Clinical Impact of Chemotherapy-Related Adverse Events in Patients with Metastatic Breast Cancer in an Integrated Health Care System

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ABSTRACT

BACKGROUND: Stage IV breast cancer, also known as metastatic breast cancer (mBC), is not a curable condition. However, treatment can prolong life, delay the progression of the cancer, or improve quality of life. Currently, patients with mBC are often treated with chemotherapy. Patients often experience adverse events from chemotherapy during the treatment cycle, which leads to chemotherapy modifications such as dose delay, dose reduction, or discontinuation of chemotherapy. Previous studies have evaluated the rates of adverse events that occur from the use of chemotherapy; however, few studies have evaluated the clinical impact on the chemotherapy regimen once the adverse event occurs. This study evaluates the clinical impact on the chemotherapy regimen from chemotherapy-related adverse events in patients with mBC in an integrated health care delivery system.

OBJECTIVES: To assess the adverse events in patients with mBC and evaluate the clinical impact on the chemotherapy regimen from these adverse events in an integrated health care delivery system.

METHODS: This study is a retrospective cohort of patients with mBC newly initiated on chemotherapy. The first infusion was defined as the index date. Patients were aged > 18 years at time of index date and had 6 months or more of Kaiser membership and drug eligibility prior to the index date and continuous membership and drug eligibility throughout follow-up. Adverse events were identified after the index date and during the follow-up using ICD-9-CM diagnosis and procedure codes. Single or multiple episodes of care were created from the adverse events. Chart review was conducted to establish whether the adverse event was related to chemotherapy and if any modification to the chemotherapy regimen occurred—a dose delay, dose reduction, or discontinuation was considered a clinical impact on therapy. Multivariate logistic regression was used to examine factors associated with clinical impact versus no clinical impact from the delivery of chemotherapy treatment.

RESULTS: A total of 1,682 patients with mBC were identified during our time period with an average follow-up of 2.21 years on first-line chemotherapy (SD = 1.83). 909 patients (54%) had at least 1 adverse event, and 773 patients (46%) did not have any adverse events during follow-up. Significant differences at baseline between these 2 groups included race, peripheral vascular disease, and length of stay ($P < 0.05$). From the 909 patients who had at least 1 adverse event, 185 patients (20%) experienced an impact on their chemotherapy regimens. Patients with single episodes of care with any chemotherapy regimen impact experienced mostly hematological, infection/pyrexia, and gastrointestinal-related adverse events. In multiple episodes of care, neurological impact was more frequent than gastrointestinal-related effects. Patients with hospitalizations of > 3 days experienced the most impact, demonstrating that severe adverse events

have more impact on chemotherapy regimens. In our multivariate analysis, patients aged > 65 years, having more than 1 comorbidity and having longer duration in days for each episode of care were all associated with clinical impact. Black and Hispanic patients were more likely to have a modification in their chemotherapy compared with white patients.

CONCLUSIONS: This retrospective analysis demonstrates that chemotherapy-related adverse events in patients with mBC have an impact on the delivery of chemotherapy regimens. Having multiple comorbidities, increased age, and prolonged hospitalizations because of adverse events appear to be some of the primary factors related to chemotherapy modification.

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What is already known about this subject

- Stage IV breast cancer, also known as metastatic breast cancer (mBC), is not a curable condition; however, treatment can prolong life, delay the progression of the cancer, or improve quality of life.
- Although chemotherapy is given in cycles, patients often experience adverse events from chemotherapy during the cycle, which leads to chemotherapy modification, such as dose delay, dose reduction, or discontinuation of chemotherapy.
- Few retrospective studies have evaluated the clinical impact from adverse events on chemotherapy treatments, and studies that have did not evaluate chemotherapy modification because of chemotherapy adverse events.

What this study adds

- This study used an episode of care method to evaluate chemotherapy adverse events in order to provide a more real-world approach that reflects the common practice of our health care delivery system.
- A chart review was conducted to determine if the episode of care-related adverse event was from chemotherapy or disease progression.
- Factors such as multiple comorbidities, increased age, and prolonged hospitalizations because of adverse events appear to be some of the primary factors related to chemotherapy modification.

Breast cancer is one of the most common malignancies in women. In 2013, it was estimated that 232,340 women in the United States were diagnosed with breast cancer, and that 39,620 women died of breast cancer.¹ Breast cancer remains a serious health care problem and accounts for approximately one third of cancers in the United States.¹ Overall survival varies by breast cancer stage.² People diagnosed with stage 0, I, or II breast cancers tend to have higher overall survival rates than people diagnosed with stage III or IV breast cancer; however, overall survival rates are averages and vary depending on each person's diagnosis and treatment.² Stage IV, also known as metastatic breast cancer (mBC) is not a curable condition; however, treatment can prolong life, delay the progression of the cancer, or improve quality of life.^{3,4} Approximately 6% of women with incident breast cancer have metastatic disease at initial presentation, and the median survival of individuals with mBC is 18 to 24 months, although the range in survival spans between a few months to many years and depends on the type of breast cancer.^{4,5} Breast cancer can be treated with different modalities. One modality is chemotherapy, which can be given as a sequential single agent or in combination to slow, stop, or kill the growth of cancer cells. Chemotherapy is given in cycles, such as 21 or 28 days, which allows the body to recover from the side effects of the medicines.

