

Original Article

Peripheral Neuropathy and Falling Risk in 65 Patients Years Old and Older Receiving Chemotherapy: A Prospective Study

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Abstract

Objectives: Chemotherapy-related peripheral neuropathy is known to increase the risk of falls in the elderly. This study aims to assess the developmental state of peripheral neuropathy and the risk of falls in 65 years and older recipients of chemotherapy.

Methods: The study population comprised patients over 65 years who were first treated with chemotherapy for solid and haematological cancer between February 1, 2016, and October 31, 2017, in a day treatment unit of a hospital in Eskisehir, Turkey. We collected data every month for 6 months using the Individual Identification Form, the National Cancer Institute Common Sense of Toxicity Criteria Sensory and Motor Neuropathy Scale and the Hendrich-II Falling Risks Scale. The quantitative data were expressed as medians. Furthermore, we evaluated the comparison of measurements at different time points with a normal distribution, analysis of variance at repeated measures and normal non-dispersive score variables by the Friedman test.

Results: The number of neuropathic patients increased in the sixth month than the first month in the 6-month follow-up period. In addition, it was determined that the Hendrich-II Falling Risks Scale score increased in the fifth and sixth months than the first and second months.

Conclusion: This study revealed that the degree of neuropathy and the risk of falling increased in the sixth month than the first month for individuals over 65 years who received chemotherapy. Hence, no statistically significant correlation existed between age and neuropathy grade and age and risk of falls in this study.

Keywords: Aged, chemotherapy, peripheral neuropathy, risk of falls

Introduction

With increasing advancements in the field of health services around the world, including Turkey, a global upsurge is witnessed in the ageing population (Turkey Statistical Institute, 2016; International Agency for Research on Cancer, 2015). The Turkey Statistical Institute reveals that, at present, 8.3% of the Turkish

population is older than 65 years (Turkey Statistical Institute, 2016). Apparently, cancer is a chronic disease that increases with age (International Agency for Research on Cancer, 2015). Recent years have acknowledged tremendous technological developments in the diagnostics and treatment of cancer; however, patients extensively experience physical and

psychological changes, both from the disease course and adverse effects of treatments. In geriatric patients with cancer, both falling and falling-related problems are common repercussions of cancer treatment, along with the physiological decline that accompanies ageing (Eyigor, 2012; CDC, 2015).

Reportedly, chemotherapy-related peripheral neuropathy is the leading cause of an increase in the risk of falls and balance and walking problems in elderly individuals (Ward et al., 2014; Kolb et al., 2016). Nurgalieva et al. (2010) demonstrated that patients (aged 65–69 years) treated with a platinum–taxane combination therapy for breast, ovary and lung cancers had a lower risk of developing peripheral neuropathy than did patients older than 80 years. Ward et al. (2014) established that 73% of falls in patients diagnosed with cancer resulted in fractures, most commonly femoral neck fractures. However, a majority of patients treated with chemotherapy and biological treatment are not even aware that they are at the risk of falling; in fact, patients apply protective measures against falling after they have experienced a fall. To date, no investigation has been conducted on the development of peripheral neuropathy and the risk of falling in elderly patients who receive chemotherapy in Turkey. Hence, this study aims to evaluate the correlation between the developmental state of peripheral neuropathy and the risk of falls in patients over 65 years who received chemotherapy.

Hypotheses of study

H_0 = There is no relationship between age, developmental state of peripheral neuropathy and the risk of falls

H_1 =There is relationship between age, developmental state of peripheral neuropathy and the risk of falls

Methods

The aim and type of the research: This prospective sectional study was conducted to assess the developmental state of peripheral neuropathy and the risk of falls in patients over 65 years who received chemotherapy.

The population and sample of the research: The study cohort comprised patients over 65 years who were first treated with chemotherapy

for solid and haematological cancer between February 1, 2016, and October 31, 2017, in an outpatient treatment unit of a hospital in Eskisehir, Turkey. We enrolled only those patients in this study who fulfilled the following specified selection criteria: (a) undergoing the same chemotherapy protocol for 6 months; receiving 24 points or higher from the Standardized Mini-Mental Test (SMMT); (c) being able to walk at least 15 metres; (d) no nervous system, musculoskeletal system, skin-specific diseases, or any other disease that affects these regions; (e) nonalcoholic; (e) and agreeing to participate in the study.

