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Investigation of Adverse-Event-Related Costs for Patients With Metastatic Breast Cancer in a Real-World Setting

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Background. Existing treatments for metastatic breast cancer (mBC) are often effective but can cause adverse events (AEs). This study aimed to identify AEs associated with chemotherapies commonly used in mBC treatment (phase 1) and to quantify the economic impact of these AEs (phase 2).

Materials and Methods. Patients in phase 1 had at least one claim for therapy for mBC, with at least one episode with single or multiple agents. The most common chemotherapy-related complications were identified using medical and pharmacy claims data. In phase 2, patients meeting study criteria were divided into four treatment cohorts by the line of treatment and chemotherapy received: first-line taxane-treated patients, second-line taxane-treated patients, first-line capecitabine-treated patients, and second-line capecitabine-treated patients. Average monthly AE-related health care costs per cohort were stratified by cost component. Total monthly costs per number of AEs were also calculated.

Results. On average, patients in phase 1 ($n = 1,551$) had 2 episodes of treatment, with a mean duration of 131 days. The most frequently noted complications were anemia (50.7% of mBC treatment episodes), bilirubin elevation (26.4%), and leukopenia (24.8%). In phase 2, costs related to AEs were primarily driven by incremental inpatient, outpatient, and pharmacy costs. Increases in average monthly costs ranged from $854 (9.0%) to $5,320 (69.5%), according to cohort. Overall costs increased with increasing numbers of AEs.

Conclusion. Chemotherapy-related AEs in patients with mBC are associated with a substantial economic burden that increases with the number of AEs reported. **The Oncologist** 2014; 19:901–908

Implications for Practice: Existing treatments for metastatic breast cancer (mBC) are effective but frequently are accompanied by adverse events (AEs), which may affect treatment adherence and effectiveness and impose a significant economic burden. In this study, the first to assess the costs associated with AEs related to mBC chemotherapies, we found that the presence of AEs was associated with increases of up to 69.5% in monthly costs. These findings emphasize the importance of including the side effect potential of various treatment options in clinical decision making, given that therapies associated with fewer, less severe complications can improve patients' clinical outcomes and reduce treatment costs.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women in the U.S. and the second leading cancer-related cause of death among women nationwide [1]. The exact prevalence of metastatic breast cancer (mBC) in the U.S. is unknown, but it is estimated that 150,000 to 250,000 U.S. women are currently living with the disease [2]. Existing treatments for mBC, especially traditional chemotherapies, are often effective but can cause both immediate and sometimes long-term health concerns. Specifically, these agents can cause a wide variety of side effects related to their cytotoxic chemotherapy toxicities.

Side effects related to traditional chemotherapies can have clinical, functional, and economic consequences, resulting in dose delays and reductions, negative impact on quality of life, and additional treatment and hospitalization costs. The magnitude of the economic impact of these side effects in mBC, however, has not been quantified. The goal of this research was to identify the prevalence of adverse events (AEs) seen in patients with mBC receiving chemotherapy in the U.S. and to quantify the economic impact of these AEs, especially in patients using two common chemotherapies: taxanes and capecitabine.

The objective of this study was twofold and was conducted in two phases. The objective of the first phase was to assess the prevalence of chemotherapy-related AEs among patients with

mBC. Patients receiving all types of chemotherapy and all lines of treatment were included. The second phase was to further quantify the economic impact of chemotherapy-related complication costs among patients with mBC who were treated with taxanes (i.e., paclitaxel or docetaxel) or with capecitabine-based regimens in the first- and second-line settings. A large commercial claims database, the PharMetrics Integrated Database (IMS Health, Danbury, CT, http://www.imshealth.com), was used to assess these two objectives.

MATERIALS AND METHODS

Data Source

Because the study was conducted in two phases, based on data availability, data from April 1, 2004, to March 31, 2009, were extracted from the PharMetrics Integrated Database as the data source for phase 1 of the study, and data from January 1, 2000, to December 31, 2010, were used for phase 2. The PharMetrics database is representative of the commercially insured population in the U.S. The database comprises medical and pharmacy claims for more than 70 million members from more than 100 health plans and covers all census regions, with particular concentration in the South and the Midwest. Data elements in the database include patient demographics, health plan enrollment information, inpatient and outpatient diagnoses and procedures, outpatient prescription drug dispensing claims, and financial information. The database is fully de-identified and compliant with the Health Insurance Portability and Accountability Act of 1996. Consequently, the study was exempt from an Institutional Review Board approval.