Although chemotherapy is given in cycles, patients often experience adverse events from chemotherapy during the cycle, which leads to a chemotherapy modification that may include dose delay, dose reduction, or discontinuation of chemotherapy. Studies have reported that interrupting chemotherapy cycles or not providing a high percentage of relative dose intensity will not improve the patient's disease progression thus decreasing overall survival rates.⁶⁻⁹ Few retrospective studies have evaluated the clinical impact from adverse events on chemotherapy. One study used retrospective U.S. data that included the general population; however, the patients were aged less than 63 years and had newly diagnosed breast cancer during the time period of April 1, 1998, to December 31, 2002.¹⁰ Another study was a population-based assessment of hospitalizations because of chemotherapy adverse events within the Medicare population. The patients were aged 65 years or more and had all stages of breast cancer during the time period of 1991 to 1996. In addition, the study focused on chemotherapy adverse events in the hospital setting but did not quantify other health care resource utilization in this population.¹¹

Although these studies evaluated rates of chemotherapy adverse events, they did not evaluate the clinical impact of adverse events on chemotherapy treatment for patients with mBC and aged older than 18 years. Consequently, the objectives for this study were to describe chemotherapy-related adverse events in patients with mBC receiving chemotherapy

and to evaluate the clinical impact on the chemotherapy regimen from these adverse events in an integrated health care delivery system. We applied an episode of care method to provide a more real-world approach, reflecting the common practice of our health care delivery system, and we conducted a chart review to determine if the episode of care-related adverse events were from chemotherapy or from disease progression.

Methods

Study Setting and Data

Kaiser Permanente Southern California (KPSC) is an integrated health care delivery system with approximately 3.6 million members. The KPSC membership currently represents 15% of the population in the Southern California region, and this membership closely mirrors the Southern California population; it is racially diverse and includes the entire socioeconomic spectrum.¹² Data were derived from the KPSC Health Plan (KPSC HP) database and The Kaiser Permanente Regional Cancer Registry (CANREG) database. The KPSC HP database contains information on patient demographics, diagnoses, prescriptions, laboratory results, and medical and hospital encounters. KPSC HP has an electronic health medical record system that allows for more detailed information to be accessed and included in studies. For all reportable cancers, the CANREG database is a compilation of data collected at the registry level from each of the 14 KPSC hospitals and contains information on patients who are newly diagnosed or who received at least part of their first course of treatment for cancer at a KPSC hospital. The CANREG data are provided to the Surveillance, Epidemiology, and End Results (SEER) program, a part of the National Cancer Institute that collects cancer data in the United States and compiles national cancer statistics. The diagnoses are validated and confirmed cancer diagnoses, which makes the KPSC CANREG applicable when conducting various retrospective or prospective longitudinal studies. The institutional review board for KPSC approved this study.

Design and Study Population

A retrospective cohort database analysis was conducted during the study enrollment period from January 1, 2007, to December 31, 2011. Patients with mBC were either selected from the KPSC CANREG or by using medical claims from the following algorithm (Figure 1)¹³: patients had more than 2 medical encounters within 90 days between January 1, 2007, and December 31, 2011, with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 197.xx-198.xx. The date of metastatic diagnosis was defined as the metastatic disease index date. We identified patients with breast cancer using the ICD-9-CM codes 174.xx or 233.0x. These codes had to be identified prior to the mBC date starting from January 1, 2002 (5 years prior) or 90 days after the mBC date. Patients had to be female and aged more

FIGURE 1 mBC Study Population Diagram

KPSC=Kaiser Permanente Southern California; mBC=metastatic breast cancer.

than 18 years on the date of diagnosis. We excluded patients with any other cancers 12 months prior to the diagnosis date (140.xx to 165.xx, 170.xx to 173.xx, 175.xx to 176.xx, 179.xx to 195.xx, 196.xx, 199.xx to 209.xx, 230x-234.x [except 233.0x], 235.x-239.x [except 238.3, 239.3], and V10.x [except V10.3]). Patients had to have 6 months of continuous membership and

drug benefit prior to the mBC date and throughout follow-up (Figure 1).

