

A population-based study of pulmonary monitoring and toxicity for patients with testicular cancer treated with bleomycin

M.J. Raphael MD,^{*†} M.D. Lougheed MD,^{‡§||} X. Wei MSc,^{*||} S. Karim MD,[#] A.G. Robinson MD,^{*†} P.L. Bedard MD,^{**} and C.M. Booth MD^{*†‡||}

ABSTRACT

Background Bleomycin is commonly used to treat advanced testicular cancer and can be associated with severe pulmonary toxicity. The primary objective of the present study was to describe the use of pulmonary function tests (PFTs) and chest imaging before, during, and after treatment with bleomycin.

Methods To identify all incident cases of testicular cancer treated with bleomycin-based chemotherapy in the Canadian province of Ontario during 2005–2010, the Ontario Cancer Registry was linked with chemotherapy treatment records. Health administrative databases were used to describe use of PFTs, chest imaging, and physician visits for respiratory complaints.

Results Of 394 patients treated with orchiectomy and chemotherapy who received at least 1 dose of bleomycin, 93% had complete chemotherapy records available. In the 4 weeks before, during, and within 2 years after finishing bleomycin-based chemotherapy, PFTs were performed in 17%, 17%, and 29% of patients respectively. Chest imaging was performed in 68%, 62%, and 98% of patients in the same time periods. In the 2 years after bleomycin-based chemotherapy, 23% of treated patients had a physician visit for respiratory symptoms. That rate was substantially higher for men with greater exposure to bleomycin: 40% (24 of 60) for 10–12 doses bleomycin compared with 21% (53 of 250) for 7–9 doses and with 14% (8 of 58) for 1–6 doses ($p = 0.002$).

Conclusions Quality improvement initiatives are needed to increase baseline rates of chest imaging within 4 weeks of starting chemotherapy for testicular cancer; to understand why such a high proportion of men have chest imaging during bleomycin-based chemotherapy; and to mitigate the excess pulmonary toxicity seen with increasing exposure to bleomycin.

Key Words Testicular cancer, bleomycin, treatment adverse events, population-based outcome studies

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INTRODUCTION

Testicular cancer is a highly treatable malignancy, with a cure rate exceeding 95%^{1–3}. Standard first-line treatment for advanced disease is 4 cycles of bleomycin–etoposide–cisplatin (BEP) for patients with intermediate- or poor-risk disease and 3 cycles of BEP or 4 cycles of etoposide–cisplatin for good-risk disease^{4–6}. Patients with stage I disease can receive 1–2 cycles of adjuvant BEP after orchiectomy. Although BEP produces a high cure rate, bleomycin is associated with potentially life-threatening lung injury, including pneumonitis and pulmonary fibrosis^{7–10}.

Bleomycin-induced lung injury presents in a nonspecific subacute manner, with nonproductive cough, dyspnea, and chest discomfort. There are no uniformly agreed-upon diagnostic criteria, nor any definitive diagnostic tests¹¹. As a result, definitions of bleomycin-induced lung injury vary, making it difficult to estimate the true incidence. Given that limitation, Necchi *et al.*¹² performed a meta-analysis of randomized trials evaluating patients with metastatic germ-cell tumours who received first-line chemotherapy. For patients treated with bleomycin regimens, the pooled probability of any-grade pulmonary toxicity was 12%. However, information about the burden of pulmonary toxicity

Correspondence to: Christopher Booth, Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, 10 Stuart Street, Kingston, Ontario K7L 3N6.

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for men treated with bleomycin-based regimens in routine clinical practice, outside of the clinical trial setting, is limited. Furthermore, information about the use of either or both of chest radiography or pulmonary function tests (PFTs) before, during, and after bleomycin-based chemotherapy is limited. All consensus guidelines recommend chest imaging at baseline for staging and in the post-treatment period for response assessment and recurrence detection^{4–6}. However, the guidelines offer no recommendations about whether imaging should be done during treatment for either response assessment or for pulmonary surveillance to identify early signs of bleomycin-induced lung injury. Similarly, they offer no advice about if, when, or how often PFTs should be done during bleomycin-based chemotherapy.

