Author's personal copy

PharmacoEconomics (2013) 31:753–766
DOI 10.1007/s40273-013-0081-2

REVIEW ARTICLE

The Economic Burden of Toxicities Associated with Cancer Treatment: Review of the Literature and Analysis of Nausea and Vomiting, Diarrhoea, Oral Mucositis and Fatigue

Alan Carlotto · Virginia L. Hogsett · Elyse M. Maiorini · Janet G. Razulis · Stephen T. Sonis

Published online: 21 August 2013
© Springer International Publishing Switzerland 2013

Abstract Side effects or toxicities are frequent, undesirable companions of almost all forms of non-surgical cancer therapy. It is unusual for patients to complete treatment with radiation or chemotherapy without experiencing at least one form of therapy-associated tissue injury or systemic side effect. Often, toxicities do not occur as solitary events; rather, they result in clusters of symptoms that share a common biological aetiology. Like any disease, cancer treatment-related toxicities (CTRTs) vary in their severity. But, in contrast to most diseases in which incidence is described as being present or absent, the current approach to CTRT typically limits reporting to severe cases only. Not only does this dilute the frequency with which CTRTs occur, but it also undermines our ability to determine the full burden of their impact and to accurately assess the cost effectiveness of potential toxicity interventions. In this article, we report the results of a directed literature review for the years 2000–2012, in which we studied and compared three tissue-based toxicities (nausea and vomiting, diarrhoea, and oral mucositis) and one systemic toxicity (fatigue). Our results confirm the heavy burden of resource use and cost associated with CTRTs. The inclusion of fatigue in our analysis provided an opportunity to compare and contrast a toxicity in which there are both acute and chronic consequences. Our findings also demonstrate a number of challenges to, and opportunities for, future study. Among the most obvious are the lack of provider consistency in diagnosis and grading, especially when there is no global agreement on severity scales. Compounding this inconsistency is the disconnect between healthcare providers and patients that exists when describing toxicity severity and impact. In many cases, cancer can be thought of as a chronic disease that requires prolonged but episodic treatment once the acute disease is eradicated. This change reflects increasing treatment successes, but it also implies that the burden of CTRTs will be expanded and prolonged. Creation of hierarchical attribution of costs in the presence of simultaneous CTRTs, accurate coding, and consistent tracking tools for toxicities will be imperative for effective appraisal of the costs associated with cancer treatment regimen toxicities.

A. Carlotto · V. L. Hogsett · E. M. Maiorini · S. T. Sonis
Harvard School of Dental Medicine,
Boston, MA, USA

J. G. Razulis · S. T. Sonis (✉)
Division of Oral Medicine,
Brigham and Women's Hospital,
75 Francis Street, Boston, MA 02115, USA
e-mail: ssonis@partners.org

Author's personal copy

Key Points for Decision Makers

- The health and economic impact of cancer regimen-related toxicities is largely under-reported. Toxicities associated with standard cancer therapy regimens are common, clinically significant and likely to increase in prevalence and illness burden.
- There is no standard methodology for assigning or determining the cost and health burden of regimen-related toxicities.
- Acute tissue-centric toxicities such as those affecting the gastrointestinal tract (oral mucositis, diarrhoea, and nausea and vomiting) elicit significant incremental costs associated with primary cancer therapy, which are largely attributable to increased hospitalization rates and lengths of hospital stays.
- The economic burden of systemic and chronic toxicities (i.e. fatigue) has not been adequately studied. Nonetheless, long-term disability that hinders return to work significantly contributes to their true cost.

1 Introduction

Estimated to cost US$124.6 billion in 2010, the diagnosis and management of cancer account for approximately 5 % of the annual US healthcare expenditures of close to US$2.5 trillion [1]. Fuelling this expense are the acquisition and delivery costs of an expanding portfolio of treatment options, the direct and indirect costs of managing the acute and long-term side effects of therapy, and the number of newly diagnosed patients, given that males and females in the USA have 45 and 38 % lifetime risks of developing cancer, respectively [2]. While cancer regimen-related toxicities are routinely documented as a component of overall treatment assessment, the impact of side effects on patients' symptoms, treatment tolerance, and health and economic outcomes have not been fully appreciated. While it is clear that toxicities of any grade are relevant to patients' quality of life and ability to function, many fiscal and resource use analyses have been limited to severe toxicities of grades 3 or 4. Because of factors such as the difficulty of standardizing toxicity reporting, errors in diagnosis, and under-reporting of toxicities by patients, coding or cost attribution have proved a challenge in ascribing the financial burden of toxicity management.

Development of at least one toxicity during treatment is almost universal among cancer patients, and many patients suffer from more toxicities. In a survey of 18 studies that assessed the prevalence rates of multiple symptoms in cancer patients, Kim et al. [3] reported that roughly 40 % of all patients experienced more than one symptom. Importantly, it has become increasingly clear that toxicities rarely occur independently. Rather, they tend to occur in clusters, with common biology being the defining theme of toxicity groupings that occur in the same patient [4].

The range of regimen-related toxicities is broad, extending from those associated with specific tissue compartments (e.g. mucositis, dermatitis and fibrosis) to others that are more generalized (e.g. fatigue, depression and cognitive dysfunction). In addition to being classified on the basis of their tissue targets, toxicities have also been classified as acute or chronic. The former occur during patients' active treatment and include nausea, vomiting, diarrhoea, mucositis and rash. The latter typically involve side effects that linger far beyond treatment completion and include fatigue, peripheral neuropathy and cognitive dysfunction. The economic burden of both is significant.

Studies investigating the financial impact of the side effects and toxicities of cancer therapy have described both direct and indirect costs. Direct costs are those attributable to the medical management of a toxicity, while the indirect costs are those ascribed to time lost from work, caregiver costs, etc. Given the increasing interest in identifying factors that contribute to accelerated healthcare costs, particularly those associated with cancer, our group sought to evaluate, define and review the incremental contribution of specific toxicities associated with various cancer treatment modalities. To standardize cost assessment and comparisons, this review focuses on US and Canadian studies.

We focused our review on three tissue-based toxicities (nausea and vomiting, oral mucositis, and diarrhoea) and one systemic toxicity (fatigue). Our justification for choosing these toxicities was four-fold: (1) they are among the most common; (2) they are the most studied; (3) they have treatment options ranging from standard-of-care prophylaxis to no effective treatment; and (4) the timelines of their onset and duration vary. All of the tissue-based toxicities we evaluated are associated with the gastrointestinal tract. We observed that tissue-related toxicities provide insight into a variety of direct costs, while systemic toxicities reveal more information about the nature of indirect costs associated with cancer treatment. It was hoped that analyzing these toxicities and grouping them in this manner would provide a broad picture of the timeline, types of costs and magnitudes of associated costs.

2 Methods

A systematic literature search was conducted to identify English-language articles published between 1 January 2000 and 31 July 2012 that provided data on the direct costs, indirect costs and/or healthcare resource utilization

Author's personal copy

associated with managing nausea and vomiting, mucositis, diarrhoea and fatigue in cancer patients treated with radiation therapy, chemotherapy, a combination of radiation and chemotherapy, and/or stem cell transplantation.