Sample Selection and Study Design

Sample selection criteria for the study are described in supplemental online Figure 1. Patients were identified as having mBC if they had at least two independent diagnoses of secondary malignant neoplasm (International Classification of Diseases, ninth revision (ICD-9) codes 197.xx and 198.xx) within 90 days apart, and if they had at least two independent diagnoses of breast cancer (ICD-9 code 174.xx) during the 365-day period prior to the first diagnosis of secondary malignant neoplasm (disease index date) or at least one diagnosis during the 365 days before and one within 90 days after the disease index date. In addition, patients with a diagnosis of cancers other than breast cancer (ICD-9 codes 140.xx–165.xx, 170.xx–173.xx, 175.xx, 176.xx, 179.xx–195.xx, and 199.xx–209.xx) prior to the first claim with a diagnosis of breast cancer were excluded [3]. Men were also excluded from the study because they may display different profiles than women due to the different pathogenesis in the evolution and progression of their respective disease paths [4].

In the phase 1 analysis, patients must have had at least one medical or pharmacy claim for selected chemotherapeutic agents, anti-HER2 agents, or antiangiogenic therapies for mBC on or after the disease index date. The index date was defined as the date of the first claim of therapeutic treatment following mBC diagnosis. Patients were required to be at least 18 years of age or older as of the study index date and to have been continuously enrolled in their health care plan for at least 365 days before and 30 days after the index date.

Chemotherapy treatment episodes were defined for each patient who met the sample selection criteria (supplemental online Fig. 2). The initiation date of a treatment episode was defined as the date of the first claim of the first chemotherapy regimen, and the treatment episode continued until either a gap in treatment of at least 45 consecutive days or a change in treatment regimen (i.e., adding or subtracting a therapeutic agent or switching therapies). Treatment regimens were identified based on agents used as monotherapy, as combination therapy with endocrine therapies, or as multiple agents combined to treat mBC during the first 4 weeks following initiation of treatment with the first agent. For the purpose of this study, selected chemotherapeutics, anti-HER2 agents, or antiangiogenic therapies included albumin-bound paclitaxel, capecitabine, cyclophosphamide, docetaxel, doxorubicin, gemcitabine, lapatinib, paclitaxel, trastuzumab, bevacizumab, and vinorelbine. Endocrine therapies, such as aromatase inhibitors, estrogen-receptor down regulators, or selective estrogen-receptor modulators, could be used as adjunctive therapy. In order to capture outcomes at a treatment-episode level, patients were followed across all treatment episodes up to the end of continuous health plan enrollment or the end of data availability, whichever occurred first. Only episodes of at least 30 days were considered in the analysis.

Based on the results of phase 1, the following four study cohorts were included for phase 2 based on two common chemotherapy classes [1]: first-line taxane-treated patients [2], second-line taxane-treated patients [4], first-line capecitabine-treated patients [5], second-line capecitabine-treated patients. Taxanes and capecitabine were selected because they were the most frequently administered medications overall and were the most commonly used intravenous and oral agents, respectively. The four treatment cohorts were not mutually exclusive because selected patients could have received taxanes as first-line therapy and capecitabine as second-line therapy, or vice versa.

Chemotherapy-Related AEs

By reviewing product labels for each selected treatment agent, a total 22 AEs associated with chemotherapy were selected (supplemental online Table 1). Diagnosis, procedure, and national drug codes in the medical and pharmacy claims were used to identify those AEs that fell within each treatment episode. In phase 1, the most frequent chemotherapy-related AEs were identified, and AE rates were reported for all episodes of treatment as well as for the most prevalent monotherapy and combination regimens. In phase 2, to study the cost associated with chemotherapy-related AEs, the 22 AEs were further grouped into 9 system/organ categories: "blood/bone marrow complications" (e.g., anemia, leukopenia), "constitutional symptoms" (e.g., fatigue, pyrexia), "infections" (e.g., neutropenia, pharyngitis, other infections), "musculoskeletal/soft tissue symptoms" (e.g., arthralgia, peripheral neuropathy), "hepatobiliary/pancreatic symptoms" (e.g., bilirubin elevation; alkaline phosphatase, alanine transaminase, or aspartate aminotransferase elevation), "pulmonary/upper respiratory syndromes" (e.g., dyspnea, edema), "myalgia," "dermatology/skin symptoms" (e.g., rash, injection site reactions), and "gastrointestinal symptoms" (e.g., diarrhea,

constipation, nausea/vomiting, decreased appetite, stomatitis, thrombocytopenia).