To address those gaps in the literature, we undertook a population-based study of men with advanced testicular cancer undergoing orchiectomy and bleomycin-based chemotherapy. The primary objective of the study was to describe the use of PFTs and chest imaging in routine clinical practice before, during, and after treatment with bleomycin for advanced testicular cancer. The secondary objective was to compare the incidence of visits to physicians for respiratory complaints before and after bleomycin exposure, as an estimate of the incurred burden of pulmonary toxicity.

METHODS

This study was designed, analyzed, and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement¹³. In accordance with the policies of ICES, small cell counts are suppressed and reported as “less than 6” so as to limit the risk of patient re-identification. Our study was approved by the Queens University Health Research Ethics Board.

Study Design and Population

This population-based retrospective cohort study was undertaken in the province of Ontario. Ontario has a population of approximately 13.5 million people, representing 38% of the Canadian population. Canada has a single-payer universal health insurance program with associated comprehensive and mandatory administrative database collection. In the province of Ontario, 14 local health integration networks (LHINs) are responsible for the regional planning, funding, and administration of local health care.

Patients were eligible for inclusion in the study if they were 16 years of age or older, had a diagnosis of seminoma or non-seminoma germ-cell tumour, underwent orchiectomy, and received at least 1 dose of bleomycin-based chemotherapy in the Canadian province of Ontario between 2005–2010. That period was selected because we had direct access to the orchiectomy pathology reports for all incident cases of testicular cancer during it. Patients were excluded from the study if complete chemotherapy details (for example, number of bleomycin doses) were not available or if the patient received chemotherapy, radiation, or retroperitoneal lymph node dissection before orchiectomy.

Data Sources

The Ontario Cancer Registry is a passive population-based cancer registry that provides diagnostic and demographic

information for at least 98% of all incident cases of cancer in the province of Ontario¹⁴. Using the Ontario Cancer Registry to identify cases, we obtained surgical pathology reports for all orchiectomy procedures performed in Ontario during 2005–2010. The data were manually abstracted into a pre-piloted electronic database and linked with several administrative health datasets through unique encoded identifiers. Electronic records from the provincial chemotherapy ordering system were used to identify treatment with bleomycin. The OHIP (Ontario Health Insurance Program) database of provincial physician billing records was used to identify PFTs, chest imaging, and visits to physicians for which the diagnostic code was a respiratory complaint. Physicians in Ontario are remunerated based on their submissions to OHIP, and so that database is believed to be comprehensive. The National Ambulatory Care Reporting System and the Canadian Institute for Health Information Discharge Abstract Database were used to identify, respectively, visits to the emergency department and hospitalizations for respiratory diagnoses. Codes from the *International Statistical Classification of Diseases and Related Health Problems*, 9th and 10th revisions, were used to identify any respiratory diagnoses in the Discharge Abstract Database, the National Ambulatory Care Reporting System, or the OHIP billing database (see supplemental Table 1).

Measures and Outcomes

Use of PFTs, chest radiography, or computed tomography chest in the 2 years before the first dose of bleomycin chemotherapy, during bleomycin treatment, and in the 2 years after the last dose of bleomycin was counted if an OHIP billing code for the respective diagnostic test was identified. The indication for testing is not recorded in the available databases, and we therefore could not differentiate testing for pulmonary toxicity screening from testing in response to new respiratory symptoms or from testing for staging.

We attempted to explore regional variability in the use of PFTs or chest imaging in the peri-bleomycin treatment period. When attempting to separately explore PFTs and chest imaging by each of the 14 LHIN regions, we encountered numerous small-value cells (that is, <6), which, according to ICES policy, cannot be presented. We therefore evaluated the use of either PFTs or chest imaging by LHIN region.