Using the PubMed/MEDLINE database, two broad free-text searches were performed to identify relevant literature. The first search was a broad "general" search, and the second was a narrower "regimen-based" search. In the general search, each toxicity was used as a search term in combination with keywords focusing on cost and resource utilization. In the regimen-based search, the same toxicities and cost keywords were used in conjunction with specific regimens. Individually searched regimens included, but were not limited to, doxorubicin/cyclophosphamide/docetaxel (AC+T), folinic acid/fluorouracil/oxaliplatin (FOLFOX) and folinic acid/fluorouracil/irinotecan (FOLFIRI). These regimens were chosen to provide a reasonable sampling of treatments for common cancer diagnoses (breast and colorectal) for which the toxicities of interest have been previously noted.

Relevant articles from the general and regimen-specific searches were combined to give a total number of articles for each toxicity (Table 1). The following limitations were placed on the searches: publication in the English language, date of publication between 1 January 2000 and 31 July 2012, and subject pool of adults aged 18 and over. Studies using targeted therapies were excluded. No exclusions were made on the basis of the geographic location of the study or specificity of the subject demographics or populations. All study types (i.e. prospective cohort, retrospective cohort, etc.), except for reviews, were included. To supplement the primary search strategy, relevant references published between 2000 and 2012 that were listed in the bibliographies of articles that were returned in the broad and narrow searches were also added if they had not been previously identified. References selected for inclusion gave direct costs and/or indirect costs associated with individually identified adverse events in cancer patients undergoing chemotherapy and/or radiation therapy. Only cost attributions obtained from primary sources were included. Those derived from secondary sources such as interviews or hypothetical modelling were excluded.

Once all of the described search criteria were applied, only articles reporting costs from Canada and the USA were identified. To clarify comparisons among costs reported in different years, as well as between the USA and Canada, all cost data reported in the results are presented both as they were originally reported in the studies cited and also in 2012 US dollars. To convert US funds from earlier years, the Bureau of Labor Statistics consumer price index (CPI) inflation calculator (http://www.bls.gov/data/inflation_calculator.htm) was used. For foreign currencies, amounts were converted using the first business day of the last year in which the data were collected, unless specifically reported otherwise in the article. For this conversion, the Federal Reserve Bank of New York Foreign Exchange Historical Rate Search functionality (http://www.newyorkfed.org/markets/fxrates/historical/fx.cfm) was used. These conversion methodologies are meant to provide the reader with a way to easily compare data from several articles written at different times, and are not intended for detailed economic interpretation. All dollars are reported in US currency unless specifically noted.

3 Results

The searches for each of the four selected toxicities were conducted independently. Of the publications, editorials and conference proceedings that were identified, 33 articles met our inclusion criteria. Papers were stratified by toxicity and filtered for content on the basis of the criteria noted in the Sect. 2. Since the screening criteria were fairly rigorous, the final analysis was based on a small yet focused group of studies (Table 1). Since the searches were conducted for each toxicity individually, the term "unique hits" describes only the unique papers found within each toxicity search. The same paper may have been identified in the searches for multiple toxicities.

A general analysis of our results was used to identify global drivers of cost (Table 2). Medications, office visits and hospital visits were the most significant drivers of cost within acute, tissue-based toxicities. While papers assessing the indirect costs of acute toxicities do exist, particularly regarding nausea and vomiting, these costs do not contribute substantially to the overall economic burden imposed by acute toxicity. However, in the case of the chronic, systemic toxicities reviewed for this article, the results were essentially the opposite. Indirect costs, particularly lost work, contributed most significantly to the economic burden imposed by chronic toxicities, with medications, hospital visits and office visits playing essentially no role.

3.1 Nausea/Vomiting

Twelve papers associated with the cost of chemotherapy-induced nausea and vomiting (CINV) met our criteria for inclusion. Of these, four were published in the USA and eight were published in other countries, including Canada, Germany, Italy, Japan and Spain. While we did not exclude papers on the basis of geographic criteria, in an effort to provide some basis for uniformity in cost/charge information, we limited our fiscal assessment for individual toxicities to studies based on US- or Canadian-generated data. Regardless of location, no publications evaluating the cost of radiation-induced nausea or vomiting were identified.

Author's personal copy

Table 1 Search outcomes[a]

Toxicity	Nausea/Vomiting	Diarrhea	Mucositis	Fatigue
General Search Terms: Number of Hits	Nausea cancer economic: 139 Nausea cancer cost: 185 Nausea cancer resource utilization: 12 Vomit cancer economic: 121 Vomit cancer cost: 159 Vomit cancer resource utilization: 11 Emesis cancer economic: 126 Emesis cancer cost: 166 Emesis cancer resource utilization: 11	Diarrhea cancer economic: 79 Diarrhea cancer cost: 96 Diarrhea cancer resource utilization: 8	Mucositis cancer economic: 64 Mucositis cancer cost: 79 Mucositis cancer resource utilization: 6	Fatigue Cancer Economic: 168 Fatigue Cancer Cost: 175 Fatigue Cancer Resource Utilization: 8 Fatigue Cancer Employment: 67 Fatigue Cancer Work: 319
Total Unique Hits for General Search	216	120	108	555
STUDY CRITERIA APPLIED				
Number of Papers Included from General Search	12	4	8	8
Regimen* - Based Search Terms: Number of Hits	Nausea "regimen" economic: 22 Nausea "regimen" cost: 30 Nausea "regimen" resource utilization: 1 Vomit "regimen" economic: 20 Vomit "regimen" cost: 32 Vomit "regimen" resource utilization: 0 Emesis "regimen" economic: 21 Emesis "regimen" cost: 34 Emesis "regimen" resource utilization: 0	Diarrhea "regimen" economic: 12 Diarrhea "regimen" cost: 13 Diarrhea "regimen" resource utilization: 0	Mucositis "regimen" economic: 6 Mucositis "regimen" cost: 13 Mucositis "regimen" resource utilization: 0	Fatigue "regimen" economic: 3 Fatigue "regimen" employment: 0 Fatigue "regimen" work: 6 Fatigue "regimen" cost: 8 Fatigue "regimen" resource utilization: 0
Total Unique Hits from Regimen-based Search	5	10	12	16
STUDY CRITERIA APPLIED				
Number of Papers Included from Regimen-based Search	0	1	0	0
Total Number of Papers Included (General and Regimen-based Searches)	12	5	8	8

A general search was performed in the PubMed/MEDLINE database, using the search terms described above. The numbers for the total unique publications for each toxicity's general search were compiled, and each paper was reviewed for the review inclusion criteria. The bibliographies of these papers were also reviewed for other potential works. A specific, regimen-based search was also conducted using the PubMed/MEDLINE database, using the regimens listed above. Again, each paper was screened for the review inclusion criteria, and its bibliography was reviewed. The total number of papers for each toxicity is listed and resulted from the combination of the general and specific searches

[a] "Regimen" included the following: "doxorubicin", "cyclophosphamide", "docetaxel", "FOLFOX" [folinic acid/fluorouracil/oxaliplatin] and "FOLFIRI" [folinic acid/fluorouracil/irinotecan]

In general, the cost of CINV was considered in three settings: prophylaxis for patients who were planned to receive moderate or highly emetogenic chemotherapy (HEC) regimens, treatment of active CINV, and emergent care (Fig. 1). While incidence rates of CINV reported in the literature vary widely, the most emetogenic chemotherapy regimens can cause nausea and vomiting in over 90 % of patients within the first 24 h after chemotherapy administration [3]. Even in populations receiving prophylaxis, the incidence of breakthrough nausea and vomiting can range from 40 to 60 % [5, 6], and in papers published within the last 5 years, the reported rates of uncontrolled CINV have been as high as 28 % [7].