Identification of Chemotherapy and Patient Follow-Up

Once the final cohort of mBC patients was established, we used pharmacy and CANREG databases to identify the

first-line chemotherapy for each patient. Chemotherapy was identified using National Drug Code numbers and Generic Product Identifiers if patients were prescribed 1 or more of the following: capecitabine, taxanes (docetaxel and paclitaxel), cyclophosphamide, doxorubicin, gemcitabine, epirubicin, vinorelbine, ixabepilone, and eribulin. Once the chemotherapy was identified for the patient with mBC, we searched the databases to ensure that no other chemotherapy regimens had been initiated in the prior 12 months. We evaluated use of chemotherapy only and did not evaluate hormonal status or examine targeted therapies. If no other chemotherapy regimens were identified, we categorized the patient by chemotherapy regimen and identified the date of the first cycle as the treatment index date. Patient follow-up was defined from the index date until disenrollment from the health plan, start of a new chemotherapy regimen, or end of the study time period (December 31, 2012), whichever came first. During the follow-up period, adverse events were identified while patients were undergoing their first-line chemotherapy regimen.

Adverse Events

Previous studies and trials were used to identify adverse events.^{10,11,14} The following adverse events were selected based on ICD-9-CM diagnosis and procedure codes and categorized into the following groups: dermatological (alopecia, injection site reaction, and rash); dehydration; dyspnea; edema; gastrointestinal (constipation, decreased appetite, diarrhea, nausea/vomiting, and stomatitis); hematological (anemia, leukopenia, neutropenia, and thrombocytopenia); hepatic (increase in liver enzymes and bilirubin); infection or pyrexia; and neurological (arthralgia, myalgia, and peripheral neuropathy). Adverse events were identified using the primary or secondary discharge position diagnosis codes and procedure codes for outpatient visits, hospitalizations, and emergency room (ER) visits (Appendix A, available in online article).

Episodes of Care

Once adverse events were identified in our cohort, we created episodes of care (EOC) for each event. As defined in the literature, an episode of care is the period initiated by patient presentation with a diagnosis of clinical condition and concluded when the condition is resolved.^{15,16} The theoretical framework for assessing episodes has been well developed in the literature^{15,16}; however, the EOC for the management of adverse events has not been applied to patients with mBC. An EOC for the same condition can include single or multiple health care visits and/or various types of health care visits, including hospitalization, ER visits, or outpatient visits. The duration of an EOC is defined as the length of time between the first and last visit for that clinical condition. We applied a 2-week gap between the date of the last visit to the next visit of the same adverse event to ensure that the EOCs were not overestimated and were per clinical expert opinion—a 2-week gap would be sufficient to create a unique EOC for each adverse event.

Two types of EOCs were created: a single EOC and a multiple EOC. A multiple EOC represented repeated health care visits for the management of an adverse event. A single EOC was defined as 1 health care resource encounter for a specific adverse event with no other health care encounter within 2 weeks from that visit. Thus, single episodes could be an outpatient visit for 1 day or a hospital visit of 3 days. A multiple episode EOC was defined as a patient having more than 1 health care resource encounter within a 2-week time period. For example, a patient could have an outpatient visit, then in 3 days have another outpatient visit, then in 2 days go to the ER, and then be admitted to the hospital for 5 days for the same condition. Since there was no 2 week gap between the encounters, these episodes were counted as 1 multiple EOC.

Defining Clinical Impact

Pharmacy claims and chart reviews were used to identify if an EOC was related to a patient's chemotherapy treatment by reading the chart notes available during the time of an adverse event occurrence and then noting if there was a modification of or clinical impact on the chemotherapy regimen. In this study, we defined any modification of a patient's chemotherapy regimen as a clinical impact. Modifications included dose delay, dose reduction, discontinuation, or no dose impact to the chemotherapy regimen during the EOC. Only patients who had an adverse event EOC related to chemotherapy were included in our analysis.

Statistical Analyses

Unadjusted descriptive statistics were conducted to summarize patient characteristics of patients with mBC who had adverse events compared with those who did not experience adverse events. Differences between these patients groups were tested using two-sided t-tests for continuous variables and the chi-square statistic for categorical variables. Using descriptive statistics, a table was created to evaluate characteristics of patients who had clinical impact (dose delay, dose reduction, discontinuation, or no dose impact) from adverse events. A multivariable logistic regression model was used to evaluate factors associated with clinical impact from adverse events on the chemotherapy regimens. Factors including age, sex, race, selected comorbid conditions (using categorical comorbidity index of 0, 1 +), single or combination chemotherapy, duration of episode of care, and various health care resource scenarios were controlled for in the model. All data were analyzed using SAS version 9.2 (SAS Institute, Cary, NC). *P* values < 0.05 were considered to be statistically significant.

