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Fall-related injuries in elderly cancer patients treated with neurotoxic chemotherapy: A retrospective cohort study

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ABSTRACT

Background: Fall-related injuries are a well-described cause of morbidity and mortality in the community-dwelling elderly population, but have not been well described in patients with cancer. Cancer treatment with chemotherapy can result in many unwanted side effects, including peripheral neuropathy if the drugs are potentially neurotoxic. Peripheral neuropathy and other side effects of chemotherapy may lead to an increased risk of fall-related injuries.

Methods: We conducted a retrospective cohort analysis using the records of 65,311 patients with breast, colon, lung, or prostate cancer treated with chemotherapy in the SEER-Medicare database from 1994 to 2007. The primary outcome was any fall-related injury defined as a traumatic fracture, dislocation, or head injury within 12 months of the first dose of chemotherapy. The sample population was divided into 3 cohorts based on whether they most frequently received a neurotoxic doublet, single agent, or a non-neurotoxic chemotherapy. Cox proportional-hazards analyses were adjusted for baseline characteristics to determine the risk of fall-related injuries among the 3 cohorts.

Results: The rate of fall-related injuries for patients receiving a doublet of neurotoxic chemotherapy (9.15 per 1000 person-months) was significantly higher than for those receiving a single neurotoxic agent (7.76 per 1000 person-months) or a non-neurotoxic agent (5.19 per 1000 person-months). Based on the Cox proportional-hazards model risk of fall-related injuries was highest for the cohort receiving a neurotoxic doublet after the model was adjusted for baseline characteristics.

Conclusions: Among elderly patients with cancer, use of neurotoxic chemotherapy is associated with an increased risk of fall-related injuries.

1. Introduction

The incidence of cancer in individuals aged 60 years and older is approaching 60% and is projected to increase.[1] Studies have shown that fit older patients with cancer may benefit from chemotherapy as much as younger patients.[2–4] As the age of patients with cancer treated with chemotherapy continues to rise, there is a growing need to recognize and try to prevent complications of treatment that are common in this population. Fall-related injuries (FRIs) are a frequent cause of morbidity and mortality in the elderly. In 2005, 1.8 million patients over the age of 65 years were treated in the emergency room for non-fatal fall injuries and 433,000 of these patients were hospitalized as a result of their injuries.[5] Every year, approximately one-third of community dwelling elderly people will experience a fall, and 5–10% of falls will result in a serious injury (major head trauma or fracture) related to the fall.[6] The rate of fall-related deaths has risen over the past decade,[7] highlighting the need for more efforts to prevent and lower the risk of falls in the elderly.

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Peripheral neuropathy can lead to and exacerbate balance and gait problems and is associated with a 2- to 3-fold increased risk of falling in community-dwelling elderly patients.[8,9] Some chemotherapeutic agents, such as platinum compounds, taxanes, and vinca alkaloids, may be neurotoxic and lead to peripheral neuropathy. Chemotherapy-induced peripheral neuropathy (CIPN) can occur in 10–40% of patients treated with neurotoxic chemotherapy and is often a dose-limiting side effect.[10] A retrospective study of the SEER-Medicare database showed that patients who received taxane-based chemotherapy are twice as likely to develop CIPN and patients treated with taxane–platinum chemotherapy combinations are 3 times as likely to develop CIPN compared to similar patients with cancer who did not receive chemotherapy.[11] Deficits caused by CIPN can include loss of sensation to touch, pinprick, and vibratory sensation and more commonly affect nerves in the lower extremities. This can lead to loss of proprioception, which can result in ataxia and significant functional impairment. In addition, CIPN can result in motor deficits, hyporeflexia, and loss of autonomic nervous function. These neurologic changes can manifest clinically as foot drop, dizziness, or orthostatic hypotension, which are syndromes that commonly contribute to falls in the elderly.[12]