The current standard of care for patients taking HEC and for most patients taking moderately emetogenic

Author's personal copy

Table 2 Cost attributions[a]

Toxicity	Direct costs					Indirect costs		
	Hospitalization	Tests and procedures[b]	Supportive care[c]	Inpatient, emergency department or outpatient visit	Medications	Lost opportunity[d]	Missed work	Effect on caregiver
Nausea/vomiting								
Burke et al. [9]	✔			✔				
Haiderali et al. [6]	✔			✔	✔	✔	✔	
Craver et al. [8][e]	✔			✔	✔			
Shih et al. [7]	✔	✔	✔	✔	✔		✔	
Iihara et al. [16]					✔			
Hamada et al. [10]			✔		✔			
Ballatori et al. [12]	✔		✔		✔		✔	✔
Lordick et al. [11]	✔			✔	✔			
Lachaine et al. [17]	✔			✔	✔	✔	✔	✔
Ihbe-Heffinger et al. [15]	✔	✔		✔	✔		✔	
Hartmann et al. [14]					✔			
Barrajon and de las Peñas [13]	✔			✔	✔			
Diarrhoea[f]								
Dranitsaris et al. [20]	✔	✔	✔	✔	✔			
Dranitsaris et al. [21]	✔	✔	✔	✔	✔			
Arbuckle et al. [24]	✔		✔	✔	✔			
Mucositis[f]								
Sonis et al. [27]	✔		✔		✔			
Elting et al. [28]	✔		✔	✔	✔			
Nonzee et al. [31]	✔	✔		✔	✔			
Peterman et al. [32]	✔		✔	✔	✔			
Elting et al. [25]	✔	✔	✔	✔	✔			
Murphy et al. [29]	✔		✔	✔	✔			
Fatigue								
McKenzie et al. [35]				✔				
Curt et al. [37]						✔	✔	✔
Hassett et al. [34]	✔			✔				
Poirier [36, 43]						✔	✔	
Lee et al. [39]						✔	✔	
Lavigne et al. [38]							✔	
Aprile et al. [33]				✔				

[a] Each paper included in the final analysis that delineated the drivers of cost and/or resource utilization associated with a toxicity is included in the table. A check mark in the table indicates that a particular direct or indirect cost was reported in the analysis of that publication. A blank cell represents the opposite: this cost was either not calculated in the analysis of the paper or was not reported

[b] Includes laboratory tests and imaging

[c] Includes intravenous fluids and feeding tube placement

[d] "Lost opportunity" is defined as the value of reduced productivity or time lost due to an individual's absence from a job

[e] For Craver et al. [8], medications were not given a dollar amount but were said to have been included in the cost of the visit

[f] Mittmann et al. [19] and Elting and Shih [18] were not included under "Diarrhoea" or "Mucositis", as it is unclear what was included in the costs for Mittman et al. [19], based on the Ontario Case Costing Initiative, and for Elting and Shih [18], based on the Hospital Cost Report Info System

Author's personal copy

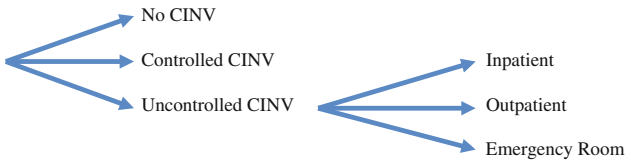

Fig. 1 Chemotherapy-induced nausea and vomiting (CINV) outcome scheme. (A patient receiving emetogenic chemotherapy can be classified as having no CINV, controlled CINV or uncontrolled CINV. Those with uncontrolled CINV are subdivided into three categories of treatment modality—namely, whether they are treated in an inpatient, outpatient or emergency department setting)

chemotherapy (MEC) typically involves a combination regimen of a neurokinin-1 (NK1) receptor antagonist (i.e. aprepitant), a serotonin antagonist and dexamethasone [5]. To evaluate the potential incremental fiscal advantage of effective prophylactic therapy, Craver et al. [8] used the Premier Perspective Database to evaluate cost differences for patients who experienced CINV versus those who did not. They assessed 8,806 patients undergoing their first cycle of chemotherapy, 76.6 % of whom received prophylaxis, the most common of which included serotonin 5-HT_3 antagonists (53 %) and dexamethasone (35.9 %). They reported per diem costs of US$2,375.20 (US$2,541.90 in 2012 values) for prophylaxed chemotherapy cycles versus US$2,725.80 (US$2,917.11 in 2012 values) for non-prophylaxed chemotherapy cycles. Their cost analysis included total all-cause healthcare costs associated with CINV management at a chemotherapy cycle level, such as medical resource utilization and rescue medications, but did not include physician costs. A similar trend was reported in an ambulatory population: the average daily patient cost among patients who received prophylactic treatment was US$1,342.80 (US$1,437.04 in 2012 values) versus US$1,614.80 (US$1,728.13 in 2012 values) among patients who did not receive prophylaxis. The financial advantage reported in this article is particularly striking when considering that the analysis included patients receiving not just HEC and MEC, but also low-emetogenic chemotherapy (LEC) and minimal emetogenic chemotherapy (MinEC) regimens [8].

A consistent trend among published studies was that breakthrough cases of CINV following aggressive emesis prophylaxis were not uncommon. Shih et al. [7] investigated the actual cost of managing uncontrolled CINV in patients who had received at least one HEC or MEC agent. They studied 2,018 patients, using claims data from the 1997–2002 Medstat MarketScan Health and Productivity Management Database to assess direct costs, work leave and hours lost from work to assess indirect costs. Although 88 % of patients received 5-HT_3 receptor antagonists, 28 % still experienced uncontrolled CINV. After excluding the costs of chemotherapy and its related adverse events, the cost of uncontrolled CINV was determined to be US$5,551 (US$6,321.81 in 2012 values) per month, resulting in an average incremental cost increase of US$1,383 (US$1,575.04 in 2012 values), compared with patients with controlled CINV. In an exploratory subgroup analysis, the same investigators found that the indirect costs of patients experiencing uncontrolled CINV were US$1,832 (US$2,086.39 in 2012 values), compared with US$1,399 (US$1,593.26 in 2012 values) in patients with controlled CINV [7].

Burke et al. [9] used the Premier Prospective Database to study 19,139 patients receiving HEC or MEC. All patients received prophylaxis but with varying regimens: 85 % received 5-HT_3 receptor antagonists; 76 % received dexamethasone; and 2 % received NK-1 antagonists. Of this population, 13.8 % experienced uncontrolled CINV or CINV severe enough to require a hospital visit. Sixty-four percent of CINV-associated visits were inpatient visits, 26 % were outpatient visits and 10 % were emergency department visits. The mean costs were US$7,448 (US$8,247.32 in 2012 values), US$1,494 (US$1,654.34 in 2012 values) and US$918 (US$1,016.52 in 2012 values) for inpatient, outpatient and emergency department visits, respectively, with an overall mean cost of US$5,299 (US$5,867.69 in 2012 values) [9].