To estimate the incurred burden of pulmonary toxicity, we started by identifying any health system visit for a respiratory symptom in the 2-year periods before and after exposure to at least 1 dose of bleomycin. No algorithm to identify chemotherapy-related lung toxicity in administrative databases has been formally validated. Therefore, *a priori*, two authors (MJR, CMB) reviewed and selected the diagnostic codes to be used for the case definitions (see supplemental Table 1). Because we were concerned that many physician visits for respiratory symptoms related to chemotherapy would have been coded as another diagnostic entity, we included a very broad list of respiratory diagnoses. Given the lack of a formally validated means to identify chemotherapy-related lung toxicity, we used two forms of controls to explore the extent to which our broad list of symptoms related to treatment for testicular cancer. First, we used cases as their own controls by

measuring the proportion of patients with health system visits for pulmonary symptoms in the 2 years before bleomycin exposure compared with the 2 years after. Second, because we hypothesized that any effect would be related to cumulative bleomycin dose, we repeated the analysis, stratifying for the number of bleomycin doses received. Although the lack of specificity in the diagnostic codes might limit the reliability of the point estimate, the absolute difference between the incidences before and after bleomycin exposure should generate a reasonable estimate of the incurred burden of pulmonary toxicity associated with bleomycin exposure.

Statistical Analysis

Descriptive statistics are presented as proportions, means, and medians, as appropriate. Comparisons of proportions were made using the chi-square test. A McNemar test was used to test for changes in proportions before and after bleomycin exposure. Results were considered statistically significant at a *p* value less than 0.05. All analyses were performed in the SAS software application (version 9.4: SAS Institute, Cary, N.C., U.S.A.).

RESULTS

Study Population

Between 2005 and 2010, 552 patients were treated with orchiectomy and chemotherapy for testicular cancer in Ontario. A specific chemotherapy regimen was identified for 475 patients. Of the 394 men treated with BEP, full chemotherapy dose records were available for 368 of 394 (93%); those 368 men formed the study cohort. In that cohort, 76% (245 of 368) had non-seminoma germ-cell tumours, and 33% (123 of 368) had seminoma (Table I). The median age of patients with non-seminoma tumours was 29 years; it was 37 years for those with seminoma. In the cohort, 16% (*n* = 58) received 1–6 doses of bleomycin, 68% (*n* = 250) received 7–9 doses, and 16% (*n* = 60) received 10–12 doses.

PFTs

In the 4 weeks before bleomycin-based chemotherapy, during treatment, and within 2 years of finishing treatment, PFTs were performed in, respectively, 17% (63 of 368), 17% (61 of 368), and 29% (106 of 368) of the patients. Of patients who underwent baseline PFTs, 60% (38 of 63) and 65% (41 of 63) received further PFTs during treatment and within 2 years of finishing bleomycin-based chemotherapy respectively. The PFTs used before, during, and after chemotherapy were more common in patients with greater bleomycin exposure (Table II).

When the patients were stratified by histology, we observed no difference in the proportion of PFTs performed before (21% vs. 18%, *p* = 0.63), during (18% vs. 13%, *p* = 0.34), or after (31% vs. 23%, *p* = 0.19) bleomycin-based chemotherapy for non-seminoma tumours and seminoma respectively. When stratified by age, patients 40 years of age and older were more likely to undergo PFTs before (32% vs. 18%, *p* = 0.007), but not during (23% vs. 15%, *p* = 0.09) or after treatment (28% vs. 29%, *p* = 0.83).

TABLE I Characteristics of 368 patients with seminoma and non-seminoma testicular cancer treated with orchiectomy and bleomycin in Ontario during 2005–2010

Characteristic	Patient group		
	Overall	Non-seminoma	Seminoma
<i>Patient-related</i>			
Patients (<i>n</i>)	368	278	90
Age (years)			
Mean	32	30	37
Median	30	29	37
Age group [<i>n</i> (%)]			
16 to 39 Years	171 (47)	149 (53)	22 (24)
30 to 39 Years	118 (32)	86 (31)	32 (36)
40 to ≥50 Years	79 (22)	43 (16)	36 (40)
<i>Disease-related</i>			
Primary histology ^a [<i>n</i> (%)]			
Seminoma	123 (33)	33 (12)	90 (100)
Embryonal carcinoma	185 (50)	185 (67)	NA
Teratoma	36 (10)	36 (13)	NA
Other ^b	24 (7)	24 (9)	NA
Tumour size ^c (cm)			
Mean	4.5	4.3	5.3
Median	4	4	5
Tumour size group [<i>n</i> (%)]			
≤4 cm	200 (54)	165 (59)	35 (39)
>4 cm	159 (43)	107 (38)	52 (58)
Rete testis invasion [<i>n</i> (%)]			
Yes	134 (36)	106 (38)	28 (31)
No	94 (26)	71 (26)	23 (26)
Unstated	140 (38)	101 (36)	39 (43)
Lymphovascular invasion [<i>n</i> (%)]			
Yes	184 (50)	160 (58)	24 (27)
No	150 (41)	95 (34)	55 (61)
Unstated	34 (9)	23 (8)	11 (12)

^a Non-seminoma cases were defined as having any non-seminoma histology listed on the pathology reports.

