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Original Article

Neurotoxicity Among Survivors of Testicular Cancer: A Population-based Study

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Abstract

Aims: Neurotoxicity may affect the quality of life of survivors of testicular cancer. Understanding the burden of neurotoxicity is important to guide survivorship care. A population-based study was undertaken to describe the proportion of patients in the 'real world' with neurotoxicity.
Materials and methods: A population-based, retrospective, cohort study of patients with advanced testicular cancer treated in the province of Ontario. The Ontario Cancer Registry was linked to electronic treatment records to identify all incident cases of testicular cancer during 2000–2010. Administrative databases were used to describe health system visits for symptoms potentially related to neurotoxicity. Health system visit rates were explored by number of chemotherapy cycles among patients treated during 2005–2010 for whom complete chemotherapy details were available.
Results: During 2000–2010, 2650 patients underwent an orchiectomy for testicular cancer; 920 (33%) also received chemotherapy. The proportion of patients with health system visits for neurotoxicity in the 2 years before surgery compared with the 2 years after surgery remained stable among patients treated with orchiectomy alone (18% [303/1730] versus 18% [316/1730], $P = 0.523$); however, there was a substantial increase among patients treated with chemotherapy (16% [151/920] versus 25% [231/920], $P < 0.001$). Among patients treated with chemotherapy in 2005–2010 for whom complete details were available regarding number of treatment cycles there was a dose–response effect. The increase in health system visits for neurotoxicity from 2 years before compared with 2 years after orchiectomy was greater among patients treated with four cycles of chemotherapy (17% [21/121] versus 37% [45/121]) and three cycles of chemotherapy (17% [45/258] versus 28% [72/258]) compared with those treated with one to two cycles of chemotherapy (<13% [<6/45] versus 20% [9/45], $P = 0.013$).
Conclusions: This population-based study suggests that symptoms of neurotoxicity are common among survivors of testicular cancer and that this seems to be driven by increasing exposure to chemotherapy. Clinicians should carefully evaluate patients for neurotoxicity during the survivorship phase of treatment.

Key words: Bleomycin; neuropathy; neurotoxicity; survivorship; testicular cancer; treatment toxicity

Introduction

The advent of cisplatin-based chemotherapy transformed testicular cancer into the most curable metastatic solid malignancy, with 5-year survival rates exceeding 95% [1]. With an increasing population of young testicular cancer survivors, the importance of recognising late-effect treatment complications has been appropriately emphasised [2,3].

Although cisplatin-based chemotherapy is the cornerstone of treatment for advanced testicular cancer [4–6], there are important long-term complications, including ototoxicity, renal toxicity and neurotoxicity. Cisplatin-related peripheral sensory neuropathy is related to cumulative dose, although emerging data suggest that genomic expression may explain variability in symptom burden across patients [7–9].

Clinically, patients may experience numbness, tingling or pain in a symmetrical, distal manner, predominately affecting

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the hands and feet [10]. The incidence of long-term symptomatic neuropathy among testicular cancer patients ranges from 13 to 50% in published studies [11–15]. Across these studies, 6–29% of patients rated their neuropathy as 'disabling' or 'interfering with daily activities and/or work'. However, most of these studies were small, single institution-based studies with patients treated in the late 1980s and early 1990s. Accordingly, these reports may not reflect the burden of symptoms in routine clinical practice. To address these gaps in the literature we undertook a population-based study to describe the proportion of patients in the 'real world' with neurotoxicity.

Materials and Methods

Study Design and Population

This was a population-based, retrospective cohort study involving men with testicular cancer in the province of Ontario, Canada. Ontario has a population of about 14 million people, representing 38% of the Canadian population. Canada has a single-payer universal health insurance programme with associated comprehensive, mandatory administrative database collection. All incident cases (16 + years of age) of seminoma and non-seminoma germ cell tumour who underwent orchiectomy during 2000–2010 were included in this population-level cohort. Twenty-three cases with chemotherapy, radiation or retroperitoneal lymph node dissection before orchiectomy were excluded. The study was approved by the Research Ethics Board of Queen's University, Kingston, Canada. This study was designed, analysed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [16].

Data Sources

We obtained surgical pathology reports for all orchiectomy procedures performed in the province of Ontario from 2000 to 2010. The data were manually abstracted by trained personnel into a pre-piloted electronic database and linked using unique, encoded identifiers to several administrative health databases housed at the Institute for Clinical Evaluative Sciences. The Ontario Cancer Registry is a passive, population-based cancer registry that provides diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario [17]. The Canadian Institute for Health Information (CIHI) database provides information about orchiectomy procedures. The Ontario Health Insurance Program (OHIP) provincial physician billing records, along with electronic treatment records from regional cancer centres, identifies chemotherapy utilisation. The National Ambulatory Care Reporting System (NACRS) provides information on ambulatory and emergency visits. International Classification of Disease (ICD) 9, 10 and OHIP diagnosis codes were used to identify any neurotoxicity diagnoses in the CIHI, NACRS or OHIP billing databases (see Supplementary Table S1). Detailed chemotherapy dosing records were not available before 2005; therefore, a subgroup analysis to explore the association between the number of chemotherapy cycles and neurotoxicity was carried out among those patients treated during 2005–2010. Chemotherapy treatment records were available up to 31 December 2013.