Results

There were 1,682 patients identified as patients with mBC from our selection criteria, database algorithm, and KPSC cancer

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TABLE 1 Characteristics of Patients with Adverse Events and No Adverse Events

Patient Characteristics	Total First-Line Patients N = 1,682		Patients with Identified AE During First-Line Therapy n = 909 (54%) ^a		Patients with No Identified AE During First-Line Therapy n = 773 (46%) ^a	
Aged < 65 years, n (mean, SD)	1,002	(53 ± 8.1)	545	(53 ± 8.2)	457	(53 ± 8.0)
Aged ≥ 65 years, n (mean, SD)	680	(73 ± 6.0)	362	(73 ± 5.8)	318	(74 ± 6.2)
Single chemotherapy regimen, n (%)	1,547	(91.97)	830	(91.31)	717	(92.76)
Multiple chemotherapy regimen, n (%)	135	(8.03)	77	(8.47)	58	(7.5)
Race, n (%)						
Asian/Pacific Islander	150	(8.91)	94	(10.34)	56	(7.24)
Black	290	(17.24)	151	(16.61)	139	(17.98)
Hispanic	179	(10.64)	110	(12.10)	69	(8.93)
Other ^b	100	(5.94)	49	(5.39)	51	(6.6)
White	963	(57.25)	503	(55.34)	460	(59.51)
Insurance type, n (%)^c						
Commercial	1,643	(97.68)	879	(96.70)	764	(98.84)
Medicaid	30	(1.78)	20	(2.20)	10	(1.29)
Medicare	667	(39.65)	362	(39.82)	305	(39.46)
Comorbidities, n (%)^c						
Cerebrovascular disease	46	(2.73)	25	(2.75)	21	(2.72)
Chronic pulmonary disease	199	(11.83)	113	(12.43)	86	(11.13)
Congestive heart failure	64	(3.80)	33	(3.63)	31	(4.01)
Diabetes	275	(16.35)	147	(16.17)	128	(16.56)
Hypertension	718	(42.69)	401	(44.11)	317	(41.01)
Liver disease	14	(0.83)	9	(0.99)	5	(0.65)
Myocardial infarction	34	(2.02)	20	(2.20)	14	(1.81)
Other ^d	21	(1.25)	11	(1.21)	10	(1.29)
Peripheral vascular disease	26	(1.55)	19	(2.09)	7	(0.91)
Renal disease	154	(9.16)	87	(9.57)	67	(8.67)
Rheumatic disease	30	(1.78)	15	(1.65)	15	(1.94)
Health care resource use						
ER visits, n (%)	622	(36.97)	348	(38.28)	274	(35.44)
ER visits (mean, SD)	(2.0 ± 1.0)		(2.0 ± 1.0)		(2.0 ± 1.0)	
Hospital length of stay (mean, SD)	(3.0 ± 4.0)		(3.0 ± 5.0)		(3.0 ± 3.0)	
Hospitalization visits, n (%)	622	(36.97)	332	(36.52)	290	(37.52)
Hospitalization visits (mean, SD)	(2.0 ± 1.0)		(2.0 ± 1.0)		(2.0 ± 1.0)	
Outpatient visits, n (%)	1,682	(100.00)	909	(100.00)	773	(100.00)
Outpatient visits (mean, SD)	(13.0 ± 9.0)		(13.0 ± 9.0)		(13.0 ± 9.0)	

^aBold values signify statistical significant at $P < 0.05$.

^bNative Hawaiian/Other Pacific Islander/ Native American/other/unknown.

^cNot mutually exclusive; 1 patient could be counted more than once.

^dOther includes dementia, peptic ulcer disease, and hemiplegia or paraplegia.

AE = adverse event; ER = emergency room; SD = standard deviation.

registry (Figure 1). Table 1 summarizes the baseline characteristics of the mBC cohort and further categorizes the patients into a group with 1 or more adverse events (n = 909, 54%) and a group with no adverse events (n = 773, 46%) during follow-up. Overall, there was a higher percentage of patients aged less than 65 years (60%) with a mean age of 53 years (standard deviation [SD] = 8.1). Patients were initially started with a single chemotherapy agent as opposed to a combination chemotherapy regimen. Patients were divided according to first-line chemotherapy treatment as follows: capecitabine (67%), taxane (22%),

cyclophosphamide (9%), doxorubicin (6%); 5% of patients were started on gemcitabine, epirubicin, vinorelbine, ixabepilone, and eribulin. Patients were predominantly white (57%), and the most common comorbidities were hypertension (43%), diabetes (16%), chronic pulmonary disease (12%), and renal disease (9%). Statistical differences were shown between the 2 groups at baseline with race and peripheral vascular disease. The health care resource use for the prior 6 months was similar as well; however, at baseline patients with adverse events had longer length of stay compared with patients with no adverse events.