In a smaller study, Haiderali et al. [6] performed a prospective observational study of 178 patients receiving HEC or MEC for the first time. Both costs and incidence were determined in two ways: by information provided by the physician on the case report form, and by patient diaries. Estimated unit costs associated with services were determined in accordance with the CMS Fee Schedule, and estimated unit costs associated with medications were determined in accordance with the 2007 Red Book. Indirect costs were calculated using the current employment status and occupation of the patient as reported on the case report form. Despite the use of prophylactic medications, 61.2 % of patients receiving MEC or HEC reported experiencing CINV. The total average per patient cost of CINV was found to be US$778.53 (US$862.08 in 2012 values), with prophylactic medications contributing US$447.17 (US$495.16 in 2012 values), rescue medications contributing US$253.05 (US$280.21 in 2012 values) and indirect costs contributing US$46.39 (US$51.34 in 2012 values). In this study, of the 109 patients experiencing CINV, only 11 required additional interventions such as oncologist office visits, emergency department and urgent care visits, and inpatient hospitalization, as reported by the physician case reports. Haiderali et al. [6] reported that the average cost of an emergency department visit was US$574.85 (US$636.54 in 2012 values), and the cost for the single account of inpatient hospitalization was US$14,015.54 (US$15,519.69 in 2012 values), according to the patients themselves.

Author's personal copy

The incidence of CINV in studies performed outside the USA ranges from 39 to 71 %, depending on the prophylaxis used and the parameters of the patient population [10, 11]. In contrast to US studies, it appears that the largest burden of cost arises from the cost of antiemetic medications, both prophylactic and rescue, contributing from 44.5 to 92.2 % of the total cost of managing CINV [10–17], with hospital visits being the second most significant driver of cost.

3.2 Diarrhoea

Five retrospective analyses—two conducted in the USA and three in Canada—were identified that reported the costs and/or resource utilization associated with cancer regimen-related diarrhoea. Elting and Shih [18] included all treatment types, while the remaining four papers reported on cycled chemotherapy. None of the studies analyzed the indirect costs associated with cancer regimen-related diarrhoea, and most of the studies were skewed toward more severe forms of toxicity (grade 3 or 4).

Mittmann et al. [19] estimated costs associated with grade 3/4 diarrhoea among 1,491 patients receiving cycled chemotherapy following primary surgery for treatment of operable breast cancer. Patients were treated with docetaxel plus doxorubicin and cyclophosphamide (TAC) or with fluorouracil, doxorubicin, and cyclophosphamide (FAC), and relatively low incidences of severe diarrhoea were reported: 3.8 % for TAC and 1.8 % for FAC. An average adverse event cost per patient of Can$2,760 (US$2,717.90 in 2012 values) was calculated for severe diarrhoea. This value stemmed from the percentage occurrence of severe diarrhoea in the population of the study, multiplied by the cost per diarrhoea event, as estimated from the Ontario Case Costing Initiative. These estimates were close to the values reported by Dranitsaris et al. [19, 21].

Mittmann et al. [19] was the only study included in this analysis that reported incidence rates of diarrhoea for the studied treatment. However, their incidence rates were low when compared with other reported data for cycled chemotherapy regimens. Schwartzber et al. [22] found that 15 % of breast cancer patients experienced moderate to severe diarrhoea while receiving dose-dense doxorubicin/cyclophosphamide plus paclitaxel. Another study by Sonis et al. [23] cited a 16 % incidence rate of moderate to severe diarrhoea in patients with colon cancer who received at least three cycles of FOLFOX6 ± bevacizumab.

Dranitsaris et al. [20, 21] published two studies in 2005, which estimated costs associated with severe chemotherapy-induced diarrhoea (CID) in patients with colorectal cancer. One of the studies included 63 hospitalized subjects, and the other included both ambulatory ($n = 65$) and hospitalized ($n = 31$) individuals. Cancer therapy was the same for both subject populations and included fluoropyrimidines, irinotecan, oxaliplatin or any combination thereof, with 11.5 % of all subjects in both studies receiving concurrent radiation therapy. In each study, only resources directly related to managing the diarrhoea episode were considered, and costs were estimated for these resources on the basis of their average costs in Canadian oncology centres. Not unexpectedly, the site of treatment delivery (ambulatory or hospital) appeared to have a marked impact on the reported costs. Whereas the average attributable cost in the hospitalized population was Can$8,230 (US$7,754.22 in 2012 values), it was significantly lower [Can$2,559 (US$2,411.07 in 2012 values)] in a mixed patient population largely treated as outpatients (68 % outpatients), even in the face of severe diarrhoea.

The authors noted that patients with grade 4 diarrhoea were 11 times more likely to be hospitalized than patients with grade 3 diarrhoea, with grade 4 diarrhoea having an incremental cost of Can$4,679 (US$4,408.51 in 2012 values) compared with grade 3. Additionally, it was reported that 14.6 and 16.7 % of all subjects (mixed inpatients and outpatients) experienced uncontrolled emesis and stomatitis, respectively, highlighting the clustering of these toxicities. The authors speculated that these additional adverse events may have contributed to the length of the hospital stay and therefore affected costs. A sensitivity analysis that removed patients with uncontrolled emesis and stomatitis revealed drops in average costs of Can$59 (US$55.59 in 2012 values) and Can$187 (US$176.19 in 2012 values), respectively—values that represent the incremental costs of these toxicities in the presence of diarrhoea. They concluded that the cost of CID remained high even after exclusion of these patients with multiple toxicities from their analysis [20, 21].

Unlike the other studies in this analysis that focused on severe diarrhoea only, the study by Arbuckle et al. [24] examined the added resource use imparted by all grades of CID. Of 100 colorectal cancer patients who experienced diarrhoea during at least one cycle of chemotherapy, 52 % developed severe symptoms and the balance experienced diarrhoea of grades 1 or 2. The consequences were significant: 14 % required emergency outpatient treatment, 23 % were hospitalized, 21 % received intravenous fluid for dehydration and 7 % were prescribed octreotide. The use of these resources was not converted to costs but, when compared with the data on CID reported by Dranitsaris et al. [20, 21], the outcomes of CID were fairly similar (32.3 % of affected patients hospitalized, 25.3 % requiring intravenous fluids and 9.4 % receiving octreotide).

The paper by Elting et al. [25] was the final one included in the analysis of diarrhoea. The authors scanned the Texas statewide registry of claims for all hospitalizations between June 2000 and December 2001. Hospitalizations for the

Author's personal copy

adverse events of interest were identified using International Classification of Diseases (ICD)-9 codes. Their analysis included hospitalizations with a diagnosis of cancer and for which the admitting diagnosis or principal diagnosis was a toxicity of interest. To facilitate comparisons, charges from the registry were transformed into costs, using the 2001 Medicare cost-to-charge ratio for hospital operating expenses for the state of Texas. All cancer types and treatment modalities were included. The paper's reported estimated cost of hospitalization for management of diarrhoea was US$6,616 (US$8,443.55 in 2012 values), a value slightly greater than that reported by Dranitsaris et al. [20, 21] for an inpatient population.

3.3 Mucositis

Oral mucositis is among the best-studied regimen-related toxicities. Our review identified eight papers reporting incremental costs of oral mucositis. One study was conducted in Canada, six in the USA, and one was a multinational study, which complied data from the USA, Canada and Europe. A wide range of cancer types were covered by these papers, including head and neck cancers, carcinomas, breast cancers and hematologic/lymphatic malignancies. The treatment types likewise varied and included all major forms of cancer therapy.