Data collection: This study was approved by the Ethical Committee, and we obtained written consent from the hospital management and patients before commencing the study. Before starting the study, five patients who were not included in the scope of this study were pre-administered the test to evaluate the comprehensibility of the questions. All enrolled patients were assessed monthly for 6 months using the Individual Identification Form, the National Cancer Institute Common Toxicity Criteria Sense and Motor Neuropathy Scale (NCI-CTCAE v4.03) and the Hendrich-II Falling Risks Scale (HFRS-II).

The SMMT was first proposed by Folstein et al., standardised by Molloy and Standish and validated by Gungen et al. (2002) regarding validity and reliability. The test comprises 11 items collected under five main headings (i.e. orientation, record memory, attention and calculation, recall and language) and is evaluated over a 30-point range. While the sensitivity of the scale is 91% (23 of 24), its specificity is 95%. The SMMT is a practical test that finds application in a polyclinical environment or at bedside within a short period of 10 min by a briefly trained physician, nurse or a psychologist (Gungen et al., 2002). The NCI-CTCAE v4.03 assesses sensory and motor peripheral neuropathy, including objective and subjective measurements, and is used to determine chemotherapy-related peripheral neuropathy (National Cancer Institute, 2009). Furthermore, the HFRS-II was developed by Hendrich et al. in 1995, re-examined in 2003 to create a second version and improved in terms of validity and reliability by Atay et al. in 2009. The highest

score obtained from HFRS-II was 20 (scores ≥ 5 indicate a high risk) (Dedeli, Karagozoglu, & Kurukiz, 2012).

Data Analysis: We analysed data using the IBM SPSS 21 package program. Quantitative data were expressed as mean \pm standard error or median (Q1–Q3). The normal distribution of data was verified using the Shapiro–Wilk test. While we used the variance analysis for repeated measures, the Friedman test was used to evaluate non-normally distributed score variables. The correlation between quantitative variables was examined by the Spearman correlation analysis. Furthermore, the relationship between the categorical variables was evaluated by the χ^2 analysis. We considered $P < 0.05$ as statistically significant.

Results

In this study, we examined 39 patients. We excluded five patients from the study because of a change in their chemotherapy protocol, and four patients died. Hence, we completed the study with 30 patients. While 50% of the research cohort had solid tumours, the remaining were treated for haematological cancer.

The average age of participants was 68.46 ± 5.88 years; 63.3% were males, 33.3% underwent platinum-based chemotherapies, and 60% had a history of surgery and radiotherapy. Of all patients, 83.3% were aware of the occurrence of chemotherapy-induced neuropathic complaints, such as numbness and tingling sensation in the hands and feet, whereas 56.7% cited ignorance of the fact that these medicines increased the risk of falls (Table 1).

We observed a statistically significant difference in the 6-month follow-up of patients based on the NCI-CTCAE v4.03 ratios evaluated every month ($p < 0.001$). In addition, the degree of neuropathy increased in the sixth month as compared to the first month (first-month NCI-CTCAE v4.03 degree: 1; sixth-month NCI-CTCAE v4.03 degree: 2; $p = 0.016$; Table 2).

We determined that when the falling status of patients and the risk of falls were evaluated, 16.7% of patients had fallen. Furthermore, the risk of falling in the fifth and sixth months increased statistically significantly (first-month HFRS-II mean score: 2, fifth-month HFRS-II

mean score: 4, $p=0.023$; first-month HFRS-II mean score: 2, sixth-month HFRS-II mean score: 4, $p=0.032$; second-month HFRS-II mean score: 2, fifth-month HFRS-II mean score: 4, $p=0.016$; second-month HFRS-II mean score: 2, sixth-month HFRS-II mean score: 4, $p=0.032$; Table 2).

An investigation of the correlation between age and neuropathy development status and age and risk of falls revealed no statistically significant differences (Table 3).