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TABLE 2 Adverse Events Identified During First-Line Chemotherapy Treatment (Patient-Level Data)

Adverse Events and Other Characteristics	During First-Line Therapy
Number of unique adverse events, n (%)	N = 1,682
0	773 (46.0)
1	322 (19.1)
2	186 (11.1)
3	148 (8.8)
4	92 (5.5)
> 5	161 (9.6)
Unique adverse events by category, n (%)	N = 909
Dermatological	84 (9.2)
Alopecia	5 (0.6)
Injection site reaction	14 (1.5)
Rash	65 (7.2)
Dehydration	104 (11.4)
Dyspnea	108 (11.9)
Edema	104 (11.4)
Gastrointestinal	466 (51.3)
Constipation	129 (14.2)
Decreased appetite	37 (4.1)
Diarrhea	128 (14.1)
Nausea/vomiting	141 (15.5)
Stomatitis	31 (3.4)
Hematological	592 (65.1)
Anemia	346 (38.1)
Leukopenia	122 (13.4)
Neutropenia	88 (9.7)
Thrombocytopenia	36 (4)
Hepatic	35 (3.8)
Liver enzymes increased ^a	29 (3.2)
Bilirubin increased	6 (0.7)
Infection or pyrexia	482 (53.0)
Infection	380 (41.8)
Pyrexia	102 (11.2)
Neurological	322 (35.4)
Arthralgia	134 (14.7)
Myalgia	36 (4.0)
Peripheral neuropathy	152 (16.7)

^aLiver enzymes: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP).

Table 2 summarizes the adverse events identified after first-line chemotherapy was given during the follow-up period. The mean days of being on first-line therapy was 375 days (SD = 262 days). Unique adverse events were defined as a patient having a specific adverse event 1 or more times. More than half of the patients started on chemotherapy had an adverse event, with 1 and 2 unique adverse events being the majority (19% and 11%, respectively). Overall, hematological (65%), infection/pyrexia (53%), and gastrointestinal (51%) episodes were the most unique adverse events. Neurological (35%) and others (dehydration, dyspnea, and edema) represented 11% of the events.

TABLE 3 Summary of Episode of Care Data

AE Episode of Care Summary	During First-Line Therapy
Number of patients with 1 or more AE episodes	909
Total AE episodes	5,940
AE episodes related to chemotherapy, n (%)	5,475 (92.2)
Single episodes, n (%)^a	4,185 (76.0)
Mean number of single episodes per patient (SD)	4.7 (3.6)
1-day episode only, n (%)	4,004 (96.0)
> 1-day episode, n (%)	181 (4.3)
Mean duration of days for > 1-day episode (SD)	5.3 (1.7)
Multiple episodes, n (%)^a	1,290 (24.0)
Mean number of multiple episodes per patient (SD)	3.0 (4.0)
Mean duration of days per multiple episode (SD)	4.8 (4.6)

^aPercentages for single episodes were calculated as follows: $4,185 \div 5,475 = 76\%$. Percentages for multiple episodes were calculated as follows: $1,290 \div 5,475 = 24\%$. AE = adverse event; SD = standard deviation.

Episode of care was applied after adverse events were identified. During this time, we identified which adverse event episode of care was associated with chemotherapy. There were 5,940 episodes identified: 92.2% (5,475) were chemotherapy related (Table 3 and Appendix B, available in online article) and 8% (465) were from disease progression or other conditions not related to chemotherapy. Chart notes revealed that all the adverse events related to dyspnea were attributed to disease progression and not related to chemotherapy. We also did not identify any patients with fatigue, which is a common adverse event caused by chemotherapy. Thus, we did not include these EOC events in our analysis. There were 4,185 (76%) single episodes and 1,290 (24%) multiple episodes of care (Table 3). The single episodes consisted of 4,004 (96%) 1-day single episodes, and 181 (4%) less than 1-day single episodes. The mean duration of less than 1-day single episodes was 5.3 days (SD = 1.7 days). The duration of multiple episodes was 4.8 days (SD = 4.6 days; Table 3).

Chart notes were reviewed and pharmacy claims were used to evaluate if an EOC for an adverse event had any clinical impact (dose delay, dose reduction, or discontinuation) on chemotherapy regimens (Table 4). Of the 909 patients, there were 185 patients (20%) who had 1 or more chemotherapy modifications as opposed to 724 patients (80%) who did not have any chemotherapy modification. Of the 45 patients who experienced a single EOC, 34 patients had dose delay; 17 patients had dose reductions; and 14 patients discontinued therapy. Of the patients who experienced a multiple EOC, 116 patients had a dose delay; 80 patients had dose reductions; and 48 patients discontinued therapy. The majority of patients with single episodes who had chemotherapy modification were patients with hematological (42.3%), gastrointestinal (28.3%), and infection/pyrexia (13%) adverse events. Similar results were shown in patients with multiple EOCs; however, more of these patients with any chemotherapy modification were shown to have neurological-related adverse events (11.8%) versus

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TABLE 4 Characteristics of Patients with and Without Clinical Impact on Chemotherapy Regimen During EOC by AE Category