For cost-reporting methodology, some of the studies reported costs directly from the medical and financial records of the cancer centres, while others analyzed the resources used in treatment of mucositis and formulated a method of attributing an estimated cost to this resource usage. Many of the papers reported the severity of oral mucositis according to the National Cancer Institute (NCI) guidelines of grades 1 through 4 [26]. While Mittmann et al. [19] only reported on grade 3/4 mucositis, most of the other papers included costs and/or resource utilization for all grades of the toxicity, and a few broke down the costs of grade 1/2 versus grade 3/4. A few of the papers graded severity via methods other than the NCI criteria, such as the Oral Mucositis Assessment Scale, or did not grade severity and only tracked patient reports of mouth and throat soreness or any evidence of ulceration.

The reported incidences of oral mucositis were significant and varied by cancer type and treatment modality. Not unexpectedly, the greatest drivers of cost were those costs associated with mucositis that had an impact on the length of the hospital stay (in the haematopoietic stem cell transplant [HSCT] population) and the rate of hospitalization. The frequency of ulcerative mucositis among HSCT recipients, depending on the stomatotoxicity of the conditioning regimens, ranged from 83 % of autograft recipients to 88 % of allograft patients [27]. However, the elimination of total body irradiation for most conditioning regimens has lowered the frequency of severe mucositis to about 40 % in autologous transplant recipients.

Radiation therapy has consistently produced high levels of mucositis. A report by Elting et al. [28], using patient-reported outcomes for mucositis severity, noted that over 90 % of patients with primary tumours in the oral cavity, oropharynx, larynx or hypopharynx reported some grade of mucositis. A similarly high number was reported by Murphy et al. [29] in a head and neck cancer population receiving radiation therapy, with 76 % of the subjects reporting severe mouth/throat soreness. However, Trotti et al. [30] noted a lesser incidence, especially for cancers of the hypopharynx and larynx when compared with the oral cavity/oropharynx or in comparison with conventional radiation alone. Clearly, however, the use of concomitant chemotherapy with radiation is a risk factor for mucositis. Nonzee et al. [31] reported that ulcerative mucositis occurred in 61 % of patients being treated with concomitant chemotherapy for head and neck cancer or small cell lung cancer.

Mucositis has also been studied in patients receiving cycled chemotherapy for the treatment of lymphoma and colorectal and breast cancers. Elting and Shih [18] reported that in a study of 599 patients, oral mucositis was present in almost a quarter of chemotherapy cycles used to treat lymphoma or solid tumours. In contrast, when Mittmann et al. [19] analyzed two specific breast cancer chemotherapy regimens, they noted incidences of 7.1 and 2.0 % in patients receiving TAC and FAC, respectively. In recent studies, the incidence rates of moderate to severe patient-reported mucositis have been 49 % in breast cancer patients treated with dose-dense doxorubicin/cyclophosphamide plus paclitaxel [22] and 26 % in patients with colon cancer receiving at least three cycles of FOLFOX6 ± bevacizumab [23].

The overall mucositis costs track with severity. For example, whereas the incremental costs for mild/moderate mucositis were noted to be US$1,700 (US$1,936.06 in 2012 values) [25], they more than doubled to US$3,600 (US$4,099.89 in 2012 values) when severe grades were considered. Other studies have reported similar costs when comparing mild/moderate and severe grades: US$2,949 versus US$4,037 (US$4,315.31 versus US$5,907.40 in 2012 values) [32] and US$2,725 versus US$5,565 (US$3,477.73 versus US$7,102.23 in 2012 values) [18]. Among patients being treated for cancers of the head and neck or lung, Nonzee et al. [31] reported an incremental cost of US$18,515 (US$21,766.17 in 2012 values), greater than had been noted in other studies. The authors speculated that this difference was attributable to the site of care—namely, that studies reporting lower costs were conducted at hospitals operating at maximum capacity and discharging patients earlier in the course of their toxicity. Mittmann et al. [19] cited a cost of Can$3,151 (US$3,102.94 in 2012 values) associated with mucositis

Author's personal copy

stemming from treatment with TAC/FAC. Elting and Shih [18] estimated the cost at US$7,985 (US$10,190.71 in 2012 values) for mucositis hospitalization associated with any cancer type or treatment, based on identifying ICD-9 codes from a Texas statewide registry of claims (see the "Diarrhoea" section above for additional methodology of the study by Elting and Shih). Finally, Sonis et al. [27] noted that a 1-point increase in the peak Oral Mucositis Assessment Scale (OMAS) score was associated with US$25,405 (US$32,935.27 in 2012 values) in additional hospital charges in stem cell patients.

Other studies have reported resource use as a cost surrogate. Murphy et al. [29] did not report direct costs but did cite various resource consumption in the management of mucositis in head and neck cancer patients receiving radiation therapy with or without chemotherapy. The authors noted that 30 % of the subjects were hospitalized directly as a consequence of mucositis, 51 % received feeding tubes and 78 % received opioid prescriptions for mouth and throat pain.

3.4 Fatigue

Eight papers were identified that reported the costs associated with fatigue due to radiation therapy, chemotherapy or a combination of both (Table 3). Of these, five were published in the USA, one in Italy, one in Australia and one in Korea. Unlike the costs associated with the tissue-based toxicities that were studied, costs attributable to fatigue were primarily descriptive and were associated with the disease burden and its impact on functionality. Ascription of quantifiable hard costs was not assigned.

4 Acute Fatigue

Fatigue is an almost universal symptom during and shortly after radiation and chemotherapy. In the literature that was reviewed, fatigue as an acute symptom was studied both during cancer therapy and generally until 6 months after completion of the therapy. Direct and indirect costs as a result of acute fatigue were reported.

The direct cost of fatigue reported in the literature was due to unplanned patient presentations to the hospital after chemotherapy. According to studies in Australia and Italy, 2–23 % of all unplanned hospital presentations and admissions of patients within 6 months of chemotherapy were due to fatigue [33–35]. In one study, which reported that 17.6 % of unplanned presentations to the hospital after chemotherapy were due to fatigue, it was specified that 10.9 % of breast cancer patients, 21.4 % of gastrointestinal cancer patients and 22.1 % of lung cancer patients presented for fatigue [33].

The remaining literature concerning costs associated with acute fatigue reported indirect costs to patients and their families during therapy and within 1 month after completion of the therapy. In one study in which patients received radiation therapy, chemotherapy or a combination of both, 48 % of the participants reported some fatigue at baseline, increasing to 97 % at the completion of therapy and diminishing to 55 % at the 1-month follow-up visit [36]. In the same study, 73 % of participants were working at the beginning of their radiation therapy. This number decreased to 58 % by the end of radiation therapy and increased to 82 % 1 month post-treatment. Those study participants who were working at the end of radiation therapy had lower fatigue scores than those who were not working. The literature also reported that 45–75 % of participants who were employed at the beginning of cancer therapy made changes to their employment status specifically as a result of fatigue [36, 37]. These changes included stopping work altogether, changing the type of duties performed, working from home, decreasing the number of hours worked per week and taking time off work. According to one study, more than 20 % of patients stopped working completely or went on disability as result of fatigue, and patients used an average of 4.2 sick leave or vacation leave days per month during and immediately after treatment, as a result of fatigue [37]. Eleven percent of patients also needed to use unpaid family and medical leave because of acute fatigue [37]. In addition to time off work and changes in work duties, other costs associated with acute fatigue included the need to hire help to take care of daily chores. For 22 % of patients, this included cleaning; for 18 %, it included yard work; and for 5 %, it included cooking [37].