Measures and End Points

There is no formally validated algorithm to identify chemotherapy-related neurotoxicity in administrative databases. Therefore, two authors (M.J.R. and C.M.B) reviewed and selected the diagnostic codes to be used for the case definitions (see Supplementary Table S1). Many of the codes overlapped neurological and musculoskeletal symptoms. In our results, we do not provide estimates of rates of specific neurotoxicity diagnoses because we believe this would suggest an element of granularity and specificity, which our data simply do not support. Given the lack of a formally validated means to identify chemotherapy-related neurotoxicity, we used two forms of controls to explore the extent to which these symptoms relate to treatment for testicular cancer. First, we used cases as their own controls. To do so, we measured the proportion of patients with health system visits for neurotoxicity symptoms in the 2 years before orchiectomy compared with the 2 years after orchiectomy. Second, because we hypothesised that this effect would be restricted to chemotherapy, we repeated this analysis stratifying for chemotherapy exposure in order to generate a reasonable estimate of the incurred burden of neurotoxicity associated with chemotherapy use in routine clinical practice. Finally, to explore whether there was a dose response to chemotherapy exposure we repeated this analysis by number of treatment cycles delivered.

Statistical Analysis

Comparisons of proportions between study groups were made using the chi-squared test. McNemar's test was used to test for changes over time. Results were considered statistically significant at $P < 0.05$. All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study Population

From 2000 to 2010, 2650 patients underwent orchiectomy for testicular cancer (see Supplementary Figure S1 and Table 1). Among this cohort, 33% (920 patients) were treated with chemotherapy. The median age was 34 years and 65% (1712/2650) had pure seminoma. Patients treated with chemotherapy were older and had higher risk pathological features (tumour size, rete testis/lymphovascular invasion) compared with patients with orchiectomy alone. Detailed chemotherapy treatment records were available for 424 patients treated with Bleomycin, Etoposide,

Table 1
Characteristics of the patients with testicular cancer treated with orchiectomy in Ontario during 2000–2010 ($n = 2650$)

Characteristic	All patients	Orchiectomy alone	Orchiectomy and chemotherapy
	$n = 2650$	$n = 1730$	$n = 920$
Age (years)			
Mean/median	35/34	36/35	33/32
16–20	161 (6%)	77 (4%)	84 (9%)
20–29	737 (28%)	445 (26%)	292 (32%)
30–39	914 (34%)	590 (34%)	324 (35%)
40–49	580 (22%)	425 (25%)	155 (17%)
50+	258 (10%)	135 (8%)	46 (5%)
Histology			
Pure seminoma	1564 (59%)	1279 (74%)	285 (31%)
Non-seminoma	1086 (41%)	451 (26%)	635 (69%)
Tumour size (cm)			
Mean/median	4.3/4	4.1/4	4.6/4
≤4 cm	1450 (55%)	983 (57%)	467 (51%)
>4 cm	1120 (42%)	700 (40%)	420 (46%)
Unstated	80 (3%)	47 (3%)	33 (4%)
Rete testis invasion			
Yes	762 (29%)	446 (26%)	316 (34%)
No	931 (35%)	700 (40%)	231 (25%)
Unstated	957 (36%)	584 (34%)	373 (41%)
Lymphovascular invasion			
Yes	734 (28%)	294 (17%)	440 (48%)
No	1373 (52%)	1051 (61%)	322 (35%)
Unstated	543 (20%)	385 (22%)	158 (17%)

Cisplatin (BEP) or Etoposide, Cisplatin (EP) during 2005–2010. Forty-five patients (11%), 258 patients (61%) and 121 patients (29%) were treated with one to two, three and four cycles of treatment, respectively.

Neurotoxicity Outcomes Among the Entire Cohort (2000–2010)

In the entire cohort of patients, 17% (454/2650) had a health system visit for neurotoxicity in the 2 years before orchiectomy. Most of these diagnoses were musculoskeletal in nature (e.g. leg cramps/leg pain/joint pain/arthralgia). In the 2 years before orchiectomy there was no difference in the baseline rate of neurotoxicity health system visits among those who were subsequently treated with chemotherapy (16% [151/920]) versus those who were not treated with chemotherapy (18% [303/1730]) ($P = 0.474$). Additionally, there was no difference in the distribution of specific diagnoses; that is, the specific coded diagnoses were generally all musculoskeletal in nature.