Discussion

Peripheral neuropathy is the leading adverse effect of taxane- and platinum-based chemotherapy (Hershman et al., 2014; Hong, Tian, & Wu, 2014; Bao et al., 2016). In this study, patients were treated with chemotherapy for the first time over a period of 6 months, and the number of neuropathies increased in the sixth month compared with the first month of the study. In a study, 50% of 50 patients (mean age: 48 years) with breast cancer undergoing taxane-based chemotherapy had grade 1 neuropathy and these complaints gradually decreased after the termination of chemotherapy (Hershman et al., 2014). Another study reported that chemotherapy increased the incidence of neuropathy in progressive treatments (Kautio et al., 2011). Leonard et al. (2005) reported that patients receiving oxaliplatin-based chemotherapy demonstrated a directly proportionate increase of dysesthesia and paraesthesia with a cumulative dose of oxaliplatin. In a meta-analysis, 68.1% of patients in the first month following chemotherapy and 30% in the second month were related to chemotherapy-related peripheral neuropathy (Seretny et al., 2014). The results of this study are parallel to those in the literature. In addition to drugs, obesity, inactivity, diabetes mellitus and ageing have been proven to affect the development of peripheral neuropathy (Nurgalieva et al., 2010; Bao et al., 2016; Ylitalo, 2012).

In this study, patients with no nervous system, musculoskeletal system, skin diseases or any diseases that could affect these areas, and who could walk, at least, 15 metres were included; thus, we attempted to control these factors. The severity of peripheral neuropathy increased with chemotherapy, and a moderately significant

positive correlation was observed between age and peripheral neuropathy in the first month following chemotherapy administration. Based on these results, nurses should evaluate pharmacological and non-pharmacological methods regarding neuropathic findings before and after chemotherapy, and coordinate with health professionals for patient management by considering these results.

Reportedly, peripheral neuropathy is a critical risk factor for falls (Richardson, & Hurvitz, 1995), and an increased risk of falling is related to peripheral neuropathy (Bao et al., 2016; Tofthagen, Overcash, & Kip, 2012; Marshall, 2016). Patients report difficulties when doing housework, being in a work environment and performing activities of daily living (Beijers et al., 2016; Gewandter et al., 2013) while undergoing chemotherapy.

Table 1. Distribution of socio-demographic characteristics

Characteristics	$\bar{x} \pm sd$	
Old(year)	68.46±5.88	
Gender	n	%
Female	11	36.7
Male	19	63.3
Chemotherapy drugs		
Platinum based	15	50
Taxan based	8	26.7
Azacitidine	6	20
Decitabine	1	3.3
Previously applied therapy		
Non	12	40
Surgical treatment	15	50
Radiotherapy	2	6.7
Radiotherapy and surgical treatment	1	3.3
Chronic disease		
Non	12	40
Chronic obstructive pulmonary disease	3	10
Cardiovascular disease	4	13.3
Hypertension	11	36.7
Use of auxiliary devices		
Non	20	66.7
Walking stick	7	23.3
Wheelchair	3	10
Frequency of getting help		
Ever	12	40
Occasionally	11	36.7
Always	7	23.3
Knowing the state of neuropathy		
I know	25	83.3
I do not know	5	16.7
Knowing the state of risk of fall		
I know	13	43.3
I do not know	17	56.7
Fall state		
Yes	5	16.7
No	25	83.3
Total	30	100

Table 2. Distribution of NCI-CTCAE v4.03 grade ve HFRS-II score according to months

Evaluation time	NCI-CTCAE v4.03		HFRS-II	
	Median(Q1-Q3)	p	Median(Q1-Q3)	p
1. month	1(0-1) ^a	<0.001*	2(1-4.25) ^g	<0.001*
2. month	1(0-2) ^b		2(1-4.25) ^h	
3. month	1(0-2) ^c		2(1.75-5) ⁱ	
4. month	1(1-2) ^d		3(1.75-5) ^j	
5. month	2(1-2) ^e		4(2-6.25) ^k	
6. month	2(1-2) ^f		4(2-6.25) ^l	
	Significant differences between a and f groups (p=0.016) **		Significant differences between g and l groups (p=0.032); g and k groups(p=0.023); H and l groups (p=0.032);h and k groups (p=0.016)**	