^b Yolk sac tumour and choriocarcinoma.

^c Tumour size is unstated for 9 patients.

Pulmonary Imaging

Chest imaging (either chest radiography or computed tomography chest) was performed in 68% (251 of 368), 62% (227 of 368), and 98% (359 of 368) of patients in, respectively, the 4 weeks before, during, and within 2 years of finishing bleomycin-based chemotherapy. In the 8 weeks before chemotherapy, 90% of patients (331 of 368) underwent chest imaging. Of the 227 patients who underwent imaging during chemotherapy, radiography was used in 57% (129 of 227); computed tomography chest in 15% (34 of 227); and both, in 28% (64 of 227). Chest imaging during treatment increased substantially with an increasing number of bleomycin doses (Table II). Of patients who received PFTs during chemotherapy, 84% (51 of 61) also underwent chest imaging.

TABLE II Use of pulmonary function tests and chest imaging in 368 patients with testicular cancer treated with bleomycin–etoposide–cisplatin (BEP) chemotherapy in Ontario during 2005–2010.

Variable	Bleomycin doses [<i>n</i> (%)]			<i>p</i> Value
	1–6 (<i>n</i> =58)	7–9 (<i>n</i> =250)	10–12 (<i>n</i> =60)	
Pulmonary function tests				
Within 4 weeks before BEP	15 (26)	35 (14)	13 (22)	0.057
During BEP	9 (16)	33 (13)	19 (33)	0.002
Within 2 years after BEP	10 (17)	64 (26)	32 (53)	<0.001
Chest imaging ^a				
Within 4 weeks before BEP	37 (64)	168 (67)	46 (77)	0.270
During BEP	32 (55)	149 (60)	46 (77)	0.027
Within 2 years after BEP ^b	>51 (>88)	243 (97)	>53 (>88)	0.400

^a Chest radiography, chest computed tomography, or both.^b Per ICES policy, cells were suppressed to ensure that precise small cell values cannot be determined.

When the patients were stratified by histology (non-seminoma and seminoma respectively), we observed no difference between those with pulmonary imaging before (69% vs. 64%, $p = 0.38$) or during (60% vs. 66%, $p = 0.38$) bleomycin-based chemotherapy, but we observed that the rate was higher after bleomycin-based chemotherapy (99% vs. 94%, $p = 0.03$). When patients were stratified by age (≥ 40 years and < 40 years respectively), we observed no difference between those with pulmonary imaging before (73% vs. 67%, $p = 0.26$), during (67% vs. 60%, $p = 0.26$), or after (97% vs. 100%, $p = 0.11$) bleomycin-based chemotherapy.

Regional Variation in Practice

During 2005–2010, the lowest-volume LHIN region treated 11 patients, and the highest-volume LHIN region treated 60 patients. The median number of treated patients was 24.

The percentage of patients within each LHIN who underwent chest imaging ranged from 42% to 88% in the 4 weeks before, 41% to 91% during, and 92% to 100% within 2 years of finishing bleomycin-based chemotherapy. The corresponding percentages of patients who underwent PFTs ranged from less than 10% to 86% before, less than 10% to 50% during, and less than 10% to 64% after finishing bleomycin-based chemotherapy.

Of patients treated with 1–6 doses of bleomycin, the percentage undergoing PFTs or chest imaging ranged from 43% to 100%, from 0% to 100%, and from 67% to 100% in the 4 weeks before, during, and within 2 years of finishing bleomycin-based chemotherapy. For patients treated with 7–9 doses of bleomycin, the percentages were 44% to 100%, 42% to 100%, and 89% to 100%, and for those treated with 10–12 doses of bleomycin, the percentages were 50% to 100%, 67% to 100%, and 100%.