Statistical Analysis

Descriptive statistics were used to report patient characteristics, including age, region of residence, comorbidities [6], prior cancer treatments, and resource utilization (inpatient admission, outpatient visit, emergency room [ER] visit) during the 1-year period prior to the initiation of first-line treatment for mBC. Comorbidities were identified using ICD-9 and Healthcare Common Procedure Coding System procedure codes and included all comorbidities, excluding cancers present in the Charlson Comorbidity Index [5] and other selected comorbidities [6].

In phase 2, total health care costs were measured from a payer perspective (i.e., the amount paid or reimbursed by the insurer [commercial plan] for a service or a prescription, which excludes the member liability) and included both pharmacy costs (chemotherapy and administration and nonchemotherapy-related drugs) and medical costs (inpatient, ER visits, outpatient, and other medical services). Costs were observed during the treatment episodes, and the average monthly costs were determined by dividing the total costs incurred during a treatment episode by the episode length in months. Incremental costs associated with chemotherapy-related AEs were then estimated by comparing average costs between AE- and AE-free cohorts for the first- and second-line taxane and first- and second-line capecitabine treatment groups. The inverse probability weighting (IPW) method [7–9] was used to balance patient characteristics between cohorts, and the adjusted incremental cost differences between AE and AE-free cohorts in each treatment group were reported. All costs were adjusted for inflation to 2010 U.S. dollars.

In addition, sensitivity analyses were conducted by stratifying patients in each cohort by the number of AEs reported per treatment episode. The relationship between total monthly costs and the number of AEs was evaluated to identify whether greater monthly costs were incurred by patients with more AEs.

Results

Phase 1

A total of 2,233 patients met the sample selection criteria. Among these 2,233 patients with mBC, 60% had at least one prescription for a taxane, and 35% had at least one prescription for capecitabine. There were 3,157 eligible treatment episodes for mBC noted among 1,551 patients who had at least one episode of treatment with single or multiple agents for at least 30 days. The mean age was 57 years (Table 1). On average, these patients had 2 episodes of treatment each (median: 2 episodes), with a mean treatment duration of 131 days.

Among eligible episodes of treatment, the most commonly used monotherapy regimens were capecitabine (17.6%), taxanes (14.3%), and trastuzumab (13.8%). The most commonly used combinations of chemotherapy- or biologic-based treatments were trastuzumab-based regimens (19.9%), taxane-based regimens (9.6%), and capecitabine-based regimens

Table 1. Baseline characteristics of patients with episodes of at least 30 days

Characteristics	Results
Total number of patients	1,551
Age, years, mean ± SD	57.32 ± 11.76
Older than 65 years, n (%)	353 (22.8)
Region, n (%)	
East	425 (27.4)
Midwest	485 (31.3)
South	482 (31.1)
West	159 (10.3)
Charlson Comorbidity Index, mean (SD)	0.58 ± 0.95
Resource utilization, mean ± SD	
Inpatient	0.50 ± 0.86
Outpatient	15.93 ± 9.57
Emergency room	0.35 ± 0.82
Prior cancer treatments, n (%)	
Chemotherapy	711 (45.8)
Endocrine therapy	450 (29.0)
Radiation therapy	10 (0.6)
Surgery	21 (1.4)
Selected comorbidities, n (%)	
Arthritis	935 (60.3)
Benign/inflammatory bowel	361 (23.3)
Coagulopathy	563 (36.3)
Common rheumatologic diseases	869 (56.0)
Cystitis or vaginitis or stone	317 (20.4)
Diabetes with no complications	184 (11.9)
Hypertension with no complications	441 (28.4)
Mild to moderate liver disease	270 (17.4)
Mild to moderate pulmonary disease	578 (37.3)
Other endocrine disorders	185 (11.9)
Severe pulmonary disease	491 (31.7)
Thyroid condition	683 (44.0)

(5.9%) (Table 2). These treatment regimens included endocrine therapies for approximately 18% of patients. The most prevalent chemotherapy-related AEs noted overall were anemia (50.7%), bilirubin elevation (26.4%), leukopenia (24.8%), infection (19.2%), and dyspnea (18.6%) (Table 3). The AE rates for the most prevalent monotherapy (capecitabine) and combination therapy (trastuzumab-based regimens) are reported in Table 3.