Fatigue associated with radiation therapy and chemotherapy does not place an economic burden solely on the patient. The literature reports that caregivers of patients undergoing these therapies often must make changes to their employment status as well. During therapy, one study found that 20 % of primary caregivers took more time off work, 18 % accepted fewer responsibilities and 11 % reduced their work hours. The same study reported that 65 % of patients indicated that their fatigue resulted in their primary caregivers taking at least 1 day off work in a typical month, with a mean of 4.5 days. Furthermore, 12 % of cancer patients in the study reported that their primary caregiver was forced to take unpaid leave or to even stop working completely during their cancer treatment [37].

5 Delayed Fatigue

In addition to costs associated with fatigue during and immediately after cancer therapy, the literature reported

Table 3 Chronic fatigue search summary[a]

References	Treatment	Timing of fatigue	Results
McKenzie et al. [35]	Chemotherapy	Acute (within 6 months)	32 unplanned hospital presentations (8.8 %) were for fatigue
Aprile et al. [33]	Chemotherapy	Acute (within 90 days of chemotherapy)	Fatigue/asthenia accounted for 23.02 % of unplanned presentations, with 17.6 % of patients making an unplanned presentation for fatigue
			For breast cancer, 10.88 % of patients made an unplanned hospital presentation for fatigue. For gastrointestinal cancer, 21.41 % did, and for lung cancer, 22.09 % did
Hassett et al. [34]	Chemotherapy	Acute (within 1 year of diagnosis)	2 % of chemotherapy recipients were hospitalized or visited an emergency department for "constitutional symptoms or nonspecific complications of treatments", including fatigue
Poirier [36, 43]	Radiation therapy ± chemotherapy	Acute (before, during and 1 month post-therapy)	Before therapy, 48 % of patients reported generally mild fatigue. At the completion of therapy, 97 % of patients reported fatigue, with 30 % reporting moderate/severe fatigue
			At 1-month follow-up, 55 % continued to report some fatigue. 73 % of patients were working at the start of radiation therapy, 58 % were working by the end of radiation therapy and 82 % were working 1 month post-treatment
			Patients worked an average of 12–60 h/week at the time of diagnosis, 0–60 h at the start of radiation, 0–48 h by the end of treatment and 0–48 h at 1 month post-treatment
			45 % of patients employed at the start of radiation made changes in their employment during the therapy course, including stopping work altogether, changing types of duties, working from home, or decreasing hours or days worked per week. Side effects of treatment, including fatigue, were the major reasons for making changes in employment
Curt et al. [37]	Chemotherapy ± radiation therapy	Mixed (40 % had last treatment within the previous 2 years, 60 % had treatment 2+ years previously)	>75 % of patients employed at the time of diagnosis changed employment status because of fatigue
			>20 % of patients stopped working completely/went on disability
			On average, 4.2 sick/vacation days per month were used as a result of fatigue
			With extreme fatigue, 28 % of patients discontinued work altogether, 23 % went on disability and 11 % used unpaid family and medical leave because of fatigue
			Patients hired help to take care of daily chores such as cleaning (22 %), yard work (18 %) and cooking (5 %)
			Primary caregivers of patients took more time off work (20 %), accepted fewer responsibilities (18 %) or reduced their worked hours (11 %)
			12 % of patients reported that their primary caregiver was forced to take unpaid leave or to stop working completely
			65 % of patients indicated that their fatigue resulted in their primary caregivers taking at least 1 day (mean 4.5 days) off work in a typical month

Author's personal copy

Author's personal copy

Table 3 continued

References	Treatment	Timing of fatigue	Results
Lee et al. [39]	Subtotal or total gastrectomy ± chemotherapy/radiation therapy	Delayed (21–36 months after diagnosis)	Among all cancer survivors who were working, 50 % described being "easily fatigued and exhausted", compared with 22.4 % of the general population Of those survivors who were homemakers, 73.4 % were "easily fatigued and exhausted", compared with 58 % of the general population Of survivors not working, 12.6 % were not working because of fatigue, compared with 4.4 % of general population Of cancer survivors, 54.2 % of those who had versus 52.9 % of those who had not received radiation were working. Of cancer survivors, 45.4 % of those who had versus 55.3 % of those who had not received chemotherapy were working
Lavigne et al. [38]	Radiation therapy ± chemotherapy	Delayed (completed radiation treatment at least 12 months prior)	Fatigue was independently associated with work performance loss of 1.55 % ($p = 0.05$)

[a] Additional details on the treatment, timeline of data collection, and key results detailed in several of the publications included in the final analysis, addressing fatigue as a short- and long-term adverse effect of cancer therapy

fatigue as a late symptom of therapy in cancer survivors. Even a year or more after completion of radiation therapy and/or chemotherapy, a sizeable number of patients continued to experience fatigue and resultant loss of work performance specifically as a result of their therapy. In one study, fatigue was independently associated with work performance (a loss of 1.55 %) even after ending radiation at least 12 months prior [38]. Another study examined cancer survivors who had been treated with radiation therapy, chemotherapy and/or surgery, and evaluated fatigue levels and employment status in survivors as compared with the general population. Of these survivors who were working 2–3 years after their diagnosis, 50 % still described being "easily fatigued and exhausted". Of those not working 2–3 years after their diagnosis, 12.6 % were not working because of fatigue, compared with 4.4 % of the general population who were not working because of fatigue. The study also investigated the relationship between treatment type and employment status. It found that among cancer survivors, 54.2 % of those who had versus 52.9 % of those who had not received radiation therapy were working, and 45.4 % of those who had versus 55.3 % of those who had not received chemotherapy were working [39].

6 Discussion

Toxicities and side effects of cancer therapies are, seemingly, an accepted physiological, quality of life, and economic cost of treatment. The threshold for "acceptability" seems to vary depending on who is being asked. As the results of many studies have suggested, it seems that healthcare providers tend to underestimate the frequency, severity and impact of most treatment-related toxicities. Indeed, the disparities in the toxicity incidence rates reported by patients and those reported by their healthcare providers are well established and remarkable [40, 41]. The now common practice of only reporting severe toxicity levels (grades 3 or 4) in publications describing the results of clinical trials underscores the impression that symptoms of lesser value are not worth reporting and are fundamentally not relevant to patient outcomes. Compounding this dilution in clinical toxicity assessment is the fact that uniform reporting criteria and scales are lacking. Grading of oral mucositis, for example, may be done with at least a dozen scales that vary widely in their criteria. Despite these shortcomings, with the increasing interest in the fiscal aspects of healthcare, it is now widely accepted that cancer regimen-related toxicities are substantive contributors to the overall burden of the disease.

In general, studies of toxicity costs have been stratified by toxicity, disease or treatment regimen. The former are

Author's personal copy

primarily of interest when one is trying to build a case for the cost effectiveness of a targeted intervention. If a drug company has a product that effectively ameliorates diarrhoea, it is necessary to demonstrate that the cost of preventive or anti-diarrhoeal therapy provides an economic advantage over the cost of managing the toxicity or its consequences once it develops. For example, the costs of CINV among patients who are effectively prophylaxed with HEC or MEC is markedly lower than the cost of managing the condition once it develops [5, 6, 9].