Pulmonary Toxicity

In the 2-year period before starting chemotherapy, 19% of the patients (71 of 368) made a health system visit for a respiratory symptom. The most common diagnoses (not mutually exclusive) were chronic obstructive pulmonary disease or asthma (42%, 30 of 71), acute bronchitis (42%, 30 of 71), and lower respiratory tract infection (24%, 17 of 71). Of those patients, 39% (28 of 71) saw a physician for a

respiratory complaint in the 2-year period after chemotherapy. Of the 81% of men who had not seen a physician for a respiratory complaint before starting chemotherapy (294 of 368), 19% (57 of 294) saw a physician for a respiratory complaint in the 2-year period after chemotherapy. Overall, after chemotherapy, 23% of all men (85 of 368) made a health care visit for respiratory symptoms within the subsequent 2 years. Pulmonary fibrosis codes were specifically used in 2% of men (8 of 368).

Increasing cumulative bleomycin exposure was associated with increasing likelihood of respiratory toxicity (Table III). The proportion of patients seeking health care before compared with after BEP for respiratory symptoms was 19% compared with 14% for men who received 1–6 doses of bleomycin ($p = 0.549$), 20% compared with 21% for men who received 7–9 doses of bleomycin ($p = 0.902$), and 15% compared with 40% for men who received 10–12 doses of bleomycin ($p = 0.003$). Using PFTs as another marker of potential bleomycin lung toxicity, the proportion of men undergoing PFTs before compared with after BEP was 26% compared with 17% for men who received 1–6 doses of bleomycin ($p = 0.302$), 14% compared with 26% for men who received 7–9 doses of bleomycin ($p = 0.002$), and 22% compared with 53% for men who received 10–12 doses of bleomycin ($p < 0.001$). Figure 1 shows the temporal distribution of PFTs and chest imaging use.

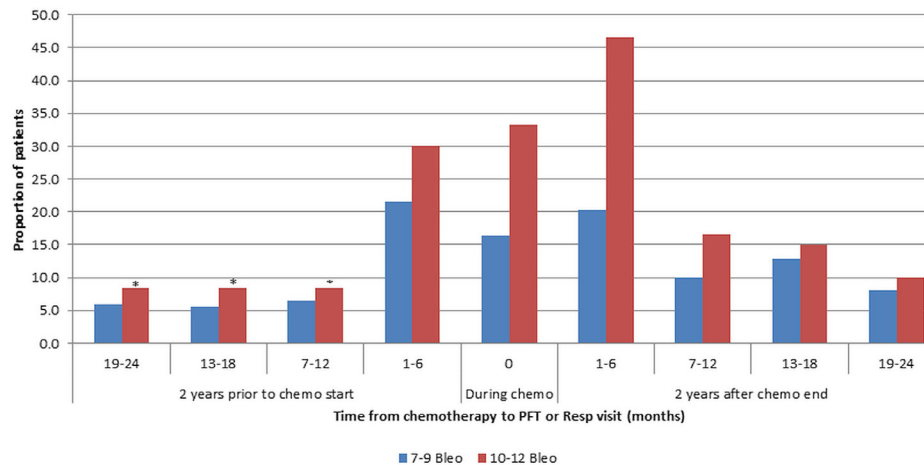
DISCUSSION

To our knowledge, the present population-based study is the first to report patterns of pulmonary monitoring and associated pulmonary outcomes in men treated with bleomycin-based chemotherapy for advanced testicular cancer. Several important findings emerged.

First, in contradiction to clinical practice guidelines, one third of the patients received no baseline chest imaging within 4 weeks of starting chemotherapy for advanced testicular cancer. Second, despite a lack of evidence to support the practice, most men underwent PFTs and chest imaging during the delivery of BEP chemotherapy. High rates of PFT and chest imaging use were observed regardless of the number of bleomycin doses delivered. The use of PFTs

TABLE III Health services utilization for respiratory symptoms by 368 patients with testicular cancer treated with bleomycin–etoposide–cisplatin (BEP) chemotherapy in Ontario during 2005–2010

Bleomycin received	Pts (n)	Health services utilization with respect to BEP administration					
		Respiratory visits			Pulmonary function tests		
		2 Years before	2 Years after	p Value	2 Years before	2 Years after	p Value
1–6 Doses	58	11 (19)	8 (14)	0.549	15 (26)	10 (17)	0.302
7–9 Doses	250	51 (20)	53 (21)	0.902	35 (14)	64 (26)	0.002
10–12 Doses	60	9 (15)	24 (40)	0.003	13 (22)	32 (53)	<0.001