Phase 2

A total of 3,222 patients (mean age: 57 years) met the sample selection criteria of phase 2 of the study. Of these patients, 2,678 received first-line therapy and 1,084 received second-line therapy. In general, patients who did not experience AEs had better comorbidity profiles at baseline than those who did experience any AEs. The IPW method was used in the cost analysis to account for these differences between groups. In the treatment groups receiving taxanes, 94.6% and 94.4% of patients receiving first- and second-line

Table 2. Description of treatment regimens for mBC

Treatment episodes for mBC	*n*	%
Total number of treatment episodes	3,157	
Monotherapy regimens[a]		
Capecitabine	557	17.6
Trastuzumab	435	13.8
Docetaxel	264	8.4
Gemcitabine	240	7.6
Vinorelbine	207	6.6
Paclitaxel	188	6.0
Doxorubicin	133	4.2
Albumin-bound paclitaxel	108	3.4
Bevacizumab	43	1.4
Lapatinib	31	1.0
Cyclophosphamide	19	0.6
Combinations of chemotherapeutics, anti-HER2 agents, or antiangiogenics[a]		
Lapatinib plus capecitabine	64	2.0
Doxorubicin plus cyclophosphamide	62	2.0
Docetaxel plus capecitabine	55	1.7
Gemcitabine plus paclitaxel	45	1.4
Bevacizumab plus paclitaxel	43	1.4
Doxorubicin plus docetaxel or doxorubicin plus paclitaxel	14	<1
Trastuzumab-based regimens[a]		
Trastuzumab plus vinorelbine	172	5.4
Trastuzumab plus docetaxel	90	2.9
Trastuzumab plus gemcitabine	81	2.6
Trastuzumab plus capecitabine	66	2.1
Trastuzumab plus carboplatin	66	2.1
Trastuzumab plus albumin-bound paclitaxel	57	1.8
Trastuzumab plus paclitaxel	55	1.7
Trastuzumab plus doxorubicin	11	<1
Trastuzumab plus bevacizumab	6	<1
Trastuzumab plus lapatinib	4	<1

[a]May include combinations with endocrine therapies.
Abbreviation: mBC, metastatic breast cancer.

treatment, respectively, experienced at least one AE during their treatment episodes. In the cohorts receiving capecitabine, 83.7% and 84.0% of patients receiving first- and second-line treatment, respectively, experienced one AE or more during the treatment episodes (Table 4). Nausea/vomiting were the most common AEs associated with both types of treatments.

When evaluating the taxane cohorts, AEs were associated with a 38.7% increase in monthly costs ($3,547) among patients receiving first-line taxane therapy (Fig. 1). Incremental costs in this cohort were driven mainly by increased hospitalization costs and non-chemotherapy-related drug costs. Among patients receiving second-line taxane therapy, AEs were associated with a 69.5% increase in monthly costs ($5,320) (Fig. 1). Incremental costs in this cohort were driven mainly by increased pharmacy costs related to both chemotherapies and other drug intake. Among patients receiving

first-line therapy, the most costly AEs were skin-related symptoms, hepatobiliary/pancreatic, and pulmonary/upper respiratory, whereas constitutional, pulmonary/upper respiratory, and skin-related symptoms were the most costly AEs among patients receiving second-line therapy (Fig. 2).

When evaluating the capecitabine cohort, AEs were associated with a 9.0% increase in monthly costs ($854) among patients receiving first-line capecitabine therapy (Fig. 1). Incremental costs among these patients were driven mainly by inpatient and non-chemotherapy-related drug costs. Among patients in the capecitabine cohort receiving second-line therapy, AEs were associated with an 82.9% increase in monthly costs ($4,933) (Fig. 1). Incremental costs among these patients were driven mainly by outpatient and inpatient costs. Among patients receiving first-line therapy, the most costly AEs were constitutional, pulmonary/upper respiratory, and skin related, whereas pulmonary/upper respiratory system, blood/bone marrow, and infection AEs were the most costly among patients receiving second-line therapy (Fig. 2).

