanos EH, Chen SC, Drexler H et al. Making the grade: The impact of low-grade toxicities on patient preference for treatment with novel agents. J Natl Compr Cancer Netw 2015; 13:1490–1495.

12. Ghadjar P, Hayoz S, Berhnard J et al. Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: First results of the randomized trial SAKK 09/10. J Clin Oncol 2015;33:4158–4166.

13. Loprinzi CL, Qin R, Dakhil SR et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). J Clin Oncol 2014;32: 997–1005.

14. Greenlee H, Hershman DL, Shi Z et al. BMI, lifestyle factors and taxane-induced neuropathy in breast cancer patients: The Pathways Study. J Natl Cancer Inst 2016;109. doi:https://doi.org/10.1093/jnci/djw206.

15. Bao T, Basal C, Seluzicki C et al. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: Prevalence, risk factors, and fall risk. Breast Cancer Res Treat 2016;159:327–333.

16. Park SB, Lin CS, Krishnan AV et al. Long-term neuropathy after oxaliplatin treatment: Challenging the dictum of reversibility. ***The Oncologist*** 2011;16:708–716.

17. Lichtman SM, Hollis D, Miller AA et al. Prospective evaluation of the relationship of patient age and paclitaxel clinical pharmacology: Cancer and Leukemia Group B (CALGB 9762). J Clin Oncol 2006;24:1846–1851.

18. Bicher A, Sarosy G, Kohn E et al. Age does not influence taxol dose intensity in recurrent carcinoma of the ovary. Cancer 1993;71: 594–600.

19. Smoreburg CH, ten Tije AJ, Verweij J et al. Altered clearance of unbound paclitaxel in elderly patients with metastatic breast cancer. Eur J Cancer 2003;39:196–202.

20. Cleeland CS, Sloan JA, Cella D et al. Recommendations for including multiple symptoms as endpoints in cancer clinical trials: A report from the ASCPRO (Assessing the Symptoms of Cancer Using Patient-Reported Outcomes) Multisystem Task Force. Cancer 2013;119:411–420.

21. Atkinson TM, Ryan SJ, Bennett AV et al. The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): A systemic review. Supportive Care in Cancer 2016;24:3669–3676.