Comparing the proportion of patients with health system visits for neurotoxicity 2 years before versus 2 years after orchiectomy, there was a significant increase among patients treated with chemotherapy (16% [151/920] versus 25% [231/920], $P < 0.001$), but not among patients treated with orchiectomy alone (18% [303/1730] versus 18% [316/1730], $P = 0.523$). Among those not treated with chemotherapy, the most common neurotoxicity diagnoses remained musculoskeletal in nature (e.g. leg cramps/leg pain/joint pain/arthralgia). By contrast, among those treated with chemotherapy, there was a shift towards neurological diagnoses (e.g. idiopathic peripheral neuritis, polyneuropathy).

As shown in Table 2, the baseline incidence of health system visits for neurotoxicity was similar when stratified by age and subsequent chemotherapy treatment. Among patients treated with chemotherapy there was an absolute 8% increase in health system visits for neurotoxicity among patients younger than 40 years old (16% [109/700] versus 24% [168/700], $P < 0.001$) and an absolute 10% increase in visits for patients aged 40 years or older (19% [42/220] versus 29% [63/220], $P = 0.006$); this difference between age groups was not statistically significant ($P = 0.364$).

Neurotoxicity Outcomes in the Subcohort Treated with Chemotherapy

From 2000 to 2004, 1018 patients underwent orchiectomy for testicular cancer. Among this cohort, 36% (368 patients) were treated with chemotherapy. In the 2 years before orchiectomy, 17% (63/368) had health system visits for neurotoxicity. In the 2 years after orchiectomy, 20% (75 patients) had health system visits for neurotoxicity.

From 2005 to 2010, 1632 patients underwent orchiectomy for testicular cancer. Among this cohort, 34% (552 patients) were treated with chemotherapy; 77% (424/552) had detailed treatment regimen records. Among these patients with detailed treatment regimen records, 17% (71/424) had health system visits for neurotoxicity in the 2-year period before orchiectomy. There was a dose–response

Table 2
Health care utilisation for neurotoxicity symptoms among survivors of testicular cancer treated in Ontario during 2000–2010 in the 2-year period before and 2-year period after orchiectomy stratified by receipt of chemotherapy and age ($n = 2650$)

	Orchiectomy alone	Orchiectomy and chemotherapy
All cases ($n = 2650$)		
Neurotoxicity visits before	18% (303/1730)	16% (151/920)
Neurotoxicity visits after	18% (316/1730)	25% (231/920)
	$P = 0.523$	$P < 0.001$
<40 years of age ($n = 1812$)		
Neurotoxicity visits before	16% (178/1112)	16% (109/700)
Neurotoxicity visits after	16% (180/1112)	24% (168/700)
	$P = 0.890$	$P < 0.001$
40+ years of age ($n = 838$)		
Neurotoxicity visits before	20% (125/618)	19% (42/220)
Neurotoxicity visits after	22% (136/618)	29% (63/220)
	$P = 0.398$	$P = 0.006$

effect with an increasing number of cycles of chemotherapy associated with increased health system visits for neurotoxicity (Table 3). The increase in health system visits for neurotoxicity from 2 years before compared with 2 years after orchiectomy was greater among patients treated with four cycles of chemotherapy (17% [21/121] versus 37% [45/121]) and three cycles of chemotherapy (17% [45/258] versus 28% [72/258]) compared with those with one to two cycles of chemotherapy (<13% [<6/45] versus 20% [9/45], $P = 0.013$).

Discussion

In this population-based study we describe neurotoxicity late effects associated with chemotherapy for testicular cancer. The major finding of this study was an approximate 10–20% absolute increase in healthcare utilisation for symptoms of neurotoxicity after chemotherapy. This translates to one in five survivors previously treated with four cycles of BEP/EP seeking medical care for this potential treatment-related complication. This is important information that will better inform the counselling and consenting of patients requiring treatment for advanced testicular cancer. Moreover, it reinforces the need to evaluate men for neurotoxicity concerns in the survivorship phase of their testicular cancer treatment. The risk increases with cumulative number of chemotherapy cycles. Importantly, there seems to be a clinically significant increase in neurotoxicity between three and four cycles of chemotherapy. Given the ongoing controversy as to whether four cycles of EP is an appropriate substitute for three cycles of BEP for metastatic good-risk testicular cancer [18], the added burden of neurotoxicity with four compared with three cycles may be an important treatment consideration.