Falls and FRIs are uncommonly measured outcomes and elderly patients are underrepresented in most oncology clinical trials.[13] A systematic review of the literature identified seven studies that reported an incidence of falls in patients with cancer (22–37% of patients reporting at least one fall in 12 months) that was similar to those in community-dwelling people 65 years of age or older. The authors of the review found several significant methodological problems with these studies, which limited the conclusions regarding risk factors for falls in patients with cancer.[14] A small, single institution study showed that among patients with lymphoma who are hospitalized for an autologous stem cell transplant, in-hospital falls were associated with lower overall survival and higher non-relapse mortality.[15] In another prospective longitudinal study, patients with a history of a fall in the 6 months prior to starting chemotherapy were more likely to experience grade 3–5 toxicities from chemotherapy.[16]

Falls and FRIs appear to play an important role in the treatment outcomes of elderly patients with chemotherapy, but there is little information in the literature about how often these events occur and which patients are at greatest risk. The primary aim of this retrospective cohort study was to describe the prevalence of fall-related injuries in a specific population of elderly patients with cancer. The secondary aim of the study was to explore the correlation between neurotoxic chemotherapy and fall-related injuries in the elderly cancer population. Based on the increased risk of falls in elderly individuals with peripheral neuropathy, we hypothesize that elderly patients treated with neurotoxic chemotherapy have a greater risk of FRIs.

2. Methods and Materials

2.1. Sample

We analyzed the SEER-Medicare database from 1994 to 2007. The SEER (Surveillance, Epidemiology, and End Results) program is a population-based cancer registry that encompasses about 14% of the US population. The registry includes information on cancer incidence, staging, initial therapy, and survival. It is linked to Medicare administrative claims data, which includes information on demographics, Medicare enrollment, and outpatient and inpatient claims. Approximately 97% of all adults in the US older than 65 years of age have Medicare as their primary insurance.[17]

We included patients who were diagnosed with breast, colon, lung, and prostate cancer between the years 1995 and 2007, who received their first dose of chemotherapy within 12 months of diagnosis. These four tumor types were chosen because of their high prevalence. Despite the differences between patients with these separate tumor types, we chose to include all of these patients in order to have a large enough sample size to detect differences in the rates of FRIs between the different chemotherapy groups. The observation period was defined as 12 months before the diagnosis of cancer (to account for baseline comorbidity) until 12 months after the first dose of chemotherapy. Patients were excluded for the reasons outlined in Fig. 1. For patients who had different cancers diagnosed more than 2 years apart, we only observed the period of time surrounding the first cancer diagnosis. We also excluded any patient who had a FRI at any time in the year prior to cancer diagnosis. We did this because a history of prior FRI is already known to be the strongest predictor of future FRIs and these patients were thought to be too frail to be included.

2.2. Design

The use of ICD-9 codes and J codes to identify the administration of chemotherapy has been previously well described.[18,19] The administration of chemotherapy was identified by the ICD-9 codes listed in Appendix A. The neurotoxic chemotherapy agents of interest were: cisplatin, carboplatin, vinorelbine, vincristine, vinblastine, oxaliplatin, paclitaxel, and docetaxel. Patients were divided into two cohorts depending on whether they most frequently received a neurotoxic doublet or a single neurotoxic agent within the 12-month period after the first chemotherapy administration. For example if a patient received 3 months of doublet neurotoxic chemotherapy and 1 month of single agent neurotoxic chemotherapy, they were placed in the doublet group. These cohorts were compared to a non-neurotoxic cohort composed of patients that received any other specific chemotherapeutic drug as listed in Appendix B. Patients were excluded from the analysis if there was a code for chemotherapy administration, but no specific chemotherapeutic agent could be identified by J code.