However, studies of this type, in which the toxicity-producing regimens are bundled, assume that there is equivalence in the fiscal impact across treatment types. They do not necessarily take into account the potential differences in the impacts that specific regimens might have on the costs of the designated toxicities. This assumption could lead to erroneous conclusions. Take mucositis as an example. Costs attributed to mucositis vary dramatically among patients in which the condition is induced by cycled chemotherapy, high-dose chemotherapy as part of HSCT conditioning regimens, or fractionated radiation.

Additional factors challenge accurate assignment of costs to toxicities. First, it is rare for a toxicity to occur in isolation. Rather, patients often develop multiple toxicities. As a result, assignment of costs is often judgmental. For example, gastrointestinal toxicities tend to cluster. A patient might have simultaneous nausea, vomiting, diarrhoea and mucositis. If the patient is hospitalized for dehydration, how does one assign causality and cost? Second, ICD-9 codes are often used as the basis for establishing links between toxicity, diagnosis and costs. Aside from omitting any element of gradation, the true accuracy of ICD-9 coding as a manifestation of clinical diagnosis is, in many cases, questionable. Third, most cost assessments omit the cost of non-prescription medicines. Finally, the majority of cost analyses do not include indirect costs such as lost opportunity, lost work time and loss of caregiver time.

The results of this analysis are illustrative of both the significance of toxicities as a driver of the cumulative cost of cancer care and the challenges that exist in assigning true dollar values to toxicities. We specifically selected three gastrointestinal tissue-based toxicities and one systemic toxicity. This mix allowed us to compare costs among side effects targeting the same system and to evaluate a toxicity for which a large proportion of the costs are chronic and are distributed across years of survival. As noted in Table 1, the number of studies that met our modest inclusion criteria was relatively sparse and resulted in significant pruning to arrive at a cadre of evaluable and comparable papers.

Nonetheless, despite a relatively small number of studies, we were able to confirm trends in cost drivers across toxicities. We also observed that cost drivers of tissue-related toxicities were different from those noted for fatigue. Among the gastrointestinal toxicities, the most consistent driver of cost was attributable to hospitalization (Table 2). In the USA, the direct cost of CINV reported in the literature ranged from US$2,421 to US$7,448 per episode for inpatients compared with US$1,364 to US$1,494 per episode for outpatients and US$918 to US$1,987 per emergency department visit [8, 9].

The large incremental cost associated with mucositis was consistently attributable to a higher prevalence of hospitalization or extended hospital stay. For instance, roughly 68 % of the US$18,515 (US$21,766.17 in 2012 values) in incremental costs associated with mucositis reported by Nonzee et al. [31] was due to extended inpatient hospitalization. This finding is consistent with those of other studies [42]. Secondly, we noted that unplanned office or emergency department visits were consistent contributors to tissue-related toxicity costs. This finding is in agreement with those of other investigators. For example, Elting et al. [28] reported that fewer than 6 % of patients without mucositis visited the emergency department, compared with 40 % of all mucositis patients. Nonzee et al. [31] noted that mucositis patients spent over US$100 (US$117.56 in 2012 values) more on pharmaceutical costs than non-mucositis patients did. Finally, none of the studies analyzed the indirect costs associated with mucositis toxicity. Medications, tests and procedures specifically associated with the diagnosis and management of the toxicity or its sequelae were also consistent cost drivers.

Analysis of costs associated with fatigue yielded a different picture. Acute cancer treatment-related fatigue is most likely associated with anaemia secondary to myelosuppression. And while the costs associated with acute fatigue are not trivial, the fact that fatigue symptoms become chronic and stretch into months and years beyond the cessation of active cancer treatment results in indirect costs that are difficult to assess accurately. However, it is clear that the impact of late fatigue, while not a "direct" medical cost of cancer, results in a huge economic hit in terms of lost opportunity, work and productivity. And, although we focus on fatigue as being representative, it is one of a handful of lingering toxicities of cancer treatment (i.e. lymphoedema, fibrosis, cognitive dysfunction and xerostomia) that incur chronic direct and indirect costs.

It is likely that toxicity-driven costs will accelerate. New cancer therapies continue to evolve, and with them come unique toxicities or amplification of existing ones. With the manifestation of new toxicities, especially those that are treatment limiting, comes motivation to develop potential interventions for prevention or amelioration in an unceasing round, like a dog chasing its tail. Thanks to

Author's personal copy

advancements in research and modern medicine, cancer survivorship is on the rise. But a consequence of this increased survival rate is that patients are at risk of developing toxicities for a longer period of time and, thus, it may be necessary to redefine toxicities. For example, we know that the risk of second malignancies is a consequence of some forms of cancer therapy. Is the diagnosis, treatment and management of a second tumour a toxicity of the first?

This review clearly demonstrates that the fiscal burden of regimen-related toxicities is substantial. It also reveals the desirability of standardizing mechanisms by which accurate data is collected relative to individual and clustering toxicities and, specifically, the way costs are assigned. As the incremental costs of toxicity management as part of total cancer therapy continue to increase, they might jeopardize primary resource allocation for primary tumour treatment. Thus, there is a huge incentive for development of cost-effective ways to ameliorate undesirable side effects.

Late toxicities are barely on the oncology world's radar but are likely to become an increasing burden on healthcare and disability costs. With the combination of extended working lives, an aging population and the increased risk of cancer with age, it seems timely to better understand the fiscal consequences of chronic toxicities. While the focus of pharmacological management has been on allowing patients to complete effective cancer therapy, the long-term consequences of treatment can no longer be ignored. Indeed, this need provides a significant opportunity for new classes of interventional agents.

7 Conclusions

Rarely are cancer patients spared from treatment-related toxicities. Often, patients suffer not just one but multiple treatment side effects, some of which are dose limiting and all of which impart significant health-related quality of life and economic burdens. As researchers scramble to develop new cancer therapies, including targeted agents, the frequency, number, and short- and long-term fiscal burdens of oncology supportive care are likely to escalate dramatically. The addition of effective therapeutic interventions aimed at preventing or minimizing the incidence, course and duration of regimen-related toxicities is likely to provide significant cost savings to the overall care of patients with cancer.

Author Contributions A. Carlotto, V. L. Hogsett and E. M. Maiorini contributed equally to the performance of searches, data summarization and manuscript preparation. J. G. Razulis analyzed data and contributed to the manuscript preparation. S. T. Sonis was the study principal investigator, contributed to the study design, data analysis and manuscript preparation, and is the overall guarantor of the study content.

Conflicts of Interest The authors have no conflicts of interest related to the content of this manuscript.