Although the exact mechanism of cisplatin-induced neuropathy remains unknown, cisplatin seems to accumulate in the large dorsal root ganglia neurons and interferes with cellular metabolism and axo-plasmatic transport [19]. Studies have shown that circulating platinum complexes can be detected in the plasma up to 20 years after treatment [20]. There is a significant relationship between increasing levels of residual platinum and neurotoxicity [21]. Unfortunately, there are no effective methods for the prevention of cisplatin-induced neuropathy and treatment options are limited [22]. A randomised trial by the German Testicular Cancer Study Group evaluated whether carboplatin, a platinum analogue with less neurotoxicity, could be used in place of cisplatin. However, the substitution of carboplatin for cisplatin led to an increased risk of relapse (32% versus 13%) and death (16% versus 3%), thus confirming the critical importance of cisplatin in the curative treatment of testicular cancer [23].

This study adds to a growing body of literature examining survivorship issues for men with advanced testicular cancer. Recently, the Platinum Study collaborative initiative has reported on morbidity outcomes for a cohort of 1200 testicular cancer survivors. Among patients treated with the contemporary chemotherapy regimens, BEP × 3, BEP × 4

Table 3
Health care utilisation for neurotoxicity in the 2 years before and after orchiectomy among survivors of testicular cancer treated in Ontario during 2005–2010 ($n = 424$)

	Cycles 1–2 ($n = 45$)	Cycle 3 ($n = 258$)	Cycle 4 ($n = 121$)	P
Neurotoxicity visits before orchiectomy	<6 (<13%)*	45 (17%)	21 (17%)	
Neurotoxicity visits after orchiectomy	9 (20%)	72 (28%)	45 (37%)	
Absolute percentage increase before versus after orchiectomy	NA	11%	20%	0.013

* As per the policy of the Institute for Clinical Evaluative Sciences, small cells (<6) are suppressed so that precise values cannot be determined to limit risk of patient reidentification.

and EP × 4, the rates of patient-reported neuropathy were 21, 32 and 30%, respectively [24]. In a subsequent publication, based on the combination of patient-reported outcomes and prescribed medication use, the Platinum Study group reported a 56% incidence of any grade neuropathy (as per CTCAE 4.03), with a 13% incidence of grade 3 neuropathy [25]. However, the Platinum Study group is a collaboration of expert, high-volume, academic treatment centres [26]. Our data describe outcomes in routine practice in a population-based setting and identify comparable estimates of neurotoxicity symptoms (28% with three cycles of BEP or EP, 37% with four cycles of BEP or EP).

Our study should be interpreted in the context of certain methodological limitations. There is no formally validated algorithm to identify chemotherapy-related neurotoxicity in the administrative databases. Many of the codes used in this study overlapped neurological and musculoskeletal symptoms. This limits the precision of the estimated symptom burden. We attempted to overcome this limitation in two ways. First, we used cases as their own controls (i.e. compared the incidence of our selected neurotoxicity definition before and after orchiectomy). Second, we stratified our analyses by receipt of chemotherapy (confirming neurotoxicity was limited to chemotherapy-treated cases, as would be expected). Although the reliability of the point estimate of neurotoxicity before or after chemotherapy may be limited, we believe that the absolute difference between these two time points represents a reliable estimate of the incurred neurotoxicity burden. Moreover, we observed a dose–response relationship between increasing chemotherapy exposure and symptoms of neurotoxicity. Our study is limited by lack of information regarding the severity, chronicity, symptom details and treatment of neurotoxicity symptoms. Also, we are not able to distinguish chemotherapy-related health system visits for neuropathy from those for Raynaud's phenomenon. However, we captured events that were of sufficient relevance to prompt a visit to a physician, suggesting that there was some negative effect on function. The increased healthcare utilisation cannot be explained by 'medicalisation' of the patient, as no such increase was seen in patients who did not receive chemotherapy.

In conclusion, this population-based study of men with advanced testicular has confirmed that there is a significant incurred burden of neurological toxicity associated with contemporary cisplatin-based chemotherapy regimens. Consistent with reports from randomised clinical trials and retrospective cohorts from large, academic, high-volume treatment centres, our data show that there is a substantial increase in healthcare utilisation for neurotoxicity symptoms following delivery of BEP/EP chemotherapy in routine clinical practice. Clinicians should carefully evaluate patients for neurotoxicity during the survivorship phase of their testicular cancer treatment. Further work is needed to identify effective strategies for the prevention and management of this common late effect of chemotherapy.

Conflicts of Interest

P.L. Bedard has received grants from Bristol-Myers Squibb, Sanofi, AstraZeneca, Genentech/Roche, Servier, Merck, Nektar, Mersana, Novartis, GlaxoSmithKline, SignalChem, PTC Therapeutics, during the conduct of the study and is the Current Chair, Investigational New Drug Committee, Canadian Clinical Trials Group; Executive Board Member, Breast International Group; Steering Committee Member, American Association for Cancer Research Project GENIE; Member, NCI-BIO Breast Cancer Immunotherapy Task Force.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.04.008.

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