2.3. Definitions

The primary outcome was any FRI within one year of a patient being given their first dose of chemotherapy. A FRI was defined as a code for hip fracture (excluding codes for pathologic or spontaneous fractures), head injury, joint dislocation, or other traumatic fracture codes (ICD-9 codes: 800–839, 850–854). In order to limit type I error, a FRI was only counted when 2 codes were found in the outpatient files (because these codes can be abstracted from radiology orders and exams as “rule out” diagnoses) or one code was found in

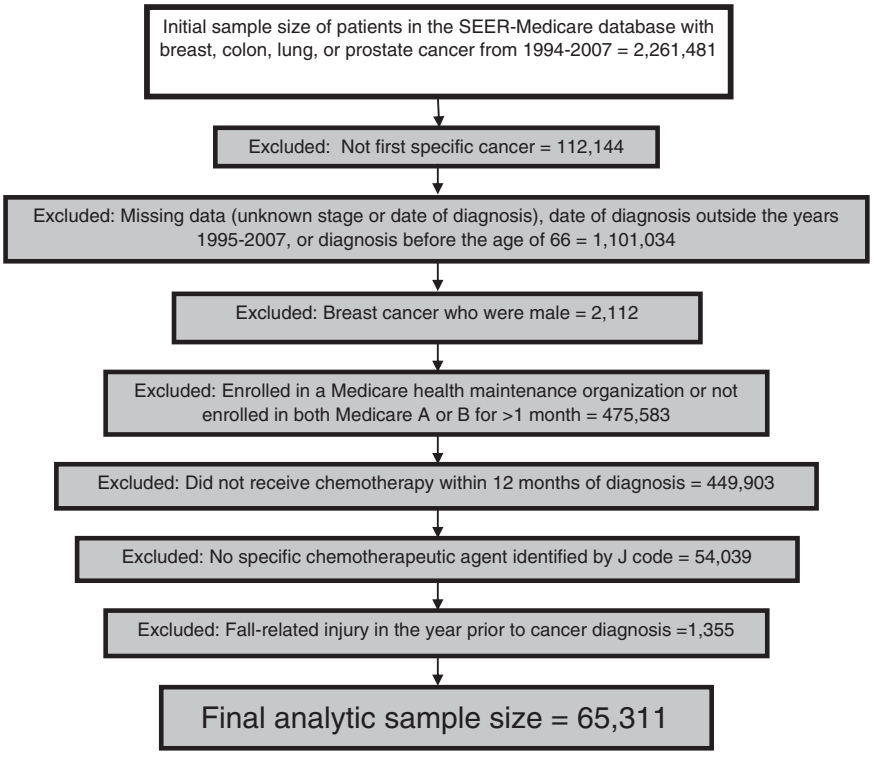

Fig. 1 – Inclusion/exclusion criteria.

the inpatient file. The time to event was calculated using the date of the earliest code.

2.4. *Data Analysis*

We used multivariate logistic regression models to adjust for age at diagnosis, tumor type, stage, race, comorbidity, history of peripheral neuropathy or history of osteoporosis (see Appendix A for ICD-9 codes). Comorbidity was calculated using an unweighted count of diagnostic codes for conditions contained in the Charlson comorbidity index,[20] as previously described.[21–23] Similar to the accounting of FRI by diagnostic codes, a condition was considered present if a code was found in the inpatient file or if 2 codes were present in the outpatient file in the 12 months prior to cancer diagnosis.

We also used the Cox proportional hazards model to measure the risk of a FRI between the cohorts and adjusted the model for the same covariates that were included in the multivariate logistic regression model. We stratified the Cox model by cancer type. We used the Kaplan–Meier method to analyze the effect of treatment type on time to FRI. Patients were censored at 12 months after first date of chemotherapy, date of death or December 31, 2007, whichever occurred first.

The study was approved by the University of California Los Angeles Institutional Research Review Board.