References

1. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010–2020. J Natl Cancer Inst. 2011;103(2):117–28.
2. Surveillance, Epidemiology and End Results (SEER) Database (2012). Lifetime risk (percent) of being diagnosed with cancer by site and race/ethnicity: males, 18 SEER areas, 2007–2009 (Table 1.15) and females, 18 SEER areas, 2007–2009 (Table 1.16). http://seer.cancer.gov/csr/1975_2009_pops09/results_merged/topic_lifetime_risk_diagnosis.pdf. Accessed May 2013.
3. Kim E, Dodd MJ, Aouizerat BE, et al. A review of the prevalence and impact of multiple symptoms in oncology patients. J Pain Symptom Manage. 2009;37(4):715–36.
4. Aprile G, Ramoni M, Keefe D, et al. Links between regimen-related toxicities in patients being treated for colorectal cancer. Curr Opin Support Palliat Care. 2009;3(1):50–4.
5. Aapro M, Molassiotis A, Dicato M, et al. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). Ann Oncol. 2012;23(8):1986–92.
6. Haiderali A, Menditto L, Good M, et al. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a US population. Support Care Cancer. 2011;19(6):843–51.
7. Shih YC, Xu Y, Elting LS. Costs of uncontrolled chemotherapy-induced nausea and vomiting among working-age cancer patients receiving highly or moderately emetogenic chemotherapy. Cancer. 2007;110(3):678–85.
8. Craver C, Gayle J, Balu S, et al. Clinical and economic burden of chemotherapy-induced nausea and vomiting among patients with cancer in a hospital outpatient setting in the United States. J Med Econ. 2011;14(1):87–98.
9. Burke TA, Wisniewski T, Ernst FR. Resource utilization and costs associated with chemotherapy-induced nausea and vomiting (CINV) following highly or moderately emetogenic chemotherapy administered in the US outpatient hospital setting. Support Care Cancer. 2011;19(1):131–40.
10. Hamada S, Hinotsu S, Hori K, et al. The cost of antiemetic therapy for chemotherapy-induced nausea and vomiting in patients receiving platinum-containing regimens in daily practice in Japan: a retrospective study. Support Care Cancer. 2012;20(4):813–20.
11. Lordick F, Ehlken B, Ihbe-Heffinger A, et al. Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Eur J Cancer. 2007;43(2):299–307.
12. Ballatori E, Roila F, Ruggeri B, et al. The cost of chemotherapy-induced nausea and vomiting in Italy. Support Care Cancer. 2007;15(1):31–8.
13. Barrajon E, de las Peñas R. Randomised double blind crossover study comparing ondansetron, granisetron and tropisetron: a cost-benefit analysis. Support Care Cancer. 2000;8(4):323–33.
14. Hartmann JT, von Vangerow A, Fels LM, et al. A randomized trial of amifostine in patients with high-dose VIC chemotherapy plus autologous blood stem cell transplantation. Br J Cancer. 2001;84(3):313–20.

Author's personal copy

15. Ihbe-Heffinger A, Ehlken B, Bernard R, et al. The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. Ann Oncol. 2004;15(3):526–36.
16. Iihara H, Ishihara M, Matsuura K, et al. Pharmacists contribute to the improved efficiency of medical practices in the outpatient cancer chemotherapy clinic. J Eval Clin Pract. 2012;18(4): 753–60.
17. Lachaine J, Yelle L, Kaizer L, et al. Chemotherapy-induced emesis: quality of life and economic impact in the context of current practice in Canada. Support Cancer Ther. 2005;2(3): 181–7.
18. Elting L, Shih Y. The economic burden of supportive care of cancer patients. Support Care Cancer. 2004;12(4):219–26.
19. Mittmann N, Verma S, Koo M, et al. Cost effectiveness of TAC versus FAC in adjuvant treatment of node-positive breast cancer. Curr Oncol. 2010;17(1):7–16.
20. Dranitsaris G, Maroun J, Shah A, et al. Estimating the cost of illness in colorectal cancer patients who were hospitalized for severe chemotherapy induced diarrhea. Can J Gastroenterol. 2005;19(2):83–7.
21. Dranitsaris G, Maroun J, Shah A, et al. Severe chemotherapy-induced diarrhea in patients with colorectal cancer: a cost of illness analysis. Support Care Cancer. 2005;13(5):318–24.
22. Schwartzber LS, Sonis ST, Walker MS, et al. Single nucleotide polymorphism (SNP) Bayesian networks (BNs) predict risk of chemotherapy-induced side effects in patients with breast cancer receiving dose dense (DD) doxorubicin/cyclophosphamide plus paclitaxel (AC+T) [abstract no. 700107; poster no. P1-15-12]. San Antonio Breast Cancer Symposium; San Antonio; 4–8 Dec 2012.
23. Sonis ST, Schwartzber LS, Walker MS, et al. Predicting risk of chemotherapy-induced side effects in patients with colon cancer with single-nucleotide polymorphism (SNP) Bayesian networks (BNs). J Clin Oncol. 2012;30(Suppl 34);Abstract no. 344.
24. Arbuckle RB, Huber SL, Zacker C, et al. The consequences of diarrhea occurring during chemotherapy for colorectal cancer: a retrospective study. Oncologist. 2000;5(3):250–9.
25. Elting LS, Cooksley C, Chambers M, et al. The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis. Cancer. 2003;98(7):1531–9.
26. National Cancer Institute. Common terminology criteria for adverse events (CTCAE), version 4.0. Bethesda: US Department of Health and Human Services, National Institutes of Health; 2010.
27. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol. 2001;19(8):2201–5.
28. Elting LS, Cooksley CD, Chambers MS, et al. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys. 2007;68(4):1110–20.
29. Murphy BA, Beaumont JL, Isitt J, et al. Mucositis-related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy. J Pain Symptom Manage. 2009;38(4):522–32.
30. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol. 2003;66(3):253–62.
31. Nonzee NJ, Dandade NA, Patel U, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis. Cancer. 2008;113(6):1446–52.
32. Peterman A, Cella D, Glandon G, et al. Mucositis in head and neck cancer: economic and quality of life outcomes. J Natl Cancer Inst Monogr. 2001;29:45–51.
33. Aprile G, Pisa FE, Follador A, et al. Unplanned presentations of cancer outpatients: a retrospective cohort study. Support Care Cancer. 2013;21(2):397–404.
34. Hassett MJ, O'Malley AJ, Pakes JR, et al. Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. J Nat Cancer Inst. 2006;98(16):1108–17.
35. McKenzie H, Hayes L, White K, et al. Chemotherapy outpatients' unplanned presentations to hospital: a retrospective study. Support Care Cancer. 2011;19(7):963–9.
36. Poirier Patricia. Factors affecting performance of usual activities during radiation therapy. Oncology Nursing Forum. 2007;34(4): 827–34.
37. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the fatigue coalition. Oncologist. 2000;5(5):353–60.
38. Lavigne JE, Griggs JJ, Tu XM, et al. Hot flashes, fatigue, treatment exposures and work productivity in breast cancer survivors. J Cancer Surviv. 2008;2(4):296–302.
39. Lee MK, Lee KM, Bae JM, et al. Employment status and work-related difficulties in stomach cancer survivors compared with the general population. British J Cancer. 2008;98(4):708–15.
40. Greimel ER, Bjelic-Radisic V, Pfisterer J, et al. Toxicity and quality of life outcomes in ovarian cancer patients participating in randomized controlled trials. Support Care Cancer. 2011;19: 1421–7.
41. Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse events? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol. 2004;22:3485–90.
42. Ihbe-Heffinger A, Paessens B, Berger K, et al. The impact of chemotherapy-induced side effects on medical care usage and cost in German hospital care—an observational analysis on non-small-cell lung cancer patients. Support Care Cancer (Epub 2013 Jan 23).
43. Poirier P. The relationship of sick leave benefits, employment patterns, and individual characteristics to radiation therapy-related fatigue. Oncol Nurs Forum. 2006;33(3):593–601.