AE and Health Care Resource Characteristics	Chemotherapy Modification (Dose Delay, Dose Reduction, or Discontinuation)		No Chemotherapy Modification	
	Patients During First-Line Therapy N = 185 (20%)		Patients During First-Line Therapy N = 724 (80%)	
Single EOC	Patients, n (%) ^a	EOC, n (%) ^a	Patients, n (%) ^a	EOC, n (%) ^a
Total	45	109	724	4,076
Dermatological	2 (4.4)	2 (2.2)	66 (9.1)	111 (2.7)
Dehydration	6 (13.3)	7 (7.6)	37 (5.1)	53 (1.3)
Edema	1 (2.2)	1 (1.1)	93 (12.8)	158 (3.9)
Gastrointestinal	25 (55.6)	26 (28.3)	353 (48.7)	749 (18.4)
Hematological	27 (60.0)	39 (42.3)	306 (42.2)	1,348 (33.1)
Hepatic	1 (2.2)	1 (1.1)	25 (3.4)	65 (1.6)
Infection or Pyrexia	20 (44.5)	29 (31.5)	252 (34.8)	526 (12.9)
Neurological	3 (6.7)	4 (4.3)	280 (38.6)	1,066 (26.2)
Multiple EOC				
Total	160	484	400	806
Dermatological	7 (4.4)	7 (1.8)	14 (3.9)	14 (1.7)
Dehydration	16 (10.0)	17 (4.3)	69 (19.2)	78 (9.5)
Edema	8 (5.0)	9 (2.3)	11 (3.1)	12 (1.5)
Gastrointestinal	90 (56.3)	107 (26.8)	129 (35.8)	171 (20.8)
Hematological	117 (73.1)	181 (45.3)	138 (38.3)	239 (29.1)
Hepatic	1 (0.6)	1 (0.3)	12 (3.3)	12 (1.5)
Infection or pyrexia	69 (43.1)	115 (28.7)	135 (33.8)	220 (26.8)
Neurological	31 (18.4)	47 (11.8)	41 (11.4)	60 (7.3)
HCRU-related to any EOC				
Total	185	470	724	8,707
Hospital visits ^b	180 (97.3)	70 (14.9)	229 (26.7)	111 (1.3)
Hospitalization 1 day + ER visit	1 (0.5)	1 (0.2)	45 (5.2)	81 (0.9)
Hospitalization 2 days + ER visit	9 (4.9)	10 (2.1)	63 (7.3)	117 (1.3)
Hospitalization 3 days	37 (20.0)	54 (11.5)	56 (6.5)	76 (0.9)
Hospitalization >3 days	152 (82.2)	308 (65.5)	61 (7.1)	60 (0.7)
More than 1 outpatient visit ^c	173 (93.5)	445 (94.6)	403 (55.6)	4,773 (54.8)
1 outpatient visit + ER visit	1 (0.5)	2 (0.4)	33 (3.8)	4,328 (49.7)

Note: Descriptive statistics were conducted between patients with any chemotherapy modification versus no chemotherapy modification and between EOC for any chemotherapy modification group versus no chemotherapy modification group.

^aBold values signify statistical significance at $P < 0.05$.

^bPatients with ≥ 1 hospital visits versus those with no hospitalizations.

^cPatients with > 1 outpatient visits versus those with 1 outpatient visit.

AE = adverse event; EOC = episode of care; ER = emergency room; HCRU = health care resource utilization.

infection/pyrexia (7.8%). Table 4 also shows evaluation of health care resource utilization for clinical impact. Patients who had hospital visits with length of stay of 3 or more days (65.5%), were shown to have the most clinical impact compared with those who stayed less than 3 days.

Table 5 lists the significant factors associated with any chemotherapy modification versus no chemotherapy modification. Factors such as age (> 65 years), comorbidity (> 1 comorbidity), and longer duration of days for each EOC were associated with clinical impact. Black and Hispanic patients were more likely to have a modification in their chemotherapy treatment compared with white patients.

Discussion

The results of this study demonstrate that adverse events related to chemotherapy in patients with mBC have significant impact on their chemotherapy regimens in an integrated health care delivery system. This is the first study to apply an EOC framework to understand health care delivery for adverse events in mBC women aged more than 18 years and who are undergoing chemotherapy. Approximately 23% of patients experienced a multiple EOC for an adverse event, which was associated with an increased risk of clinical impact. Our study also showed a positive association with patients having longer hospital length of stays and clinical impact. Adverse events from chemotherapy

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TABLE 5 Factors Associated with Chemotherapy Regimen Modification and Without Chemotherapy Modification from Multivariate Logistic Regression in mBC Patients