3. Results

The initial sample size of patients in the SEER-Medicare database with breast, colon, lung, or prostate cancer was 2,261,481. Fig. 1 shows the sequence of exclusion criteria we used to get a final analytic sample size which was 65,311. The baseline characteristics of the cohorts are shown in Table 1. The majority of patients in our sample had a diagnosis of lung cancer (n = 35,373) and made up most of patients in the doublet (n = 14,955) and single agent (n = 18,192) cohorts. The breast (n = 11,788) and colon (n = 17,374) groups made up most of the remainder of the sample. There were very few patients with prostate cancer (n = 776) who received any chemotherapy within one year of diagnosis. Most of the patients in the non-neurotoxic group had a diagnosis of colon cancer (n = 14,737). The proportion of patients with a Charlson comorbidity index of 2 or more was similar in the doublet and single agent groups (48% and 47% respectively), but significantly more than in the non-neurotoxic group (36%). Most of the patients in our sample were white (86%). The doublet and single agent groups had higher proportions of patients with stage 4 cancers (44% and 43%, respectively) compared to the non-neurotoxic group (19%). The prevalence of peripheral neuropathy in our sample was 29%.

The majority of FRIs were fractures (78.3%) and fractures of the neck of the femur were the most common type of these injuries (25.4%). The next most common types of fractures were of the vertebral column (16.2%), the humerus (9.7%), and the ribs (6.4%). The remaining FRIs were dislocations (12.3%) and head injuries (9.4%).

The rate of FRIs (after censoring for death) was significantly higher among patients that received a neurotoxic doublet (9.15 per 1000 person-months) compared to those who received a single neurotoxic agent (7.76 per 1000 person-months) or those who received a non-neurotoxic agent (5.19 per 1000 person-months) as shown in Table 2. Fig. 2 shows the cumulative incidence of FRI for each cohort. After accounting

Table 1 – Baseline characteristics.

	Full sample (n = 65,311) %	Doublet (n = 15,211) %	Single (n = 24,579) %	Non-neurotoxic (n = 25,521) %	p-Value
Age					
65–69	27%	27%	28%	26%	<0.0001
70–74	31%	34%	31%	30%	
75–79	26%	26%	25%	26%	
80+	16%	13%	16%	18%	
Gender					
Male	45%	59%	47%	34%	<0.0001
Female	55%	41%	53%	66%	
Cancer type					
Breast	18%	1%	15%	31%	<0.0001
Colon	27%	0%	10%	58%	
Lung	54%	98%	74%	9%	
Prostate	1%	0%	1%	2%	
Comorbidity index					
0	36%	28%	31%	44%	<0.0001
1	22%	24%	22%	20%	
2+	43%	48%	47%	36%	
Stage					
1	11%	11%	9%	14%	<0.0001
2	19%	6%	12%	34%	
3	36%	39%	36%	33%	
4	34%	44%	43%	19%	
Peripheral neuropathy					
No	71%	73%	70%	72%	<0.0001
Yes	29%	27%	30%	28%	
Race					
White	86%	88%	85%	85%	<0.0001
Black	7%	7%	8%	7%	
Hispanic	3%	3%	3%	4%	
Asian	4%	3%	4%	4%	
Other	0%	0%	0%	0%	
Months to 1st chemo					
0 to 3	77%	83%	80%	71%	<0.0001
4 to 6	19%	14%	16%	24%	
7 to 9	3%	2%	3%	4%	
10 to 12	1%	1%	1%	1%	
Months of chemo					
0 to 3	53%	58%	53%	49%	<0.0001
4 to 6	33%	32%	33%	33%	
7 to 9	13%	8%	12%	16%	
10 to 12	2%	1%	2%	2%	

for the patients who drop out of the sample due to death within 12 months after first chemotherapy, more than 10% in the doublet cohort and approximately 9% in the single cohort had sustained at least one FRI. This was significantly higher than the 6% of people who experienced a FRI in the non-neurotoxic cohort. The median event-free survival was 5.9 months for the doublet group, 7.6 months for the single group, and not reached for the non-neurotoxic group after 12 months of follow-up (Fig. 3).

In the multivariate logistic regression model for all tumor types combined, we found that receipt of either a doublet of neurotoxic chemotherapies or a single neurotoxic drug was associated with an increased probability of a FRI compared to receipt of a non-neurotoxic drug with odd ratios (OR) of 1.26 (95% CI, 1.15–1.39) and 1.14 (95% CI, 1.05–1.24), respectively (see Table 3). Increasing comorbidity burden, female gender, osteoporosis, and advanced age were associated with greater odds of a FRI. Asian or black race and stage 2 cancer were associated with a decreased probability of a FRI. History of peripheral neuropathy had no significant effect on the probability of a FRI.