*Two Way Anova; **Friedman test

Table 3. Correlation between age, NCI-CTCAE v4.03 grade and HFRS-II score

	Age		Age
1.month NCI-CTCAE v4.03 grade		1. month HFRS-II	
r	0.412	r	0.264
p	0.024	p	0.158
2. month NCI-CTCAE v4.03 grade		2. month HFRS-II	
r	0.301	r	0.210
p	0.106	p	0.264
3. month NCI-CTCAE v4.03 grade		3. month HFRS-II	
r	0.270	r	0.254
p	0.149	p	0.175
4. month NCI-CTCAE v4.03 grade		4. month HFRS-II	
r	0.365	r	0.255
p	0.047	p	0.173
5. month NCI-CTCAE v4.03 grade		5. month HFRS-II	
r	0.333	r	0.134
p	0.072	p	0.479
6. month NCI-CTCAE v4.03 grade		6. month HFRS-II	
r	0.312	r	0.050
p	0.093	p	0.792

This study determined that in the following months of chemotherapy, patients had a higher risk of falling related to the degree of neuropathy and that age alone did not affect the risk of falling. A retrospective evaluation of patients who underwent chemotherapy between 1994 and 2007 revealed that the ratio of injuries associated

with falls per 1000 persons/month was 9.15 for double neurotoxic chemotherapy patients, 7.76 for single neurotoxic chemotherapy patients and 5.19 for patients who received no neurotoxic chemotherapy (Ward et al., 2014). Oka et al. (2005) significantly established a correlation between axonal neuropathy and falls. In addition,

Gewandter et al. (2013) established a significant correlation between motor neuropathy and falls. Another two studies reported that patients who developed chemotherapy-related neuropathy experienced more falls than patients who did not develop neuropathy (Kolb et al., 2016; Toftthagen, Overcash, & Kip, 2012). While Kolb et al. determined that the risk of an independent fall in patients with neuropathy increased with age (Kolb et al., 2016), Toftthagen, Overcash, & Kip (2012) reported that ageing did not affect the risk of falls. Toraman and Un Yildirim demonstrated (2010) that individuals over the age of 65 years who reported a direct association with falls had weaker muscles and did not maintain balance compared with healthy subjects in the same age group. Another study emphasised that fall rates augmented the mortality rate by three-fold in geriatric patients receiving chemotherapy (Wildes et al., 2013). Hence, it is recommended that chemotherapy patients who have a high risk of neuropathy should be informed about the prevention of falls by taking safety precautions regardless of age, hospital regulations, home environment and the use of assistive devices.

Conclusion

This study established that the degree of neuropathy and the risk of falling increased in the sixth month compared with the first month. In addition, no statistically significant correlation existed between age and neuropathy grade, and age and risk of falls in the study. As the study population comprised a small sample group, including patients aged 65 years or older from a single hospital, additive factors (e.g. chemotherapeutic drug, gender and the presence of chronic illness) that could affect neuropathy and fall risk could not be assessed. Hence, further extensive studies with a large sample group are warranted to evaluate the dependent factors.

Acknowledgements

The authors declare no conflict of interest.

Reference

Bao, T., Basal, C., Seluzicki, C., Li, SQ., Seidman, AD., Mao, JJ. (2016). Long term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Res Treat*, 159, 327-333.

Beijers, AJ., Vreugdenhi,l G., Oerlemans, S., Eurelings, M., Minnema, MC., Eeltink, CM., Van de Poll-Franse, LV., Mols, F. (2016). Chemotherapy-induced neuropathy in multiple myeloma: influence on quality of life and development of a questionnaire to compose common toxicity criteria grading for use in daily clinical practice. *Support Care Cancer*, 24(6), 2411-20.

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Available from: <http://webappa.cdc.gov/cgi-bin/broker.exe>. Accessed; 26.11.2015.

Eyigor, S. (2012). Approach to falls. *Ege Journal of Medicine*, 51:43-51.

Dedeli, O., Karagozoglu, S., Kurukiz, S. (2012). Determination of fall risk according to Hendrich II and Morse Fall Scale: A pilot study. *Journal of Anatolia Nursing and Health Sciences*, 15,1-9.

Gewandter, JS., Fan, L., Magnuson, A., Mustian, K., Peppone, L., Heckler, C., Hopkins, J., Tejani, M., Morrow, GR., Mohile, SG. (2013). Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): A university of Rochester CCOP study. *Support Care Cancer*, 21, 2059-66.

Gungen, C., Ertan, T., Eker, E., Yasar, R. (2002). Reliability and validity of the Standardized mini mental state examination in the diagnosis of mild dementia in Turkish population. *Turkish Psychiatric Journal*, 13(4), 273-281.