Patient and Clinical Characteristics	Chemotherapy Modification Versus No Chemotherapy Modification During First-Line Therapy OR (95% CI) ^a
Patient age groups, years	
<65 years (reference)	1.00
>65 years	2.05 (1.57-2.49)
Race	
White (reference)	1.00
Black	2.22 (1.75-2.68)
Hispanic	1.58 (1.11-1.89)
Asian/Pacific Islander	0.52 (0.31-1.21)
Comorbidities	
1+ versus 0	2.01 (1.74-2.82)
Chemotherapy regimen	
Combination versus single	1.47 (0.33-2.71)
Duration of EOC	
Single episode	1.24 (1.09-2.07)
Multiple episode	2.81 (2.42-3.56)
Health care utilization for any EOC	
Hospital visit only	0.88 (0.62-1.63)
Hospitalization 1 day + ER visit	0.91 (0.73-1.56)
Hospitalization 2 days + ER visit	2.88 (2.53-3.57)
Hospitalization 3 days	5.22 (4.88-6.05)
Hospitalization > 3 days	8.55 (7.42-9.02)
1 outpatient visit	0.28 (0.16-1.05)
1 outpatient visit + ER visit	0.33 (0.14-1.22)

^aBold numbers indicate statistical significance.

CI = confidence interval; EOC = episode of care; ER = emergency room; mBC = metastatic breast cancer; OR = odds ratio.

reported from other studies showed hematological, infection/pyrexia, and gastrointestinal episodes as the most common adverse events from chemotherapy, which we also found in our results.^{10,11} However, the rates in our study were higher, which was most likely because our patients were at the metastatic stage rather than an earlier breast cancer stage. The presence of metastatic disease and being initiated on chemotherapy are independently associated with a statistically significant increase in the odds of experiencing a serious adverse effect.^{10,11} We also found that patients older in age and with more comorbidities had a significantly higher likelihood of an impact on chemotherapy treatment. Chemotherapy is used in the elderly population; however, oncologists assess age and comorbidities in this population when considering chemotherapy because of fear of excessive toxicity.¹⁷ Chemotherapy is known to have a low therapeutic index, and with age, there are many changes that could impact the

pharmacokinetic processes, which could lead to dramatic consequences such as excessive drug levels and unacceptable toxicity.¹⁶ Racial/ethnic status was also associated with an increased risk of clinical impact in our study. Future studies will need to examine social and cultural factors that may be responsible for this finding. There was a total of 20% of patients that had chemotherapy modification to current chemotherapy regimens related to an adverse event. A previous study reported a rate of chemotherapy modification of approximately 24.7%.¹⁸

Current existing treatments for patients with mBC are effective, but they are associated with many different adverse events, and these can cause changes to the patient's chemotherapy regimen. The clinical impact has not been previously quantified, and changes in chemotherapy regimens can cause clinical, functional, and economic consequences. These findings can help managed care organizations evaluate the importance of including the side effect profile from various treatment options into clinical decision making and identify therapies that may be associated with fewer complications. This could improve patient clinical outcomes and reduce changes in chemotherapy regimens and possible costs related to adverse events. Managed care and other health care systems should always be looking for therapies that demonstrate equal or superior efficacy to current standard chemotherapy regimens, while decreasing the frequency and severity of adverse events related to these chemotherapy regimens. Newer therapies can help with economic burden by reducing potential costs incurred from treatment-related adverse events.

Limitations

Our study had some limitations. Although we used diagnosis and procedure codes to identify adverse events, we relied only on data that were available in our electronic system. All adverse events were identified with diagnosis and procedure codes, and laboratory data were not used to confirm specific adverse events such as anemia, leukopenia, neutropenia, or thrombocytopenia. Since the health care encounters were associated with diagnosis and procedure codes, we thought using those codes would suffice; however, there may be possible underestimation in these rates. We also understand that the adverse event list did not include all adverse events caused by chemotherapy; however, by reviewing the literature and previous clinical trials, the adverse events included in this study were the most common in patients using chemotherapy. A common adverse event is fatigue, and since this is mostly a patient-reported event, we could not identify it using diagnosis codes. Our sample consisted of patients on chemotherapy only; we did not evaluate the status (positive or negative) of human epidermal growth factor receptor 2 (HER2) or evaluate targeted therapies. We used our databases to identify first-line chemotherapy regimens 12 months prior to index date so could only capture what was found in our pharmacy

databases. Finally, when we evaluated adverse events, we could not report what grade (3 or 4) or apply a scale of severity to them; however, if a patient was admitted to the hospital, there was an assumption that it had some severity. Overall, our rates of health care resource utilization had all severities.

Conclusions

This study is one of the few to evaluate the clinical impact on chemotherapy regimens from chemotherapy-related adverse events in an integrated health care delivery system. This retrospective analysis demonstrates that chemotherapy-related adverse events in patients with mBC have an impact on the delivery of chemotherapy regimens. The management of mBC becomes a clinical challenge to many oncologists as the condition is chronic in nature. In this study, we see that having multiple comorbidities, increased age, and prolonged hospitalizations because of adverse events are primary factors related to chemotherapy modification. Within a managed care organization, the burden of care for these patients increases when adverse events occur. Since hospitalizations are one of the key factors of clinical impact, a goal would be to help prevent these hospitalizations in the future. Although there are various available anti-mBC therapies, the goal of treatment is palliative with prolongation of survival, optimal quality of life, and control of symptoms. Newer targeted oncology agents could minimize adverse events and alleviate overall burden on the health care system. It has been demonstrated in clinical trials and various other studies that any modification in chemotherapy regimen can lead to progressive disease and less survival rates. Newer agents that target specific pathways in cancer may decrease rates of chemotherapy-related adverse events, maintain good quality of life in patients with any stage of breast cancer, and may be optimal for subgroups of vulnerable patients. Future studies should also examine the economic impact of adverse events from patient and societal perspectives.