In the Cox proportional hazards model we found that there was a significantly higher risk of a FRI for patients who received any neurotoxic agent (Hazard Ratio (HR) = 1.15, p = 0.007) after adjusting for race, comorbidity, age, stage,

Table 2 – Rate of fall-related injuries per 1000 person-months.

	Full sample		Doublet		Single		Non-neurotoxic		p-Value [a]
	n	Rate	n	Rate	n	Rate	n	Rate	
All	3506	6.81	877	9.15	1360	7.76	1269	5.19	<0.0001
Breast	634	4.9	15	10.89	188	4.83	431	4.84	0.0048
Colon	868	5.36	5	12.41	152	5.57	711	4.77	0.0047
Lung	1961	9.04	855	9.11	1000	8.96	106	9.37	0.8627
Prostate	43	5.87	2	10.42	20	13.72	21	3.7	0.0001

[a] p-Value by log-rank test.

osteoporosis, and peripheral neuropathy (see Table 4). The risk was even higher if a patient received a neurotoxic doublet compared to a single neurotoxic agent. Similar to the logistic regression model, peripheral neuropathy was the only covariate that was not statistically significant in the model.

When we examined the effects within each tumor type, we compared the risk of FRI between patients that received any neurotoxic chemotherapy to those that received non-neurotoxic chemotherapy (due to the low numbers in the doublet groups of patients with breast, colon, and prostate cancers). Both groups of patients with colon (HR = 1.31, p = 0.002) and prostate cancers (HR = 3.6, p = 0.001) had a significantly higher risk of a FRI if they received any neurotoxic chemotherapy. There were trends toward higher risk for patients with breast cancer (HR = 1.06, p = 0.54) and for patients with lung cancer (HR = 1.05, p = 0.59), but these did not reach statistical significance.

4. Discussion

We found that among the many factors that may cause FRIs in elderly patients with cancer, treatment with neurotoxic chemotherapy may be a significant one. The significantly higher risk of FRIs among those who received a doublet of neurotoxic chemotherapy compared to those who received a single neurotoxic agent or a non-neurotoxic agent is an interesting finding. The observation that a neurotoxic doublet led to more falls than a single neurotoxic agent shows a possible association between neurotoxic chemotherapy and FRIs. When we analyzed the individual tumor types there was a significant increased risk of FRIs among patients with colon cancer and a trend toward increased risk among patients with lung and breast cancers. The prostate cancer group was too small to draw any firm conclusions from, but also showed an increase in FRIs in the neurotoxic group. In addition to neurotoxic chemotherapy, there may be multiple other factors predisposing patients to FRIs, since female gender, increasing age, higher comorbidity index, and stage 4 cancer were all significant covariates in our model. It is somewhat surprising that the risk of FRIs in the patients with lung cancer was only slightly elevated among those who received neurotoxic chemotherapy compared to those who received non-neurotoxic regimens. Falls and fall-related injuries may be a surrogate marker of frailty in patients with cancer.[16] The degree of frailty in all patients with lung cancer may be so high that it is difficult to show differences in our outcome among the three cohorts. Alternatively, the lack of a significant signal in the lung cancer cohort could be explained by the fact that patients treated with a neurotoxic doublet may tend to have a greater disease burden or more rapid progression and therefore tend to have outcomes that are similar to those of the single agent and non-neurotoxic groups.