In the sensitivity analyses stratifying patients in each cohort by the number of AEs, the total costs generally increased with increasing incidence of AEs, primarily due to increasing hospitalization costs (Fig. 3). All cost components tended to increase with an increase in the number of AEs, with the exception of costs related to chemotherapy treatment and outpatient care. A decrease was observed in costs related to chemotherapy treatment in patients receiving first- and second-line taxane therapy and in patients receiving second-line capecitabine therapy who experienced more than four AEs (relative to those in that cohort experiencing four or fewer AEs). Costs related to outpatient care decreased among patients receiving first-line capecitabine therapy who experienced more than four AEs, relative to those in that cohort experiencing four or fewer AEs.

Discussion

This study was the first to assess the economic burden of chemotherapy-related AEs for the treatment of mBC. Results of the study revealed that the most prevalent chemotherapy-related AEs were anemia (50.7%), bilirubin elevation (26.4%), leukopenia (24.8%), infection (19.2%), and dyspnea (18.6%). The economic analysis highlighted that costs related to the observed AEs were substantial and were driven primarily by incremental inpatient, outpatient, and pharmacy costs. Increases in average monthly costs related to the presence of the AEs ranged from $854 (a 9.0% increase in monthly costs) to $5,320 (69.5%), according to cohort. In general, costs increased with increasing numbers of AEs, with the exception of drug costs related to chemotherapy, which decreased among patients experiencing more than four AEs in the first- and second-line taxane cohorts and in the second-line capecitabine cohort. This observation might be explained by the treatment delay or dose reduction among patients with serious AEs.

The AE rates observed in this study reflect clinical events in a clinical setting based on data derived from a commercially insured population. These rates may be higher or lower than the AE rates reported in clinical trials because clinical trials are designed and powered primarily to identify

Table 3. Rates of chemotherapy-related adverse events by type of treatment regimen

Complication, n (%)[a]	Total number of studied treatment episodes (N = 3,157)			
	Overall	Capecitabine monotherapy	Taxane monotherapy	Trastuzumab-based therapies[b]
Anemia	1,600 (50.7)	149 (26.8)	242 (53.5)	564 (53.1)
Bilirubin elevation	833 (26.4)	121 (21.7)	117 (25.9)	319 (30.0)
Leukopenia	782 (24.8)	25 (4.5)	140 (31.0)	203 (19.1)
Infection	606 (19.2)	101 (18.1)	88 (19.5)	215 (20.2)
Dyspnea	587 (18.6)	101 (18.1)	97 (21.5)	179 (16.9)
Neutropenia	551 (17.5)	21 (3.8)	98 (21.7)	148 (13.9)
Arthralgia	377 (11.9)	67 (12.0)	45 (10.0)	157 (14.8)
Dehydration	327 (10.4)	44 (7.9)	43 (9.5)	110 (10.4)

[a]Percentages were calculated based on the total number of episodes.
[b]40.9% of the episodes of treatment with trastuzumab were in monotherapy.

Table 4. Rates of chemotherapy-related adverse events for first- and second-line treatment with taxane or capecitabine