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Clinical Impact of Chemotherapy-Related Adverse Events in Patients with Metastatic Breast Cancer in an Integrated Health Care System

APPENDIX A Diagnosis Codes Used for Identifying Adverse Events

Adverse Event	ICD-9-CM Code	HCPCS/CPT Codes
Dermatological		
Alopecia	704.0x	
Injection site reaction	999.39	
Rash	693.0x, 708.8x, 708.9x, 782.1x	
Dehydration	276.5x	
Dyspnea	786.0x	
Edema	782.3x, 514.xx, 518.4x	
Gastrointestinal		
Constipation	564.0x	
Decreased appetite	783.0x, 783.2x	
Diarrhea	558.9x, 564.5x, 787.91, 007.xx, 009.xx	
Nausea	787.0x, 787.01, 787.02, 787.03, 536.20	G9021, G9022, G9023, G9024
Stomatitis	528.0x	
Hematological		
Anemia	280.xx, 281.xx, 283.xx, 284.xx, 285.xx	S3906, S9538, C1010, C1016, C1020, C1021, C9504, C9505, P9016, P9021, P9022, P9038, P9039, P9040, P9051, P9054, P9057, P9058, Q0136, Q4055, J0885, J0886, Q9920-Q9940, Q4054, J0880, J0881, J0882, Q0137, C1774, S0112
Leukopenia	288.5x, 288.8x, 288.9x	J1440, J1441, C9119, Q4053, J2505, J2820
Neutropenia	288.0x	
Thrombocytopenia	287.3x, 287.4x, 287.5x, 444.6x, 289.84, 99.05	P9010, P9031, P9037, P9052, P9053, P9055
Hepatic		
Liver enzymes increased	790.4x, 790.5x	84450
Bilirubin increased	277.4x	81000, 81001, 81002, 81003, 82248, 82247
Infection or Pyrexia		
Infection	001.xx-018.xx, 030.xx-041.xx, 045.xx-049.xx, 050.xx-057.xx, 110.xx-118.xx, 070.xx-079.xx, 130.xx-136.xx, 460.xx-466.xx, 480.xx-488.xx, 038.0x, 038.19, 038.80, 038.9x, 995.91, 995.92	
Pyrexia	780.6x	
Neurological		
Arthralgia	719.4x, 524.62	
Myalgia	729.1x	G9025, G9026, G9027, G9028
Peripheral neuropathy	356.xx, 357.xx, 337.0x, 337.1x	
Other		
Fatigue	780.72	G9029, G9030, G9031, G9032
Pharyngitis	462.00	

CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Clinical Impact of Chemotherapy-Related Adverse Events in Patients with Metastatic Breast Cancer in an Integrated Health Care System

APPENDIX B Descriptive Data on Chemotherapy-Related EOCs Per AE Category During First-Line Therapy (Episode Level)

During First-Line Therapy, n (%)	Total Episodes N = 5,475	Total Single Episodes N = 4,185	1-Day Single Episodes n = 4,004	> 1-Day Single Episodes n = 181	Total Multiple Episodes N = 1,290	Mean Days of Multiple Episode Duration (SD)
Dermatological	134 (2.49)	113 (2.71)	111 (2.77)	2 (1.22)	21 (1.72)	5.5 (4.3)
Dehydration	155 (2.83)	60 (1.44)	50 (1.25)	10 (6.10)	95 (7.36)	4.3 (3.2)
Edema	180 (3.34)	159 (3.81)	157 (3.92)	2 (1.22)	21 (1.72)	5.2 (5.3)
Gastrointestinal	1,053 (19.54)	775 (18.59)	741 (18.51)	34 (20.73)	278 (22.75)	5.3 (4.5)
Hematological	1,807 (33.53)	1,387 (33.28)	1,317 (32.89)	70 (42.68)	420 (34.37)	6.1 (5.6)
Hepatic	79 (1.47)	66 (1.58)	65 (1.62)	1 (0.61)	13 (1.06)	4.3 (2.9)
Infections/pyrexia	890 (16.25)	555 (13.26)	498 (12.44)	57 (34.75)	335 (25.96)	4.2 (4.1)
Neurological	1,177 (21.84)	1,070 (25.67)	1,065 (26.60)	5 (3.05)	107 (8.76)	4.6 (2.9)

AE = adverse event; EOC = episode of care; SD = standard deviation.