**FIGURE 1** Use of pulmonary function tests (PFTs) or chest imaging in patients treated with bleomycin (Bleo)–etoposide–cisplatin chemotherapy (with 7–12 doses of bleomycin) for testicular cancer in Ontario during 2005–2010 ($n = 368$). Patients who received 1–6 bleomycin doses ($n = 58$) were excluded from the analysis to avoid the risk of re-identification. *Proportions are 8% or less. Per ICES policy, these bars are suppressed to ensure that precise small cell values cannot be determined. Resp visit = visit made to a health care professional about a respiratory complaint.

and chest imaging at baseline and during chemotherapy appeared to vary considerably by geographic region. Those first two findings highlight the need for clear consensus guidelines to improve the consistency of practice in Ontario for men with advanced testicular cancer.

Third, we observed a high rate of health care utilization for respiratory symptoms after treatment with BEP, which was strongly associated with a cumulative bleomycin dose of 300 IU or more.

Finally, 2% of the men had visit codes for pulmonary fibrosis in the 2 years after exposure to bleomycin, confirming the incidence of that life-threatening bleomycin complication identified in older, smaller series.

The present study offers novel insights into use of PFTs and chest imaging during BEP delivery in routine practice. Overall, 17% of men in our cohort received PFTs at baseline and 17% received PFTs during treatment. Although the retrospective nature of our data limits our ability to understand whether the PFTs received during treatment were for pulmonary surveillance or in response to symptoms, we suspect that the former reason accounts for most of the PFTs, given that 60% of men receiving PFTs during treatment also received PFTs at baseline. That almost 1 in 5 men with advanced testicular cancer receive PFTs during treatment is notable for several reasons. First, no level 1 evidence is available to guide pulmonary surveillance during BEP chemotherapy, and major consensus guidelines remain silent

on the issue^{4–6}. Clinicians cannot look to clinical trial protocols for guidance either, because some^{15–17}, but not all¹⁸, required PFT monitoring during treatment; other trials did not specify when, if, or how often PFTs were required^{8,19–21}. Moreover, there is no guidance for clinicians about how to interpret the results of PFTs during chemotherapy.

Non-consensus expert guidance variably recommends discontinuing bleomycin when a patient's CO-diffusing capacity drops by 60%²², 65%–70%²³, 25%²⁴, or 15%–25%²⁵. Other groups have challenged the accuracy of CO-diffusing capacity as a predictor of clinically significant bleomycin-induced lung injury²⁶. Thus, in a disease in which the success of treatment has been attributed to consistency of guideline-concordant care², clinicians who perform pulmonary surveillance with PFTs are left without any clear guidance about how to interpret results. Roncolato *et al.*²⁵ recently reported on the impact of PFTs on treatment decisions in a cohort of patients with advanced testicular cancer (good-, intermediate-, and poor-risk groups) enrolled in a single-arm phase II trial. Asymptomatic reductions in CO-diffusing capacity were responsible for 20% of bleomycin doses omitted and for 30% of patients receiving less than two thirds of their planned dose. Those findings are highly concerning, because multiple studies have shown that bleomycin is an integral component in the management of advanced testicular cancer; bleomycin omission or dose reduction is associated with decreases in the efficacy of treatment^{8,16–19}.

Our study adds to a growing body of literature describing pulmonary toxicity outcomes in men treated for advanced testicular cancer. To date, most of the evidence comes from secondary analyses of randomized controlled trials or reports from high-volume academic treatment centres. Determining the extent to which the data reflect outcomes in routine clinical practice is therefore difficult. Furthermore, bleomycin-induced lung injury has been variably defined in the literature as the presence of crackles on physical examination²⁷, respiratory symptoms¹⁰, or asymptomatic changes in PFTs^{8,24} and radiography^{9,10}. Reflecting those disparate definitions, the literature reports rates of bleomycin-induced lung injury ranging from 0% to 34%^{9,10,16,18,19,28–30}. A recent meta-analysis of randomized studies reported a pooled probability of any-grade pulmonary toxicity of 12%¹². In the present study, we chose to use visits to physicians for respiratory symptoms as a surrogate general marker for adverse pulmonary outcomes related to bleomycin chemotherapy. Our finding that, overall, 23% of men receive a respiratory diagnosis in the 2-year period after BEP chemotherapy is generally consistent with the prior literature. Although our study is not able to comment on the severity of pulmonary toxicity of any cause, its persistence, or its impact on quality of life, the observed 2% incidence of pulmonary fibrosis is the finding of major importance, and it accords with previous reports of smaller series^{9,10,20,31}.