We acknowledge that there may be some selection bias due to treatment decisions by physicians and unobserved differences between patients. For example, a platinum doublet is considered standard of care for treatment of patients with stages 2–4 lung cancer, but a treating physician may consider using a non-neurotoxic drug if a patient appears frail, has peripheral neuropathy, or has significant

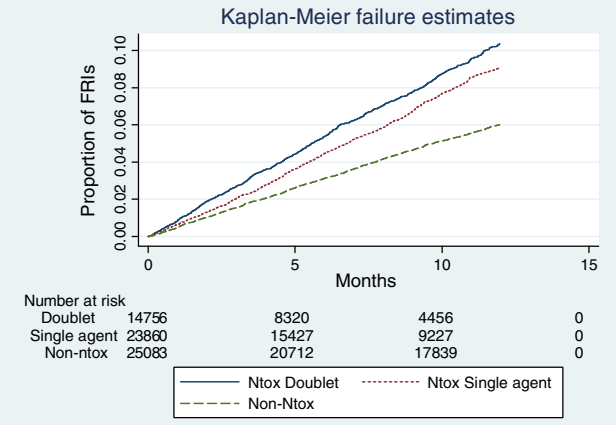

Fig. 2 – Cumulative incidence of fall-related injuries by cohort.

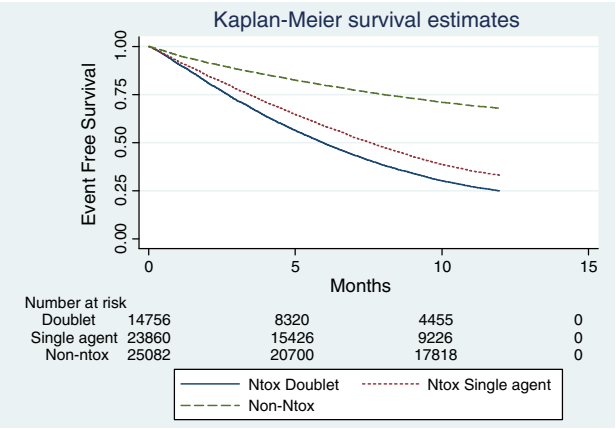

Fig. 3 – Kaplan–Meier survival curves.

Table 3 – Odds ratios for a fall-related injury in the 12 months after first chemotherapy use.

	All cancers		
	OR	95% CI	p > |z|
Chemo type			
Non-ntox	1		
Single ntox	1.14	1.05–1.24	0.002
Doublet ntox	1.26	1.15–1.39	<0.001
Gender			
Male	1.00		
Female	1.66	1.54–1.79	<0.001
Age			
65–69	1.00		
70–74	1.15	1.05–1.27	0.003
75–79	1.27	1.15–1.40	<0.001
80+	1.58	1.42–1.75	<0.001
Comorbidity			
0	1.00		
1	1.26	1.14–1.39	<0.001
2	1.32	1.21–1.43	<0.001
Race			
White			
Black	0.53	0.44–0.62	<0.001
Hispanic	0.84	0.69–1.03	0.102
Asian	0.77	0.63–0.94	0.011
Other	1.33	0.74–2.40	0.342
Stage			
1	1.00		
2	0.86	0.75–0.97	0.018
3	0.92	0.82–1.03	0.138
4	0.91	0.81–1.02	0.103
Osteoporosis			
No	1.00		
Yes	1.32	1.19–1.45	<0.001
Peripheral neuropathy			
No	1.00		
Yes	1.03	0.94–1.13	0.534

Abbreviations: ntox, neurotoxicity; OR, odds ratio; CI, confidence interval.

other comorbidities. If this is true it would bias the results toward the null hypothesis and this may explain why we found no significant differences among the cohorts with lung cancer. Due to the limitations of administrative data, we have no way to estimate performance status, which may also play an important role in deciding to treat a patient with a neurotoxic doublet or a single agent.