Hershman, DL., Lacchetti, C., Dworkin, RH., Lavoie Smith, EM., Bleeker, J., Cavaletti, G., Chauhan, C., Gavin, P., Lavino, A., Lustberg, MB., Paice, J., Schneider, B., Smith, ML., Smith, T., Terstriep, S., Wagner-Johnston, N., Bak, K., Loprinzi, CL. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*, 32(18),1941-71.

Hong, JS., Tian, J., Wu, LH. (2014). The influence of chemotherapy-induced neurotoxicity on psychological distress and sleep disturbance in cancer patients. *Curr Oncol*, 21:174-180.

International Agency for Research on Cancer (2015). 1965 to 2015: IARC, A unique institution for a changing world. Available from: https://www.iarc.fr/en/publications/books/iarc50/IARC_Ch3_web.pdf. Accessed:10.06.2017.

Kautio, AL., Haanpaa, M., Kautainen, H., Leminen, A., Kalso, E., Saarto, T. (2011). Oxaliplatin scale and National Cancer Institute-Common toxicity criteria in the assesment of chemotherapy-induced peripheral neuropathy. *Anticancer Research*, 31, 3493-96.

- Kolb, NA., Smith, GA., Singleton, JR., Beck, SL., Stoddard, GJ., Brown, S., Mooney, K. (2016). The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. *JAMA Neurol*, 73(7), 860-6.
- Leonard, GD., Wright, MA., Quinn, MG., Fioravanti, S., Harold, N., Schuler, B., Thomas, RR., Grem, JL. (2005). Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer. *BMC Cancer*, 5,116,1-10.
- Marshall TF. (2016). Effects of chemotherapy-induced-peripheral-neuropathy on spatiotemporal gait parameters and fall risk in cancer patients after the completion of chemotherapy drug treatment. Proquest LLC, Ann Arbor, USA, 11-93.
- National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06_14_QuickReference_5x7.pdf. Access: December 04, 2015.
- Nurgalieva, Z., Xia, R., Liu, C., Burau, K., Hardy, D., Du, XL. (2010). Risk of chemotherapy-induced peripheral neuropathy in large population-based cohorts of elderly patients with breast, ovarian, and lung cancer. *American Journal of Therapeutics* 17,148-158.
- Oka, N., Sugiyama, H., Kawasaki, T., Mizutani, K., Matsui, M. (2005). Falls in peripheral neuropathy. *Rinsho Shinkeiqaku*, 45(3),207-210.
- Richardson, JK., Hurvitz, EA. (1995). Peripheral neuropathy: A True risk factor for falls. *The Journals of Gerontology* 50A(4):211-15.
- Seretny, M., Currie, GL., Sena, ES., Ramnarine, S., Grant, R., MacLeod, MR., Colvin, LA., Fallon, M. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*, 155,2461-70.
- Toftthagen, C., Overcash, J., Kip, K. (2012). Falls in persons with chemotherapy-induced peripheral neuropathy. *Support Care Cancer*, 20,583-89.
- Toraman, A., Un Yildirim, N. (2010). Fall risk and physical fitness in the elderly with fall related conditions or unrelated diseases. *Turkish Journal of Geriatrics*, 13(2),105-110.
- Turkey Statistical Institute. (2016). Population and demography. Available from: <http://www.tuik.gov.tr/UstMenu.do?metod=temelists>. Accessed: 15.12.2017.
- Ward, PR., Wong, MD., Moore, R., Naeim, A. (2014). Fall-related injuries in elderly cancer patients treated with neurotoxic chemotherapy: A retrospective cohort study. *Journal of Geriatric Oncology*, 5,57-64.
- Wildes, TM., Ruwe, AP., Fournier, C., Gao, F., Carson, KR., Piccirillo, JF., Tan, B., Colditz, GA. (2013). Geriatric assessment is associated with completion of chemotherapy, toxicity and survival in older adults with cancer. *J Geriatr Oncol*, 4(3),227-234.
- Ylitalo KR. (2012). Prevalence, risk factors, and sequelae of peripheral neuropathy in a population-based cohort of mid life women. Proquest LLC, Ann Arbor, USA, 17-118.