Episode	First-line taxane	First-line capecitabine	Second-line taxane	Second-line capecitabine
Total number of patients	1,866	812	715	369
Days per episode, mean (median)	148 (106)	150 (106)	121 (78)	140 (104)
Adverse events, n (%)				
Any adverse event	1,766 (94.6)	680 (83.7)	675 (94.4)	310 (84.0)
ALP, ALT, or AST increased	222 (11.9)	76 (9.4)	80 (11.2)	52 (14.1)
Anemia	891 (47.7)	194 (23.9)	387 (54.1)	99 (26.8)
Arthralgia	195 (10.5)	123 (15.1)	67 (9.4)	53 (14.4)
Bilirubin elevation	600 (32.2)	194 (23.9)	206 (28.8)	102 (27.6)
Constipation	111 (5.9)	57 (7.0)	25 (3.5)	29 (7.9)
Decreased appetite	40 (2.1)	15 (1.8)	13 (1.8)	7 (1.9)
Diarrhea	146 (7.8)	78 (9.6)	46 (6.4)	52 (14.1)
Dehydration	267 (14.3)	76 (9.4)	73 (10.2)	49 (13.3)
Dyspnea	304 (16.3)	140 (17.2)	99 (13.8)	47 (12.7)
Edema	101 (5.4)	57 (7.0)	35 (4.9)	19 (5.1)
Fatigue	66 (3.5)	1 (0.1)	16 (2.2)	1 (0.3)
Infection	334 (17.9)	153 (18.8)	136 (19.0)	74 (20.1)
Injection site reactions	33 (1.8)	2 (0.2)	15 (2.1)	3 (0.8)
Leukopenia	804 (43.1)	54 (6.7)	325 (45.5)	44 (11.9)
Myalgia	104 (5.6)	16 (2.0)	39 (5.5)	5 (1.4)
Nausea/vomiting	1,084 (58.1)	282 (34.7)	349 (48.8)	129 (35.0)
Neutropenia	532 (28.5)	37 (4.6)	201 (28.1)	36 (9.8)
Peripheral neuropathy	46 (2.5)	18 (2.2)	24 (3.4)	12 (3.3)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	154 (8.3)	59 (7.3)	61 (8.5)	22 (6.0)
Rash	34 (1.8)	16 (2.0)	11 (1.5)	4 (1.1)
Stomatitis	18 (1.0)	8 (1.0)	3 (0.4)	5 (1.4)
Thrombocytopenia	66 (3.5)	23 (2.8)	23 (3.2)	12 (3.3)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase.

the benefits of chemotherapy and not to characterize AEs. In addition, differences between observed AE rates and those reported during clinical trials may be due to differences in patients' demographic characteristics and prognoses and to the fact that ICD-9 codes (rather than direct clinical assessment) were used to identify AEs during this study.

Very few prior studies have examined the economic outcomes associated with chemotherapy-related AEs among patients with breast cancer [10]. Some studies have been conducted to evaluate the costs associated with specific AEs (e.g., neutropenia [11–13]) among patients with breast cancer, but no study has evaluated the economic impact of
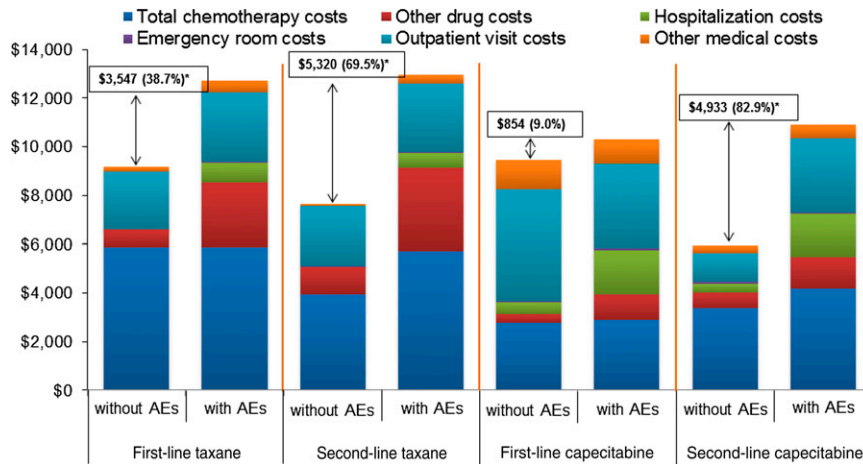
Figure 1. Monthly health care costs stratified by cost components. $*p < .05$.
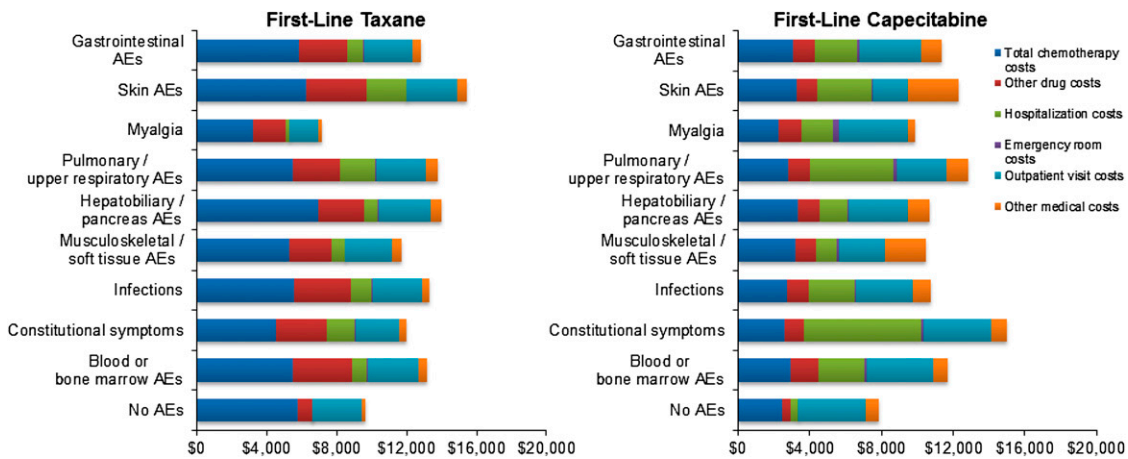Abbreviation: AEs, adverse events.