We hypothesized that patients receiving neurotoxic chemotherapy should have a higher risk of FRIs because they are more likely to develop peripheral neuropathy as a result of treatment. In our analysis of the entire sample population, a history of peripheral neuropathy prior to chemotherapy was not a significant predictor of FRIs. However, when we ran the multivariate regression model on only the patients who received non-neurotoxic chemotherapy, peripheral neuropathy was a significant predictor of FRIs. There are two possible explanations for this. One explanation is that for the groups that received neurotoxic chemotherapy, the effect of the neurotoxicity may be more significant than baseline peripheral neuropathy. Another explanation is that the sensitivity of capturing a diagnosis of peripheral neuropathy from Medicare administrative data is low, because it is a complication that rarely leads to a treatment or procedure that would be captured in the Medicare data.[24] In contrast, a diagnosis of osteoporosis should have a higher sensitivity because it often is coded when a bone density examination is ordered. A diagnosis of osteoporosis is also more likely to lead to treatment, often with an intravenous bisphosphonate, which also increases the chance it will be captured in the Medicare data. It is because of the low sensitivity of capturing accurate information on peripheral neuropathy that we chose not to analyze the number of patients with a new diagnosis of peripheral neuropathy after chemotherapy.

The annual rate of FRIs in our analysis (62–110 per 1000 people) was similar to the number of nonfatal, medically consulted fall injury episodes reported by the CDC's Injury Prevention and Control Center for community dwelling adults in the same age range (50–115 per 1000 people). Using ICD-9 codes for fractures, dislocations, and head injuries to capture FRIs appears to correlate with the CDC estimates, which are based on household interviews of a sample of the community dwelling, non-institutionalized population.[5] The annual rate of FRIs in the doublet group (110 per 1000 people) is equivalent to the rate of non-fatal fall injuries in community dwelling people ≥ 75 years old (115 per 1000 people). Although our numbers are close to the CDC estimates, it is likely that using ICD-9 codes to capture FRIs may have underestimated the actual rate of fall injury episodes in this population. Based on the higher comorbidity and intense treatment of patients with cancer one would expect this population to have a higher rate of FRIs.

One limitation of our study is that we were not able to control for all the variables that may have contributed to FRIs. The SEER-Medicare data does not include potentially important FRI risk factors such as performance status, use of psychotropic medications, and presence of orthostatic hypotension. Another limitation of our study is that a proportion of the events we recorded may be traumatic injuries not necessarily due to falls. We had initially proposed to use E-codes in the Medicare claims data to further specify what type of injuries was sustained, but we found variable reporting of these codes between each SEER registry site.[25–27]

In summary, neurotoxic chemotherapy may be associated with a higher risk of FRI in elderly patients with cancer. In addition, we have shown that the prevalence of FRIs is significantly higher than in community dwelling elderly patients. The mechanism of FRIs in this population is most likely multifactorial. Although neurotoxic chemotherapy may lead to peripheral neuropathy and subsequent gait and balance problems in some patients, other effects of chemotherapy such as fatigue, dehydration, and orthostatic hypotension are also likely contributors. Neurotoxic chemotherapeutic agents may be more emetogenic and lead to the aforementioned complications. In future trials of potentially neurotoxic chemotherapy trials it may be important to measure falls and fall-related injuries since these are important complications of treatment and may lead to premature discontinuation of therapy. As more

Table 4 – Cox proportional hazards model for a fall-related injury in the 12 months after first chemotherapy use.