When using patients as their own controls (evaluation before and after BEP chemotherapy), we observed that the excess pulmonary toxicity appears to be limited to patients treated with 10 or more doses of bleomycin. In that subset of men, 40% saw a physician for a respiratory visit in the 2-year period after chemotherapy, representing a 25% absolute increase from baseline. That observation is consistent with the findings of O'Sullivan *et al.*¹⁰, who retrospectively evaluated a prospectively maintained database of 835 men with testicular cancer treated at the Royal Marsden NHS Trust with bleomycin-containing regimens between 1982 and 1999. In the 57 patients who developed bleomycin-induced lung injury, multivariate analysis identified a cumulative bleomycin dose greater than 300 IU as the strongest risk factor (HR: 3.5).

Our study should be interpreted in the context of certain methodologic limitations. Existing patient records do not include stage data or serum tumour markers. As a result, we cannot assess the appropriateness of the number of cycles of chemotherapy or the timing of their delivery. A detailed analysis of treatment and outcomes by stage and by dose intensity is similarly limited. Because we lacked direct access to the PFT results, we were not able to assess any correlation between specific PFT findings and the decision to omit bleomycin or reduce the dose. Similarly, we lacked direct access to imaging reports and information about post-chemotherapy thoracic surgery; we therefore do not know whether the presence of lung metastases or thoracic surgery influenced the rates of PFT use, chest imaging, or respiratory complaints after BEP. We lack information related to symptom burden in patients while on chemotherapy. Only 3% of patients (12 of 368) were diagnosed with a respiratory illness during chemotherapy; however, that observation is a reflection of the nature of physician billing

patterns in Ontario. While under the care of an oncologist, the most likely primary physician billing diagnosis would be testicular cancer rather than any specific respiratory illness. Finally, the definition of pulmonary toxicity used in this study has not previously been validated and relies on the accuracy of the diagnostic coding in the administrative databases. In consideration of the multiple forms of pulmonary toxicity associated with bleomycin, and to maximize sensitivity, we made use of a broad definition to identify a general marker of adverse pulmonary outcomes, and patients were used as their own controls to explore the burden of respiratory symptoms before compared with after exposure to BEP. The consistency of our results with previously published prospective trials, and the consistency of the rates of specific diagnoses such as pulmonary fibrosis, suggests that the signal of pulmonary toxicity seen in the present study is valid.

CONCLUSIONS

This population-based study has revealed that, in contradiction to clinical practice guidelines, a substantial proportion of men treated for testicular cancer in routine practice do not undergo baseline chest imaging within 4 weeks of starting chemotherapy. Quality improvement efforts are needed to understand and rectify this situation. In contrast, in the absence of any evidence or recommendation for the practice, a high proportion of men undergo chest imaging and receive PFTs during bleomycin-based chemotherapy. Given the lack of clear guidance about when to perform chest imaging or PFTs during chemotherapy and how results should guide management, the practice of routine testing during chemotherapy should be reconsidered and subjected to prospective study. Finally, a substantial proportion of men treated with BEP seek medical attention after chemotherapy for respiratory symptoms, a circumstance that is strongly associated with the cumulative dose of bleomycin. Further research is needed to better understand the late treatment effects of BEP in survivors of testicular cancer.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Department of Medicine, University of Toronto, Toronto, ON; †Department of Oncology, ‡Department of

Public Health Sciences, and [§]Division of Respiriology, Department of Medicine, Queen's University, Kingston, ON; ^{||}ICES, Toronto, ON; [#]Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB; ^{**}Division of Medical Oncology and Hematology, Department of Medicine, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON.

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