Figure 2. Average monthly health care costs stratified by types of AEs. Results are presented for first-line therapies. Findings were similar for second-line therapies.
Abbreviation: AEs, adverse events.

a comprehensive list of chemotherapy-related AEs among patients with mBC in a clinical setting. Hasset et al. reported the frequency and cost of serious chemotherapy-related AEs among a younger population newly diagnosed with breast cancer [14]. In their estimation, patients who experienced serious chemotherapy-related AEs had large incremental expenditures for hospitalizations ($12,907 per person per year), prescriptions ($1,908 per person per year), and pre-scription copayments ($120 per person per year) compared with those who did not experience serious chemotherapy-related AEs. This is consistent with our finding that inpatient and other-drug costs are among the main drivers of in-cremental costs associated with AEs. Studies of patients with colon cancer have also identified significant economic costs related to chemotherapy-associated AEs, at an average of more than $500 per month for capecitabine-related complications [15,16].

The findings of the current study suggest that treatment-related AEs occur frequently among patients receiving che-motherapy for mBC, and such AEs are associated with

a substantial economic burden, as reflected by increases in monthly expenses of up to 69.5%, for which these increases are driven mostly by incremental inpatient, outpatient, and pharmacy costs. These findings emphasize the importance of considering AEs during treatment decisions in mBC because therapies that are associated with a decrease in frequency and severity of complications can improve patients' clinical outcomes and reduce treatment costs.

This study was subject to the common limitations of retrospective, observational studies based on health care claims data, including errors and omissions in the database. However, these are expected to affect both cohorts similarly and thus were unlikely to alter the conclusions of the study. In addition, the study sample comprised only patients with commercial health plan coverage and a few dual-eligible patients (Medicare and commercial or Medicaid and commer-cial) and only have reimbursement information from the private payer; this limits the generalizability of the findings to public payers. Nevertheless, claims data were used in the study because they are a valid, large-sample source of clinical
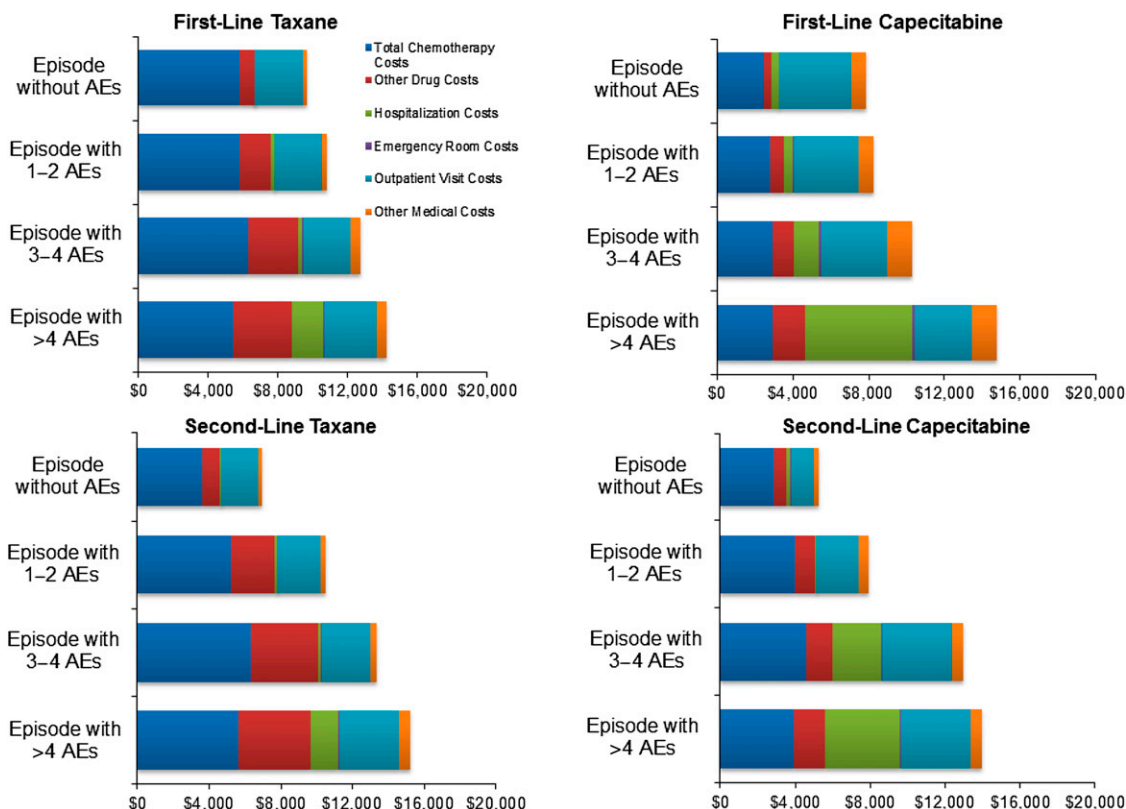
Figure 3. Health care costs by cohort and number of AEs reported.
Abbreviation: AEs, adverse events.