	All tumor types		Breast		Colon		Lung		Prostate	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Non-ntox	1.00		1.00		1.00		1.00		1.00	
Any ntox	1.15	1.04–1.28	1.06	0.89–1.26	1.31	1.10–1.56	1.06	0.86–1.29	3.62	1.74–7.55
Single ntox	1.13	1.02–1.26								
Doublet ntox	1.28	1.12–1.45								
Gender										
Male	1.00		N/A							
Female	1.54	1.43–1.67			1.80	1.55–2.09	1.42	1.30–1.56	N/A	
Race										
White	1.00		1.00		1.00		1.00		1.00	
Black	0.54	0.46–0.64	0.75	0.55–1.02	0.34	0.22–0.52	0.55	0.44–0.69	0.29	0.04–2.13
Hispanic	0.83	0.68–1.02	0.85	0.56–1.29	0.75	0.51–1.11	0.90	0.68–1.20	0.48	0.06–3.60
Asian	0.71	0.59–0.87	0.64	0.40–1.04	0.90	0.66–1.24	0.61	0.45–0.82	1.21	0.16–9.02
Other	1.20	0.68–2.11	1.41	0.35–5.64	1.41	0.45–4.38	0.92	0.41–2.06	20.84	2.46–176.69
Comorbidity										
CCI 0	1.00		1.00		1.00		1.00		1.00	
CCI 1	1.25	1.14–1.38	1.31	1.06–1.63	1.22	1.01–1.48	1.20	1.06–1.37	1.55	0.51–4.76
CCI 2+	1.35	1.24–1.47	1.37	1.13–1.66	1.38	1.17–1.61	1.27	1.13–1.42	3.66	1.68–7.97
Age										
65–69	1.00		1.00		1.00		1.00		1.00	
70–74	1.18	1.07–1.29	1.49	1.22–1.82	0.92	0.75–1.13	1.17	1.04–1.32	1.16	0.39–3.51
75–79	1.32	1.20–1.46	1.74	1.40–2.17	1.20	0.98–1.46	1.23	1.08–1.39	2.00	0.69–5.75
80+	1.71	1.54–1.89	2.25	1.72–2.94	1.68	1.38–2.05	1.49	1.29–1.71	3.08	1.08–8.84
Stage										
1	1.00		1.00		1.00		1.00		1.00	
2	0.89	0.78–1.01	0.91	0.74–1.11	0.80	0.59–1.08	0.79	0.61–1.03	N/A	
3	1.06	0.94–1.19	0.81	0.62–1.07	0.95	0.72–1.26	1.10	0.94–1.28	N/A	
4	1.57	1.40–1.77	1.77	1.26–2.48	1.40	1.04–1.90	1.54	1.33–1.79	1.02	0.45–2.34
Osteoporosis										
No	1.00		1.00		1.00		1.00		1.00	
Yes	1.32	1.20–1.46	1.05	0.84–1.30	1.53	1.25–1.86	1.34	1.17–1.52	1.79	0.63–5.06
Peripheral neuropathy										
No	1.00		1.00		1.00		1.00		1.00	
Yes	1.06	0.97–1.15	1.25	1.00–1.55	1.02	0.85–1.22	1.04	0.92–1.17	0.55	0.23–1.29

Abbreviations: HR, hazard ratio; CI, confidence interval; ntox, neurotoxicity; CCI, Charlson comorbidity index; N/A, not applicable.

elderly patients are treated with chemotherapy in the community, the ability to predict and prevent falls will not only reduce morbidity and mortality, but also lower the overall cost of cancer care for these patients.

Disclosures and Conflict of Interest Statements

The authors declare that they do not have any conflicts of interest.

Author Contributions

Concept and design: P.R. Ward, M.D. Wong and A. Naeim.
Data collection: P.R. Ward and M.D. Wong.
Analysis and interpretation of data: P.R. Ward and R. Moore.
Manuscript writing and approval: P.R. Ward, A. Naeim and M.D. Wong.

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Appendix A

ICD-9 codes used to define outcome variables:

Fall-related injury, 800–829 (fractures); 830–839 (dislocations); 850–854 (intracranial injury).
Peripheral neuropathy, 356 (hereditary and idiopathic peripheral neuropathy); 357 (inflammatory and toxic neuropathy).
Osteoporosis, 733.

Appendix B

Non-neurotoxic drugs included: aldesleukin, asparaginase, bleomycin sulfate, carmustine, cladribine, cyclophosphamide, cytarbine, dacarbazine, dactinomycin, daunorubicin hydrochloride, doxorubicin hydrochloride, etoposide, floxuridine, fludarabine phosphate, fluorouracil, gemcitabine, idarubicin hydrochloride, interferon, irinotecan, mechlorethamine hydrochloride, melphalan, mesna, methotrexate sodium, mitomycin, mitoxantrone hydrochloride, pegaspargase, pentostatin, plicamycin, porfimer sodium, rituximab, streptozocin, thiotepa, topotecan, epirubicin, gemtuzumab, trastuzumab, denileukin, alemtuzumab, cetuximab, bevacizumab, and capecitabine.

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