practice data. A further limitation of the study findings is that patient characteristics could not be completely balanced among the patient cohorts even after applying IPW. Consequently, some of the cost differences that were observed could be due to unknown differences between patients in various clinical measures. It is also true that incremental costs noted in the study may not be due solely to the studied AEs. Moreover, the AEs noted in this study as being potentially related to chemotherapy were identified, based on a literature review, to be the complications most frequently associated with chemotherapy for mBC. A causal relationship between patients' therapy and these AEs cannot, however, be confirmed. Furthermore, because chemotherapy-related AEs were recorded only during treatment episodes, those that may have occurred after the end of treatment episodes were not considered in the analysis. Finally, not all AEs related to use of specific therapies can be captured in this type of analysis, which recorded only AEs for which a medical service was required and a diagnosis code was generated. This limitation may lead to underestimation of the burden of the studied AEs.

Conclusion

This study was the first to assess costs associated with AEs related to treatment of mBC. In summary, findings of the study indicate that there is a strong need for therapies that demonstrate equal or superior efficacy to traditional chemotherapy regimens while decreasing the frequency and severity of AEs related to these treatments. Such therapies will help improve patients' clinical outcomes because reduced AE rates promote treatment adherence and persistence. In addition, these therapies can promote better economic outcomes by reducing or avoiding costs incurred as a result of treatment-related AEs. Findings of the study also reveal that AEs related to chemotherapy are associated with a substantial economic burden that is primarily explained by increased inpatient, outpatient, and pharmacy costs. In addition, the analysis of health care costs stratified by the number of observed AEs clearly shows that the economic burden of AEs increases with the number of reported chemotherapy-related AEs. Further research should examine the clinical impact of chemotherapy-related AEs and their impact on patient outcomes.

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Conception/Design: Annie Guerin, Sara Hurvitz, Melissa Brammer, Ellie Guardino, Zheng-Yi Zhou, Dominick Latremouille-Viau, Eric Q. Wu, Deepa Lalla
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Data analysis and interpretation: Annie Guerin, Sara Hurvitz, Zheng-Yi Zhou, Dominick Latremouille-Viau, Eric Q. Wu, Deepa Lalla
Manuscript writing: Annie Guerin, Zheng-Yi Zhou, Dominick Latremouille-Viau, Eric Q. Wu, Deepa Lalla
Final approval of manuscript: Annie Guerin, Sara Hurvitz, Melissa Brammer, Ellie Guardino, Zheng-Yi Zhou, Dominick Latremouille-Viau, Eric Q. Wu, Deepa Lalla
Other: Genentech, Inc.

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